Clinical Study Protocol	
Drug Substance	XR-NTX
Study Code	NTX-204725-1
EudraCT Code	2011-002858-31
Edition Number	3C
Date	12. Jun 2012

Optimal Prevention of Overdose Deaths and Opioid Relapse Following Discharge: A Multi-Center RCT

Sponsor: The Norwegian Centre for Addiction Research, University of Oslo, Norway, Research Director Jørgen Bramness, Professor MD

Funding: Norwegian Research Council (unrestricted grant # 204725/V50)

National Coordinating Investigator (PI) & Sponsor Representative: Lars Tanum MD, PhD

Project Coordinator: Nikolaj Kunøe PhD

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change
B	April 1st 2012		
C	Jun 12th 2012		

SPONSOR SIGNATURE PAGE

Title	Optimal Prevention of Overdose Deaths and Opioid Relapse Following Discharge: A Multi-Center RCT
Protocol ID no:	NTX-SBX
EudraCT no:	2011-002858-31

Sponsor signatory approval

I hereby declare that I will conduct the study in compliance with the Protocol, ICH GCP and the applicable regulatory requirements:

1.1 Jørgen G. Bramness, Professor, MD
Research Director, Norwegian Centre for Addiction Research,
University of Oslo, Norway

Sponsor signature	*Date*

PI signatory approval

I hereby declare that I will conduct the study in compliance with the Protocol, ICH GCP and the applicable regulatory requirements:

1.1.1.1 Lars Tanum, assistant Professor, MD
National Coordinating Investigator (PI)

PI signature	*Date*

PROTOCOL SYNOPSIS

Optimal Prevention of Overdose Deaths and Opioid Relapse Following Discharge: A Multi-Center RCT

Principal Investigator

Lars Tanum MD, Ph.D.

Study centre(s) and number of patients planned

This study will be conducted in approximately 220 randomised patients in Norway to yield 180 evaluable patients at approximately 6 study sites. Number of patients per study site is expected to vary depending on patient availability at the different study sites. Additional sites may be added during the study.

Study period		**Phase of development**
Estimated date of first patient enrolled	Aug 31st 2012	Phase III
Estimated date of last patient completed	Sep 30th 2015	

Estimated end of study date (database lock) is Mar 31st 2016.

Objectives

This study will investigate the effectiveness and safety of sustained release naltrexone injectable suspension (VIVITROL®) (XR-NTX) in opiate dependent individuals.

The primary objectives of this study are to compare the current 1st-choice medication in Norway for opioid dependence, buprenorphine-naloxone, with extended release naltrexone on

a) abstinence from opioid use

b) overdose mortality (OD)

c) retention in treatment in situations with a high incidence of opioid use and/or OD

d) Compare the effects of any of the above medical interventions with participants who decline to receive pharmacological treatment but agree to enter a non-randomized comparison group

The secondary objectives are to:

a) Compare the effectiveness of treatment with naltrexone versus buprenorphine-naloxone across clinical – and criminal justice settings

b) Assess to what extent other variables such as mental health, use of non-opioid substances or social adjustment problems influence the treatment outcomes

c) Assess the influence of study interventions, no intervention, and/or setting on other variables such as concomitant substance use, morbidity, or recidivism.

Study design

This is a 12-week multicentre, open-label, randomised treatment study of the effectiveness and safety of sustained release naltrexone injectable suspension (VIVITROL®) (later referred to as XR-NTX) 380 mg/month versus buprenorphine-naloxone 8-24 mg/day in the treatment of opioid dependent patients, with a follow-up treatment period of 36 weeks.

Target patient population

Male or female patients, 18 to 65 years old, with a DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders, 4th edition Text Revision) diagnosis of opioid dependence, Single Episode (304.00) and confirmed by the Mini-International Neuropsychiatric Interview (MINI).

Investigational product and comparator, dosage and mode of administration

The eligible patients will be randomly assigned to one of the two treatment arms:

– XR-NTX 380 mg/month (IM)

– Buprenorphine-naloxone 8-24 mg/day (oral)

Preparations to be used in the study are:

– 380 mg naltrexone for extended release injectable suspension (XR-NTX)

– Buprenorphine-naloxone combination tablets with a buprenorphine component of 8-24 mg and a naloxone component of 2-8 mg

Buprenorphine-naloxone tablets (8-24 mg) will be administered orally once daily in accordance with existing national and local guidelines for OMT / LAR.

XR-NTX 380 mg (IM) will be injected once every four weeks.

Duration of treatment

Eligible patients will enter a detoxification period in a controlled environment of minimum 7 days for the discontinuation of all illicit substances. Prior to discharge, patients will be randomized to treatment in a 1:1 ratio to commence 12 weeks of outpatient treatment with either 3 x 380 mg/month XR-NTX fixed dose or 8-24 mg/day buprenorphine-naloxone on a flexible dose regimen. All buprenorphine-naloxone patients will start on 4 mg/day but the dose will be increased until a satisfactory effect is obtained. Patients in the naltrexone 380 mg/month treatment group will receive the 380 mg dose following randomisation and monthly thereafter.

After 12 weeks, the patients will enter a 36-week follow-up treatment study. During this part of the study they may receive either buprenorphine-naloxone or XR-NTX based on their personal preference.

Outcome variables

Effectiveness

– **Primary outcome variables:**

- Abstinence from illicit opioids assessed by the absence of non-study opioid agonists or their metabolites in oral fluid and/or patient-reported use of such opioids during the first 12 weeks of the study
- Retention in medication group at each assessment during the first 12 weeks
- Mortality at Week 48 as measured by journal and/or national mortality registry data

– **Secondary outcome variables:**

- Compare the effectiveness of the treatment interventions between the individuals recruited from criminal justice settings versus treatment settings
- Influence of the treatment interventions on non-opioid substance use, mental health, morbidity, medical treatment, and social adjustment problems
- To what extent other variables such as mental health or social adjustment problems influence the treatment outcome
- Proportion of patients in each group satisfying criteria for DSM-IV opioid dependence (304.00; except buprenorphine) at Week 12
- Proportion of patients in each group satisfying criteria for DSM-IV opioid dependence (304.00; except buprenorphine) at Week 48 or at time of leaving the study

Patient-reported outcomes (PRO)

- Number of days without use of heroin or other illicit opioids during the 85-day study period using time-line follow-back
- Craving for heroin
- Quality of life
- Mental health
- Abstinence orientation
- Sleep problems
- Opioid agonist effect rating
- Injecting drug use

– **Pharmacokinetic**

- Patients with detectable quantities of study drug in oral fluid

– **Safety**

- Incidence of adverse events (AEs)
- Incidence of AEs leading to withdrawal from the study
- Incidence of serious adverse events (SAEs)
- Incidence of AEs of special interest (overdose)

Statistical methods

Although this is an exploratory study in which precise power analyses are complicated by a lack of precedent in the existing literature, there are three null-hypotheses stating that there are

- no differences between XR-NTX 380 mg/month (IM) or buprenorphine-naloxone (8-24 mg/day) with regard to the primary outcome variables
- no difference between the treatment groups with regard to change in DSM-IV diagnostic criteria from randomisation to Week 12
- no difference between the randomized treatment groups and the non-randomized participant group with regard to the primary outcome variables

Descriptive statistics including frequency tables, graphs or scatterplots will be provided for all primary outcomes, as well as for the changes from baseline within each treatment and the differences between the treatment groups at each visit (Observed Cases (OC) and LOCF as appropriate).

All statistical tests will be two-sided with a significance level of 5%, i.e., α=0.05 unless otherwise specified. Secondary analyses will report nominal 5% levels of significance. No adjustments for multiplicity will be made for these secondary analyses. Where appropriate, model-based point estimates will be presented together with their 95% confidence interval.

Missing data will be imputed using a Last Observation Carried Forward (LOCF) approach.

A step-wise sequential testing procedure will be used for handling multiple comparisons to preserve an overall significance level of 0.05.

The primary outcome variable will be analysed using an analysis of variance (ANOVA) or regression model as appropriate including treatment, study site and baseline frequency of opioid use as explanatory variables. Study site will be treated as a random effect while all other explanatory variables will be treated as fixed effects.

Changes from randomisation to every assessment will be analysed similar to the primary objective.

Incidence rates will be calculated for AEs (including serious adverse events leading to withdrawals and deaths, if any) and reasons for premature discontinuation registered. Other safety variables that evaluate physical examinations, laboratory assessments, vital signs, ECGs and selected AEs will be analysed by means of descriptive statistics, frequency tabulations, and graphical displays as appropriate. For all participants, physical examination and laboratory assessment is performed as part of study enrolment.

Analysis populations

All data analyses, both primary and secondary, will be performed using at least one of the following analysis sets:

- The safety population will include all randomised patients who took at least one dose of study medication, classified according to the treatment actually received.

- The intention-to-treat (ITT) population will include all patients who were included and randomised to a treatment, regardless of whether first treatment dose was received or not. This population includes all drop-outs regardless of duration of participation.

- The modified intention-to-treat (MITT) population (Full Analysis Set) will include all randomised patients, classified according to the randomised treatment, who received at least one dose of study treatment and who have at least one valid assessment after randomisation. Data from the MITT population will be used for analysis of the effectiveness objectives.

- The per-protocol (PP) population, a subset of the MITT population, will include patients who completed the study treatment with no major protocol violations or deviations affecting effectiveness. Data from this population will be used as a consistency check for analysis of the primary objective.

TABLE OF CONTENTS PAGE

TITLE PAGE 1
PROTOCOL SYNOPSIS 3
TABLE OF CONTENTS 9
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS 15
1. INTRODUCTION 19
1.1 Background 19
1.2 Opioid detoxification 19
1.3 Psychosocial interventions 20
1.4 Opioid maintenance treatment (OMT) 20
1.4.1 Methadone 21
1.4.2 Buprenorphine 22
1.4.3 Buprenorphine-naloxone 23
1.4.4 OMT summary 23
1.5 Antagonist treatment 23
1.5.1 Naltrexone 24
1.5.1.1 Oral naltrexone 24
1.5.2 Extended release naltrexone 25
1.6 Drug use and the criminal justice setting 26
1.6.1 Prison-based treatment of opioid dependence 27
1.7 Rationale for this study 28
2. STUDY OBJECTIVES 30
2.1 Primary objective 30
2.2 Secondary objectives 30
3. STUDY PLAN AND PROCEDURES 34
3.1 Overall study design and flow chart 34
3.1.2 Enrolment period (up to 30 days) 35
3.1.3 Twelve-week randomised treatment period (Visit 2 to Visit 13) 35
3.1.4 Thirty-six-week non-randomised treatment period (Visit 14 to Visit 23) 36
3.1.5 Unscheduled visits 40
3.2 Rationale and risk/benefit assessment 40
3.2.1 Rationale for study design, doses, and control groups 40
3.2.2 Risk/benefit and ethical assessment 40
3.3 Selection of study population 41
3.3.1 Study selection record 41
3.3.2 Inclusion criteria 41
3.3.3 Exclusion Criteria 41

3.3.4 Interactions with study medications 42
3.3.5 Restrictions 42
3.3.6 Discontinuation of patients from treatment or assessment 42
3.3.6.1 Criteria for discontinuation / End of Study 42
3.3.6.2 Procedures for discontinuation 43
3.4 Treatments 44
3.4.1 Identity of investigational product and comparators 44
3.4.2 Doses and treatment regimens 44
3.4.3 Labelling 45
3.4.4 Storage 45
3.4.5 Accountability 45
3.5 Method of assigning patients to treatment groups 46
3.6 Pre-study, concomitant and post-study medication(s) 47
3.7 Treatment compliance 48
3.8 Psychosocial treatment and care recommended to all participants 49
4. MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES 50
4.1 Primary variable 50
4.2 Screening and demographic measurements 50
4.3 Patient-Reported Outcomes (PRO) 51
4.3.1 The Temporal Satisfaction With Life Scale (TSWLS) 52
4.3.1.1 Methods of assessment 52
4.3.1.2 Derivation or calculation of outcome variable (TSWLS) 52
4.3.2 Insomnia Severity Index (ISI) 52
4.3.2.1 Methods of assessment 52
4.3.2.2 Derivation or calculation of outcome variable (ISI) 52
4.3.3 Stages of Change Readiness and Treatment Eagerness Scale – Drugs (SOCRATES-8D) 52
4.3.3.1 Methods of assessment 52
4.3.3.2 Derivation or calculation of outcome variable (Socrates-8D) 53
4.3.4 Heroin effect, craving, & treatment satisfaction (VAS) 53
4.3.4.1 Methods of assessment 53
4.3.4.2 Derivation or calculation of outcome variable (VAS) 53
4.3.5 Hopkins' Symptom Checklist 25 (SCL-25) 53
4.3.5.1 Derivation or calculation of outcome variable (SCL-25) 53
4.4 Health Economic measurements and variables. 54
4.5 Pharmacokinetic measurements and variables 54
4.5.1 Determination of drug concentration in biological samples 54
4.5.1.1 Collection of biological samples 54
4.5.1.2 Labelling of pharmacokinetic samples 55
4.5.1.3 Shipping of pharmacokinetic samples 55

4.5.2 Drug concentration measurements, and derivation or calculation of pharmacokinetic parameters 56
4.6 Effectiveness measurement and variables 56
4.6.1 Oral fluid/saliva samples as outcome measures 56
4.6.2 Addiction Severity Index, European Version (Europ-ASI) 57
4.6.2.1 Methods of assessment 57
4.6.2.2 Derivation or calculation of outcome variable (Europ-ASI) 57
4.6.3 Mini Neuropsychiatric Interview (MINI) 57
4.6.3.1 Methods of assessment 57
4.6.3.2 Derivation or calculation of outcome variable (MINI) 58
4.6.4 Time-Line Follow-Back (TLFB) 58
4.6.4.1 Methods of assessment 58
4.6.4.2 Derivation or calculation of outcome variable (TLFB) 58
4.6.5 Registry data for mortality, morbidity, medical treatment, recidivism, prescription medications 58
4.6.5.1 Derivation or calculation of outcome variable (registries) 58
4.7 Safety measurements and adverse events as outcomes 59
4.7.4 Laboratory safety measurements and variables 60
4.7.4.1 Methods of assessment 60
4.7.4.2 Derivation or calculation of outcome variables 61
4.7.5 Vital signs and physical examination 62
4.7.5.1 Methods of assessment 62
4.8 Volume of blood sampling and handling of biological samples 62
4.8.1 Analysis of biological samples 62
4.8.1.1 Clinical chemistry samples 63
5. DATA MANAGEMENT 63
6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE 64
6.1 Statistical evaluation - general aspects 64
6.2 Description of outcome variables in relation to objectives and hypotheses 64
6.2.1 Primary objective, hypotheses, and outcome variables 64
6.2.2 Secondary objectives, hypotheses, and outcome variables 65
6.2.2.1 Secondary objective of particular interest 65
6.2.2.2 Other secondary objectives: Effectiveness 65
6.2.2.3 Other secondary objectives: Quality of Life 66
6.2.2.4 Other secondary objectives: Safety 67
6.2.2.5 Other secondary objectives: Pharmacokinetics 67
6.2.2.6 Other secondary objectives: Other registry data 67
6.3 Description of analysis sets 68
6.4 Method of statistical analysis 69
6.4.1 General aspects 69
6.4.2 Multiplicity 69
6.4.3 Primary variable 69

6.4.4 Secondary variable of particular interest 70
6.4.5 Other secondary variables 70
6.4.5.1 Non-opioid substance use 70
6.4.5.2 Visual Analogue Scales 70
6.4.5.3 SOCRATES-8D 71
6.4.5.4 Registry data on morbidity, prescriptions and criminal offences 71
6.4.5.5 TSWLS 71
6.4.6 Safety analyses 71
6.4.6.1 Physical examinations, laboratory assessments, and vital signs 71
6.4.6.2 Adverse events 72
6.4.6.3 Waist circumference 72
6.4.6.4 ISI 72
6.4.6.5 SCL-25 72
6.4.6.6 Suicidality 72
6.4.7 Pharmacokinetics 72
6.5 Determination of sample size 73
6.6 Interim analyses 74
6.7 Data and safety monitoring board 74
7. STUDY MANAGEMENT 75
7.1 Monitoring 75
7.2 Audits and inspections 76
7.3 Training of staff 76
7.4 Changes to the protocol 76
7.5 Study agreements 77
7.6 Study timetable and end of study 77
8. ETHICS 77
8.1 Ethics review 77
8.2 Ethical conduct of the study 78
8.3 Informed consent 78
8.4 Patient data protection and storage 78
9. SAFETY ASSESSMENTS 79
9.1 Definitions 79
9.1.1 Adverse Event (AE) 79
9.1.2 Serious Adverse Event (SAE) 79
9.1.3 Suspected Unexpected Serious Adverse Reaction (SUSAR) 80
9.2 Recording of adverse events 80
9.2.1 Expected Adverse Events 81
9.2.2 Diagnosis 82

9.2.3 Causality 82
9.2.4 Abnormal laboratory tests/vital signs 82
9.2.5 Rating scales/patient-reported outcomes 82
9.2.6 Adverse event of Special Interest – substance-related overdose 83
9.2.7 Follow-up of ongoing adverse events 83
9.2.8 Overdose of study medication 83
9.3 Reporting of serious adverse events (SAE) 83
9.3.1 Outcome Death 84
9.4 Procedures in case of emergency, overdose or pregnancy 84
9.4.1 Emergency contact procedure 84
9.4.2 Procedures in case of medical emergency 84
9.4.3 Procedures in case of overdose 85
9.5 Procedures in case of pregnancy 85
9.6 Procedures in case of suicide attempt or suicide 85
10. REFERENCES 87

LIST OF TABLES PAGE

Table 1a) Study plan and procedures 12-week randomized study period 37
Table 1b) Study plan and procedures 36-week post-RCT phase (4-week follow-up 38
Table 1c) Study plan and procedures, non-medicated control patients 39
Table 2 Investigational products 44
Table 3 Titration of investigational product & comparator 45
Table 4 Prohibited pre-study medications and treatments 48
Table 5 Concomitant medications and treatments that are prohibited, allowed with restrictions, or permitted during the study 48
Table 6 Patient-reported outcomes objectives and variables relating to each objective 51
Table 7 Safety objectives and variables relating to each objective 59
Table 8 Laboratory measurements 60
Table 9 Volume of blood to be drawn from each patient at enrolment / Pre-inclusion phase (inpatient) (Visit 1-2, Day -30 to 0, Week -4 to 0) 62
Table 10 Minimum sample size for the RCT 74

LIST OF FIGURES PAGE

Figure 1. Study flow chart 36

LIST OF APPENDICES

Appendix A Signatures

Appendix B Additional Safety Information

Appendix C Diagnostic Criteria for Opioid Dependence according to DSM-IV TR

Appendix D CIOMS form and instructions

LIST OF SUPPLEMENTS

Supplement 1 Contact Information on Study Sites & Investigators for Regular Correspondence, Medication Shipments, & Emergency Situations

Supplement 2 Investigators and Study Administrative Structure

Supplement 3 Dissemination Plan

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 4.7)
AIDS	Acquired immunodeficiency syndrome
Alkermes ™	Manufacturer of naltrexone for extended release injectable suspension used in this study, VIVITROL®
ALT	S-Alanine Neutrophil Count
ANC	Absolute Neutrophil Count
ANOVA	Analysis of variance
AST	S-Aspartate aminotransferase
Assessment	An observation made on a variable involving a subjective judgement (assessment)
ATC	Anatomical Therapeutic Chemical
AUC	Area under the plasma concentration-versus-time curve
BMI	Body mass index
CBC	Complete Blood Count
CBT	Cognitive behavioural treatment
CDES	Clinical Data Entry Site
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form; the document holding all evaluated data for one study participant. Also see eCRF
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DMP	Data Management Plan
DNA	Deoxyribonucleic acid
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DUS	Disease Under Study
DVM	Data Validation Manual
ECG	Electrocardiogram
eCRF	Electronic Case Report Form

Abbreviation or special term	Explanation
ECT	Electroconvulsive therapy
EMEA	European Medicines Agency. In Norway represented by NOMA (below).
EPJ	Electronic Patient Journal; the term for any computer-based system used for the recording of medical records like personal information on the patient, ongoing treatment, treatment history. Usually also includes results from laboratory analyses
End of study	End of study is defined as Database Lock, which is the time point after which no patient will be exposed to study related activities
Eudra-CT	European Union Drug Regulating Authorities Clinical Trials
Europ-ASI	Addiction Severity Index, European Version. This study uses an adapted 5th version of this instrument
FDA	Food and Drug Administration
FHI	The National Institute of Public Health in Norway. In this CSP, FHI will be used as an acronym for its Division of Forensic Toxicology, which is the designated laboratory for all routine follow-up analyses of biological samples in this study
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HbA1c	Glycosylated haemoglobin
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee; the ICH term for the ethical committee evaluating ethical aspects of research studies. In Norway, this is the Regional Ethical Committee (REC)
Investigational product	A pharmaceutical form of an active ingredient or placebo being tested in a clinical study. In this study the investigational products are once-monthly XR-NTX and daily ingested buprenorphine-naloxone
IPS	*Investigational Products Service*
IR	*Immediate Release*
IRB	Institutional Review Board, the US implementation of ICH IECs
ISF	Investigator Study File; A dossier containing all essential documents relating to conducting a clinical trial or copies of these documents.
ISI	Insomnia Severity Index

Abbreviation or special term	Explanation
LAR	Acronym for the Norwegian National OMT programme, which is the sole legal option for OMT. All opioid dependent adults in Norway have the right to receive OMT in LAR free of charge for as long as they have a treatment need. LAR enrolment is an inclusion criterion in this study
LOCF	Last Observation Carried Forward
MDD	Major Depressive Disorder
Measurement	An observation made on a variable using a measurement device.
MHRA	Medicines and Healthcare products Regulatory Agency
MINI	Mini-International Neuropsychiatric Interview
MITT	Modified intention to treat
mL	Milliliter
NOMA	Norwegian Medicines Agency. The agency tasked with ensuring that pharmacological clinical trials in Norway are compliant with EMEA directives.
NTX	Naltrexone
OAE	Other Significant Adverse Event (i.e., adverse events of particular clinical importance, other than SAE and those AE leading to discontinuation of the patient from study treatment; see definition in Section 4.7).
OC	Observed Cases
OD	Overdose Death; these are anticipated SAE's in the present study
OMT	Opioid Maintenance Treatment; medical treatment of opioid dependence with opioid agonists like methadone or buprenorphine. Norway has a single mandated OMT programme called LAR (see above)
Outcome variable	A variable (usually a derived variable) specifically defined to be used in the analysis of a study objective
Parameter	A quantity (usually unknown) that characterises the distribution of a variable in a population of patients
PP	Per-protocol
Principal Investigator	A person responsible for the conduct of a clinical study
PRO	Patient-reported outcomes
REC	Regional Ethical Committee. The Norwegian implementation of ICH IECs.
Reckit-Benckiser	Manufacturer of Subutex© (buprenorphine) and Suboxone©, (buprenorphine-naloxone) for use in OMT.
TSWLS	The Temporal Satisfaction With Life Scale, 'Present' items
SAE	Serious adverse event (see definition in Section 4.7).
SAP	Statistical Analysis Plan

Abbreviation or special term	**Explanation**
SOP	Standard Operating Procedure; In GCP, SOP denotes a detailed written instructions to achieve uniformity of the performance of a specific function
SCL-25	Hopkins' Symptom Checklist, 25-item version
SDV	Source Data Verification
SNRI	Serotonin/norepinephrine reuptake inhibitor
Sponsor	Sponsor is an ICH designated term for a person or institution undertaking special administrative responsibilities for a study, including funding. As this study is investigator-initiated, the Principal Investigator adopts the responsibilities of the Sponsor and is often entitled 'Sponsor-Investigator'
SR	Sustained release
SRX	Sustained release naltrexone
SSRI	Selective serotonin reuptake inhibitor
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Elimination half-life
TCA	Tricyclic antidepressant
TIA	Transient Ischemic Attack
TLFB	Time-line follow-back, an interviewing technique based on structured memorization (back-tracking)
TSH	Thyroid Stimulating Hormone
UTS	Urine Toxicology Screening
Washout period	Period during which prohibited medication should be washed out
WBC	White Blood Cell Count
WBDC	Web Based Data Capture
WHO	World Health Organisation
XR-NTX	Naltrexone for extended-release injectable suspension

1. INTRODUCTION

1.1 Background

Opioid dependence is considered a chronic, relapsing disorder that carries an increased risk of repeated intoxications and overdose death (1). Heroin is the most commonly abused opioid, and in the European Union an estimated 1.3 to 1.7 million individuals (about 0.5% of the adult population) are considered problem opioid users. A decreasing trend since 2000 appears to have been reversed in recent years (2). The United Nations Office on Drugs and Crime similarly estimates a low opioid use prevalence of approximately 0.6% for the USA and of 0.25% when the whole world's population is considered (3).

Although affecting a relatively small group of the general population, the impact of illicit heroin use on addicted individuals, their families and the community can be profound. Mechanisms at biological, psychological, and social levels usually contribute in continuing the addictive state, while conversely making recovery difficult. Thus, patients' engagement in their own recovery and treatment often gravitates towards relapse, making recovery a long-term process that is often only partially achieved and frequently interrupted by relapse episodes.

Opioid abuse involves greatly increased risk of mortality and morbidity, marginalization, and criminal behaviour that contributes extensively to the total crime burden and illicit economy. These problems may overwhelm entire communities. Few effective treatment options as well as the nature of the disorder itself has meant only a minority of opioid users are receiving active treatment at any one time (4). Still, treatment interventions have been developed to reduce the harm associated with opioid dependence and/or facilitate the road to improvement or recovery.

1.2 Opioid detoxification

The purpose of detoxification is to discontinue the patient's physiological dependence on opioids. Medication-free detoxification methods allow the full symptoms of withdrawal to develop and run their course, a method commonly known as 'cold turkey'. As this method is associated with high chances of dropout, relapse, and overdose, most current guidelines recommend utilizing one or several medications to ameliorate withdrawal symptoms. These include tapered methadone, tapered methadone plus adjunctive medication, other opioid agonists, adrenergic agonists like clonidine and lofexidine, buprenorphine, and other symptomatic medications (5, 6).

Detoxification can be provided in specialist inpatient units, psychiatric wards, outpatient clinics, in primary care, and in prisons. Whereas detoxification from opioids *can* be achieved in an outpatient setting, completion rates are often as low as 40-50 % of those entering treatment (7).

Although detoxification offers various opportunities for improvement, the achievement of a drug-free state is not a risk-neutral event. Among patients who have been detoxified in inpatient or residential services, an initial lapse to opioid use often occurs very soon after leaving the programme (8). The reduction or loss of tolerance that occurs during detoxification greatly increases the individual at risk of overdose upon resumption of opioid use (9). Mortality and recovery outcomes for detoxification-only patients have been found to be consistently worse than for those who receive agonist maintenance, long-term residential, or outpatient counselling treatment (10).

1.3 Psychosocial interventions

Psychosocial interventions comprise a range of non-pharmacological interventions, from psychotherapy to drug counselling and case management, from self-help groups to brief intervention sessions. In a clinical setting, these treatments are administered in out- or inpatient settings, alone or in combination, as stand-alone treatment or in conjunction with drug screening measures (saliva, hair or urine) or pharmacotherapy. Prospective studies have reported satisfactory proportions of heroin abstinence among participants receiving psychosocial treatment, e.g. 49 % in the British NTORS cohort at five years after residential treatment (11), 43 % in the American DATOS cohort at five years after methadone maintenance start (12) and up to 65 % in the Australian ATOS cohort at one year after treatment (13).

However, the risk of relapse and overdose death after discharge from residential treatment has been reported to be high (14). Release from prison has been shown to constitute a similar high-risk situation. This phenomenon suggests two main areas of improvement for psychosocial treatments of opioid dependence:

a) The transition from life as an active opioid user to abstinent, ‘straight’ member of society can often be too abrupt, triggering relapse and increasing the risk of overdose.
b) Counsellors in clinical settings are prone to underestimating the risk of relapse and overdose in the patient group; prolonging treatment beyond the initial stages of recovery may have life-saving consequences.

1.4 Opioid maintenance treatment (OMT)

One of the most widely used therapeutic modalities for the management of opioid addiction is opioid agonist maintenance treatment (OMT). In 2005, approximately 530 000 Europeans received OMT, with 80% receiving methadone and 19% buprenorphine (2).

The purpose of opioid maintenance is usually not to achieve a drug free state, but to assist the individual in reducing illicit drug use by replacing heroin with controlled administration of an opioid agonist medication. Most OMT programs thus emphasize pharmacological stabilization

of the dependent state as a means to achieve psychosocial functioning for the individual and to reduce harms and costs for society; reduction of risky and harmful behaviours is considered the main aim of treatment. Many programmes avoid stating abstinence and rehabilitation as programme goals, feeling it risks alienating patients from entering and remaining in an effective treatment.

In principle, any opioid agonist may be used as part of OMT, also termed agonist replacement therapy or agonist substitution. The current drug of choice is methadone worldwide, and many programmes also offer the mu-agonist/kappa antagonist buprenorphine. Heroin and slow-release morphine have also been used. Guidelines generally recommend that choice of OMT medication should be based on acceptability and feasibility regarding elements such as side effects, stabilizing properties, dosing frequency and risk of illicit diversion. Opioid drugs should also be safe in long-term high-dosage use.

1.4.1 Methadone

Methadone is a full opioid agonist. When taken orally, it is almost completely absorbed and has high bioavailability. Methadone is slowly metabolised, reaches peak plasma levels within 2-4 hours after administration, and the half-life is about 24 hours with a range of 13-50 hours. A stabilised patient can usually take the medication once a day without withdrawal symptoms prior to next day's intake (15). Close monitoring of effects during the first two hours after ingestion is important because the slow methadone metabolism may cause accumulation, and because other drugs may have synergistic effects on sedation and respiratory depression. There may be an increased mortality risk during the first weeks of treatment(16). Meta-analyses conclude that flexible, high-dose strategies are most effective (17, 18). The recommended dose range is 60-100 mg, sometimes up to 120 mg daily (4).

Two recent Cochrane systematic reviews & meta analyses support the effectiveness of methadone in terms of increased retention in treatment and reduced heroin use (19, 20). The first review reported that OMT has a positive influence on illicit heroin use, HIV risk-taking and criminal behaviour (with moderate to large effect sizes varying between 0.22 for HIV risk-taking and 0.70 for drug-related crime) (21). While this is strong evidence in favour of OMT findings are limited to those staying in treatment and those seeking treatment. Further, several longitudinal cohort studies indicate that those who remain in treatment have markedly reduced mortality and criminality and increased health, even when an ITT type analysis is used (22-25). Conversely, terminating treatment, and involuntarily termination in particular, is followed by increased risk of mortality and criminal involvement (26).

Although methadone is generally regarded as having few long-term problems, cardiac side effects with dose dependent QTc prolongation are reported at high dosages (27, 28). Mortality estimates indicate that serious events are infrequent (29). It is important to conduct regular medical examinations during OMT, in particular when doses are increased. Concurrent use with other medications that may cause prolonged QTc should be avoided.

1.4.2 Buprenorphine

Buprenorphine is a synthetic opioid that exerts agonism at the μ-opioid receptor while being an antagonist at the kappa receptor. As a partial agonist the maximum effect of buprenorphine is less than the maximum effect of a full agonists at the receptor. A ceiling effect is reached at about 16 to 20 mg (30). Buprenorphine is probably less likely than methadone to produce sedation or intoxication, but it may be less effective for patients needing high dosage OMT. Buprenorphine binds to the receptor almost irreversibly and the dissociation from the receptor is slow (31, 32). It will displace most other opioids from the receptor, and if buprenorphine is taken first, other opioids will be unable to displace it, even in high doses. For these reasons, buprenorphine can precipitate withdrawal in users who have taken other opioids before buprenorphine (33), but buprenorphine maintenance may protect patients against overdosing with other opioids (34). Taken orally, buprenorphine has a bioavailability of only 16%, but it increases to between 20 and 40% with sublingual administration (35). The strong binding to the opioid receptor, the active metabolite norbuprenorphine, recirculation in the enterohepatic system and the possible depot effect in the mucosa of the mouth make it possible to administer buprenorphine once a day or even thrice weekly (36).

Evidence on the efficacy of buprenorphine maintenance has come from placebo-controlled trials (37-41), fixed dosing studies comparing buprenorphine with methadone maintenance (42-49) and flexible dosing studies of the two drugs (50-53). There is some variation in the outcome measures for the different trials, but the outcome most frequently reported is treatment retention. Other measures are opioid use (self-reported and in urine analysis), use of cocaine and illicit benzodiazepines or criminal activity. Buprenorphine has been found to be superior to placebo in reducing opioid use when given in medium and high doses (up to 16 mg per day), but not in low doses (54). In some studies buprenorphine is inferior to methadone when given in comparable doses. This may be due to the ceiling effect of buprenorphine that is reached at higher doses, making it difficult for many patients to reach an adequate level of opioid substitution. The partial agonist-antagonist pharmacology of buprenorphine has been used as a rationale for its use in less controlled OMT programmes, e.g. prescription in general practice. The strong binding may cause problems in reversing opioid effects with naltrexone or naloxone.

Due to special legislative circumstances there has been a comprehensive use of buprenorphine in general practice in France. Since 1996, registered medical doctors have been allowed to prescribe buprenorphine without any special education or licensing. Approximately 20% of French general practitioners prescribe buprenorphine to patients and they treat more than half the problem heroin users in this low threshold treatment modality (55, 56). The low level of training that the physicians receive has been criticised (57), but overall this practice has been considered a success with reductions in mortality, crime rate and cases of newborn with opioid withdrawal (58).

When switching from methadone to buprenorphine a rapid change could induce withdrawal symptoms. Before introducing buprenorphine, the methadone dose should therefore be slowly

reduced until about 30 mg/day. This way the withdrawal reactions will be kept to a minimum and may be limited to some dysphoria (59).

1.4.3 Buprenorphine-naloxone

Both methadone and buprenorphine are vulnerable to diversion during administration and subsequent illicit sale and/or abuse. This has resulted in the development of a compound containing both buprenorphine and naloxone (Suboxone®). Naloxone is a medium-strength opioid antagonist with low bioavailability when taken sublingually; but when injected it has high bioavailability, making the buprenorphine-naloxone combination less attractive for diversion than ordinary buprenorphine. Studies of the most commonly marketed buprenorphine-naloxone product, Suboxone® suggest it is probably as effective as buprenorphine with regard to retention in treatment and use of opioids (60), and can be administered with less supervision and less risk of diversion (61). For these reasons, buprenorphine-naloxone is currently the first-choice medication for OMT in Norway.

1.4.4 OMT summary

The main potential of OMT with methadone or buprenorphine is its ability to significantly reduce mortality among patients, especially from opioid overdose. In addition, OMT often induces a reduction in illicit opioid use, improves quality of life and reduces patients' involvement in criminal activities. These results have made OMT the treatment recommended by the WHO for opioid dependence (4). Flexible / variable dosing regimens are currently recommended as there are individual variations with regard to medication metabolism and –response.

However, OMT is not without disadvantages; treatment dropout during the first months of treatment is often substantial, with different programmes and studies reporting 20% - 60% of all those initiated having dropped out at 6 months. Dropout patients return to pre-treatment levels of opioid use and mortality. The use of opioid agonists as therapeutic medications means there is always a risk of diversion of the prescribed medication to illicit markets, where they are sold and abused. OMT programs often utilize control measures and restrict patients' access to self-administer medication in order to avoid diversion, something patients may find intrusive and limiting of their personal freedom as citizens. The low-threshold focus of many OMT programs can also make OMT centres a difficult social scene for those patients who have developed opioid dependence but have a high level of functioning on one or several social domains (e.g. employment, family).

1.5 Antagonist treatment

A different approach to maintaining opioid dependence by use of agonists (OMT) is to complete detoxification and subsequently assist abstinence by help of antagonist medication.

By using a full antagonist like naltrexone, relapse to heroin will have little effect as its action is almost completely blocked by the antagonist. This not only provides a pharmacological protection against relapse, re-dependence, and overdose, but also provides users who wish to maintain abstinence with a considerable cognitive relief from relapse-related thoughts. Although several opioid antagonists have been produced, naltrexone is currently the medication that seems closest to fulfil clinical requirements with regard to receptor binding, half-life, and adverse effects.

1.5.1 Naltrexone

Naltrexone is the most prominent example and has been developed with substantial support from the US National Institute on Drug Abuse (NIDA) in the 1970s (62). Naltrexone binds to all three opioid receptor (OR) subtypes with the highest affinity for the μ-OR and lacks the rewarding effect of agonists (63). Naltrexone competes with opioid agonists for receptor binding sites and due to its high affinity naltrexone effectively blocks agonist binding. It also displaces full agonists such as heroin and methadone from the receptors and may thus precipitate withdrawal. To avoid major withdrawal symptoms such as nausea, vomiting and psychosis, naltrexone treatment is either induced after accomplished detoxification (four to seven days after last opioid intake) or during heavy sedation or general anaesthesia combined with adrenergic agonists like clonidine or lofexidine. Administering naltrexone during extended periods of time has the potential to significantly improve outcomes from abstinence-orientated treatment (64).

Naltrexone is pharmacodynamically similar to naloxone, but seems to exert a stronger binding to receptors, has a satisfactory level of oral bioavailability, and longer half-life when compared to naloxone.

1.5.1.1 Oral naltrexone

The oral bioavailability of naltrexone ranges from 5 to 40%, with peak plasma levels reached within one hour. Dosing regimens have ranged between 25 - 150 mg oral naltrexone daily, enabling thrice weekly dosing (100-100-150 mg).

Early research on oral naltrexone pointed to low patient engagement in treatment and high attrition rates (65). However, selected subgroups with extra social incentives for achieving abstinence may benefit from oral naltrexone treatment. Addicted physicians and business executives jeopardizing their jobs (66) and prisoners on parole (67) are reported to have better compliance with oral naltrexone treatment in combination with psychosocial counselling.

Overall, research support for oral naltrexone as an effective treatment for opioid dependence has been lacking, as exemplified by a recently updated Cochrane systematic review and meta-analysis (68). Several studies were found that had compared oral naltrexone with or without psychosocial counselling to placebo with or without psychosocial counselling (69-71), and/or to psychosocial counselling alone (67, 72). The review concluded that naltrexone alone or in combination with psychosocial counselling reduced heroin use more than placebo with or

without psychosocial counselling (73). Still, this reduction was not evident when only the results from studies without psychosocial counselling were pooled. Oral naltrexone was more effective in reducing the number of re-incarcerations than psychosocial counselling alone. Oral naltrexone had no beneficial effect on heroin relapse or treatment retention in the ten RCTs.

1.5.2 Extended release naltrexone

The initiative to develop long-acting preparations to improve outcomes for naltrexone treatment was taken in the early 1970s (74). During the 1990s, extended-release formulations were developed, making sustained release naltrexone available for investigation in larger clinical trials. Although promising, the evidence to support its effectiveness is still scarce (75).

Four RCTs on two different long-acting formulations have been reported. In the first placebo-controlled trial, an injectable naltrexone intramuscular was investigated for treatment of heroin addiction (76). The injectable preparation contained 384 mg naltrexone and released naltrexone at therapeutic levels (>1ng/ml) over the course of 1 month, similar to the currently approved 380 mg VIVITROL®. Patients receiving the 384 mg intramuscular stayed in treatment longer than patients on placebo. They also provided fewer opioid positive urine samples and reported less heroin craving.

In Russia, a recently published study (77) investigated the efficacy of 4-week naltrexone for extended release injectable suspension(VIVITROL® 380 mg) versus placebo over a 6-month period in a randomized, double-blind design (n=250). Sustained release naltrexone had a statistically significant advantage over placebo on retention, opioid use (urine samples, self-report, and naloxone challenge), mortality, and craving. VIVITROL® has previously been approved for the treatment of alcohol dependence in 2006 and is indicated for the prevention of relapse to opioid dependence, following opioid detoxification.

Studies have also investigated the effectiveness of implantable pellets containing about 2.2 g of naltrexone released during 5 to 6 months (78). At follow-up 6 months after discharge from inpatient treatment, naltrexone implants as a supplement to usual aftercare resulted in significantly greater reductions in heroin use compared to usual aftercare alone. A comparable implant releasing naltrexone for 3 to 4 months was recently reported to reduce heroin use and increase treatment retention more than oral naltrexone in a double-blind, double-placebo randomised trial (79).

Data from all the above studies on sustained release naltrexone (SRX) suggest a satisfactory safety profile. While minor adverse effects are usually more frequent in active naltrexone groups than in non-naltrexone groups, they mainly appear during periods of peak release rates (usually the first 20% of release period). Due to an overall much lower mean release of naltrexone, the intensity of symptoms is less than that of oral naltrexone. Serious adverse events seem to occur more frequently in control conditions; however, levels do not reach significance or cannot be estimated as the typical number of study participants is about n=60

and mortality rates in most SRX clinical trial arms thus far has been zero. For both intramuscular naltrexone and surgically implanted pellets, some site pain following administration is the norm.

Office-based pain management during treatment with extended-release naltrexone may be a challenge, as the use of opioid analgesia is practically impossible. Patient cases are reported where non-opioid analgesics or a regional nerve blockade were used and provided effective analgesia (80).

1.6 Drug use and the criminal justice setting

The relationship between illicit drug use and criminality is well established (81). In inmate populations throughout the world substance abuse disorders are overrepresented compared to the general population (82). In the Netherlands, as many as 79% of inmates report drug use before incarceration (83) and similar rates are reported for the USA with ca. 70% (84) and for Norway with between 60 and 70% (85, 86). During incarceration, drug-involved offenders are likely to reduce the frequency of use and to change their preferred drug of abuse compared to outside of prison (87, 88). The most frequently used drugs in prison are cannabis, followed by stimulants, benzodiazepines and opioids (89).

In- and outside of prison, heroin users play an important part in the functioning of organized and acquisitive crime, because maintaining daily heroin use is expensive and can seldom be combined with regular employment. Thus, a high incidence of penal reactions towards the patient group is difficult to avoid. Most heroin-addicted offenders will be incarcerated at least once during their lifetime and a considerable number of them repeatedly (90, 91). For many heroin users criminal justice facilities may thus become a stable element, especially for those individuals who are unable to adjust to a non-criminal way of life. For heroin-addicted individuals, incarceration implies a major behaviour change. They are either forced by the circumstances to detoxify, or they continue injecting with high risk of acquiring blood borne diseases such as HIV and high risk of overdose, as clean needles are a scarce commodity and there is rarely enough opioids to develop tolerance (92). Following prison release, many heroin-involved inmates will relapse within the first month of returning to the community (93, 94). Similarly to opioid users who have just been discharged from inpatient settings, the risk of overdose death is particularly high immediately following prison release (95, 96).

A lack of sufficiently targeted post-release services may play a role in the high risk of relapse and overdose. If inmates achieve abstinence during incarceration, they often fail to maintain it after prison release. Outside of prison the addicted individual may be largely unavailable for treatment, whereas during incarceration help including housing may be a clearly stated aim.

1.6.1 Prison-based treatment of opioid dependence

The unanimous conclusion of several reviews on criminal justice based treatment is that access to specialized addiction treatment services in prisons is seriously limited and that further programme evaluations are urgently needed (97-99). These reviews also find that prison-based therapeutic communities (TC) that provide continuity of care after release have shown beneficial effects. Five year follow-up data for 576 TC participants in a US study show reduced drug relapse and criminal recidivism (100). In Norway, the Tyrili foundation provides treatment for incarcerated drug users (101). In Oslo, Tyrili applicants spend nine months in a prison-based therapeutic community and after release they are offered to continue in a TC outside of prison.

In a Norwegian pilot study, naltrexone implants were compared with methadone maintenance and treatment commenced just before prison release. Significant reductions in heroin use at six months follow-up were found in both groups (102) and improved retention in naltrexone treatment compared to methadone maintenance. Further, the study demonstrated that long-acting naltrexone treatment is feasible in criminal justice settings with around 60% of the participants randomly allocated to naltrexone implants accepting the treatment (103). Intramuscular naltrexone that does not require surgical insertion is likely to further increase acceptability.

Oral naltrexone among criminal justice populations has been evaluated in two randomised trials (67, 104). Another two non-randomised trials on oral naltrexone are reported (105, 106). The Australian RCT by Shearer and co-workers struggled with low interest in participation and the trial was discontinued when the group randomly allocated to oral naltrexone failed to initiate treatment. The majority of eligible inmates in this study were already receiving OMT and were reluctant to detoxify. The other three trials unanimously conclude that oral naltrexone is a feasible option for inmates when combined with social incentives towards recovery and abstinence, e.g. work-release programmes and parole including follow-up by criminal justice staff. Although treatment dropout was high in these trials, those who stayed on oral naltrexone were less likely to relapse to heroin and less likely to engage in criminal activity.

Drug-involved inmates wanting to initiate treatment during incarceration will often have to make an extra effort due to a scarcity of in-prison treatment options. Nonetheless, incarceration may offer extraordinary opportunities for recovery such as a highly structured environment and reduced availability of illicit and prescription drugs.

OMT has been recommended for opioid dependent inmates, partly to reduce risk behaviours in prison, but also to reduce the high risk of post-release relapse and overdose death (95, 107). A French cohort study reported high risk of re-imprisonment and death at three years follow-up (108). Prison based OMT programmes need to be improved, i.e. treatment should be continued during imprisonment, and it should be initiated before release for opioid-dependent prisoners not receiving OMT (109). Nevertheless, opioid maintenance therapy is still controversial in criminal justice settings. Although OMT is increasingly used in European prisons (110), access is far from optimal in other parts of the world (111, 112). Restricted

access to OMT during incarceration includes highly developed countries such as the USA with a per capita prison population that is about 10-fold larger compared to Norway (113). However, a randomised-controlled trial suggested already in the 1960s that methadone maintenance (MMT) is effective to prevent relapse when initiated before prison release (114). Although prison-based methadone maintenance is available in a few US penal facilities (115), the next RCT on methadone maintenance conducted in the US criminal justice setting was reported only a few years ago (116). In this RCT, heroin addicted inmates were randomly allocated to one of three groups: methadone start and counselling before release, referral to methadone treatment after release or counselling only. At one month follow up the methadone-before-release group was more likely to continue in community treatment and more likely to provide opioid negative urine tests. This study will be followed up by a larger multi-centre trial involving sites in several US American States and by another trial that evaluates the effects of buprenorphine.

1.7 Rationale for this study

The overall rationale for this study is to compare the preventive effect of XR-NTX on overdose and opioid use relative to buprenorphine treatment use among opioid dependent patients about to complete their stay in a controlled environment.

Such a comparison with the currently recommended or standard treatment is often conducted as a routine part of phase III/IV trials for any novel medical treatment. The utility of such studies lies in their ability to inform decisions on treatment adoption on a political as well as a clinical level. Currently, buprenorphine-naloxone is the recommended first-choice treatment in many countries, and is therefore a natural comparison drug to XR-NTX. Currently, no studies have compared XR-NTX with buprenorphine-naloxone in either clinical or criminal justice settings

It is also the ambition of this study to highlight the potential impact of offering any pharmacological treatment to opioid dependent individuals in situations with a high risk of relapse and overdose.

The trial most closely resembling the present study was an open-label randomized trial by Lobmaier et al. that compared implantable naltrexone with high-level methadone programme participation among prison inmates in Norway (102, 103). Both study groups reported reduced opioid use compared to pre-treatment levels. This study was underpowered due to problems with recruitment, and attrition immediately following randomization, as well as initiating patients in the methadone group into the high-threshold methadone programme. Many of the recruitment and attrition problems are thought to have been related to the study comparison between a full agonist (methadone) and a full antagonist (naltrexone) over a time-span of six months. With less dissimilar study drugs and shorter study period, potential weaknesses of the kind seen in Lobmaier et al. (102, 103) will be addressed in the present study.

Other studies investigating the effectiveness of sustained release naltrexone (SRX) have been described above; none of these have compared SRX to buprenorphine-based OMT.

While there are several studies that have exemplified the benefit of providing medical treatment to opioid dependent individuals before discharge from prison or clinical settings (see above), WHO estimates that as many as 80% of opioid users worldwide are not in any kind of treatment – in many cases, this is due to little or no treatment being offered to users. The present study thus fills a need to continue to exemplify the benefits from more actively offering effective pharmacological interventions to opioid dependent patients in these high-risk situations.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to evaluate the effectiveness of XR-NTX 380 mg/month versus buprenorphine-naloxone 8-24 mg/day as part of "treatment as usual", assessed by the number of opioid free oral fluid samples during the RCT period.

Variables supporting the primary objective are:

- Between-group differences on opioid abstinence from randomisation to Week 12 as measured by proportion of weekly oral fluid samples positive for non-study opioid agonists or their metabolites
- Between-group differences from randomisation to each assessment on self-reported abstinence from illicit (e.g. non-study) opioids as measured using time-line follow-back.
- Between-group differences in retention in treatment at Week 12.
- Mortality registry data on mortality in the two groups from randomisation until Week 48.

2.2 Secondary objectives

A. To evaluate the effectiveness of XR-NTX across the different study settings (clinical settings versus criminal justice system).

B. To evaluate the outcome variables in the XR-NTX groups and/or buprenorphine groups compared to non-randomised, voluntary controls in criminal justice - or clinical settings.

C. To evaluate the safety and tolerability of XR-NTX in this study population.

D. To evaluate the effect of recovery-related variables on the primary outcomes.

E. Assess the impact of study medications, no medication, and/or setting on recovery-related outcomes such as craving for heroin, recidivism, morbidity, treatment for addiction or other medical problems, sleep problems, abstinence motivation, quality of life, and mental health.

Variables supporting the secondary objectives are:

1. Reduction in opoid-related craving in the XR-NTX group in the clinical and/or criminal justice settings compared to buprenorphine-naloxone and/or non-randomised controls by assessing:

   – the change from randomisation to Week 12 in VAS score for craving

   – the change from randomisation to Week 48 in VAS score for craving

2. The extent to which XR-NTX in the clinical and/or criminal justice settings reduces non-opioid substance use compared to buprenorphine-naloxone and/or non-randomised controls by assessing:

   – the number of oral fluid samples positive for illicit, non-opioid substances or their metabolites from Week 1-12 in the study. This includes (but is not restricted to) cocaine, benzoylecgonine, nitrazepam, diazepam, 7-aminonitrazepam, amphetamine, metamphetamine, zopiclon, zolpidem, oxazepam, karisoprodol, diazepam, MDMA, alprazolam

   – the change from randomisation to Week 12 in self-reported use of non-opioid substances including cocaine, amphetamines, benzodiazepines, alcohol, cannabis, and hallucinogenic drugs (e.g. LSD, MDMA, GHB)

3. To evaluate if XR-NTX in the clinical and/or criminal justice settings affects mental health, compared to buprenorphine-naloxone and/or non-randomised controls by assessing the change from randomisation to Week 12 in SCL-25 total or subscale scores.

4. To evaluate if XR-NTX in the clinical and/or criminal justice settings affects sleep quality, compared to buprenorphine-naloxone and/or non-randomised controls by assessing the change in Insomnia Severity Index (ISI) scores from randomisation to Week 12.

5. To evaluate if XR-NTX in the clinical and/or criminal justice settings affects rate of suicide or suicidal ideation, compared to buprenorphine-naloxone and/or non-randomised controls by assessing the proportion of patients in each group reporting suicidal thoughts, attempts, or registered suicidal AEs between randomisation and Week 12.

6. To evaluate the safety and tolerability of XR-NTX compared to buprenorphine-naloxone and/or non-randomised controls by:

   – evaluation of changes from baseline in frequency of substance use and treatment attrition

   – assessing the incidence of Adverse Events (AEs)

- assessing the incidence of AEs leading to withdrawal from the study
- assessing the incidence of AEs of special interest (e.g. OD, nausea, vomiting)
- assessing AEs related to insomnia
- assessing the proportion of patients reporting increase in suicidal thoughts, attempts or intentions on the Europ-ASI or that have AEs related to suicide

7. To evaluate if XR-NTX in the clinical and/or criminal justice settings affects income from illicit sales of drugs, compared to buprenorphine-naloxone and/or non-randomised controls by assessing the change from randomisation to Week 12 in self-reported days with such income and the amount of income from these sources in Norwegian Kroner (NKR; 10 NKR = approximately 1,7 US $).

8. To evaluate if XR-NTX in the clinical and/or criminal justice settings affects quality of life (QOL), compared to buprenorphine-naloxone and/or non-randomised controls by assessing the change from randomisation to any assessment in total score on the Temporal Satisfaction with Life Scale (TSWLS).

9. To evaluate if XR-NTX in the clinical and/or criminal justice settings affects motivation for abstinence compared to buprenorphine-naloxone and/or non-randomized controls by assessing the change from randomisation to Week 12 using self-reported abstinence motivation on the total or subscale levels of the Stages of Change Readiness and Treatment Eagerness Scale Drugs (SOCRATES 8D).

10. To evaluate if XR-NTX in the clinical and/or criminal justice settings affects employment or income compared to buprenorphine-naloxone and/or non-randomized controls by assessing the change from randomisation to Week 12 in days previous month in education or paid/unpaid employment on the Europ-ASI.

11. To evaluate if XR-NTX in the clinical and/or criminal justice settings affects frequency or type of hospitalization for medical or mental health reasons compared to buprenorphine-naloxone and/or non-randomized controls by assessing the number of hospitalizations in the Norwegian Patient Registry from randomisation to Week 48.

12. To evaluate if XR-NTX in the clinical and/or criminal justice settings affects recidivism/re-offending compared to buprenorphine-naloxone and/or non-randomized controls by assessing the change from randomisation and/or the year preceding study randomisation to Week 48 in the Norwegian Criminal Offences Registry.

13. To evaluate if XR-NTX in the clinical and/or criminal justice settings affects the amount of publicly available addiction treatment received (e.g. counselling, OMT) compared to buprenorphine-naloxone and/or non-randomized controls by assessing

the change from randomisation and/or the year preceding study randomisation to Week 48 in the Norwegian Patient Registry and/or the Norwegian Opioid Maintenance Treatment Registry.

14. To evaluate if XR-NTX in the clinical and/or criminal justice settings affects the frequency and/or type of medications prescribed compared to buprenorphine-naloxone and/or non-randomized controls by assessing the change from randomisation and/or the year preceding study randomisation to Week 48 in the Norwegian Prescription Registry.

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

This is a 12-week multi-centre, open-label, randomised treatment study of the clinical effectiveness and - safety of XR-NTX (VIVITROL ®) 380mg/month fixed dose and buprenorphine-naloxone 8-24 mg/day flexible dose regimen in the treatment of opioid dependent patients. The randomised treatment period is followed by 36 weeks follow-up treatment period with either XR-NTX or buprenorphine-naloxone in accordance with each participant's preferences.

This study will be conducted in approximately 220 randomised patients in Norway to yield 180 evaluable participants across two treatment settings, with 90 participants per treatment group (XR-NTX 380mg/month, and buprenorphine-naloxone 8-24 mg/day arms) in a 1:1 randomisation. Participants declining medication will be offered inclusion in a non-randomised control group with a limited follow-up assessment. Approximately six study sites will participate and 15-50 patients will be recruited per study site. Number of patients per study site is expected to vary depending on patient availability at the different study sites. Additional sites may be added during the study.

An evaluable patient is defined as a patient who received at least one dose of study treatment and who has one valid assessment at randomisation and at least one valid oral fluid or drug use self-report assessment after randomisation.

The primary outcome variable is the change and/or between-group differences from randomisation (Visit 2) to Week 12 (or final visit) in opioid-free days as assessed by one of the following:

a) Number of weekly oral fluid samples (range 1-12) negative for opioids or their metabolites (e.g. heroin, 6-monoacetylmorphine, morphine, codeine, methadone). One test negative/positive will count as 7 days' abstinence or use of opioids, respectively. Buprenorphine positive samples will not count as a relapse outcome for patients treated with buprenorphine-naloxone

b) number of self-reported opioid-free days on time-line follow-back (TLFB)

Eligibility for the study will be assessed at enrolment and randomisation. The patients will be randomised to treatment groups at visit two, after having fulfilled all inclusion criteria and none of the exclusion criteria. See figure 1 for study flow chart, and table 1 for schedule of assessments. All visits allow a visit window of ±2 days calculated from randomisation.

The study comprises three periods:
1) enrolment period of up to 30 days, see Section 3.1.2
2) a 12-week randomised treatment period, see Section 3.1.3.
3) a 36-week non-randomized treatment period, see Section 3.1.4.

Participants completing the first two study periods will visit the investigator at least five times, while participants completing period 3 will visit the investigator at least 14 times.

3.1.2 Enrolment period (up to 30 days)

To be eligible for the enrolment visit (Visit 1) the patients or inmates will be evaluated and shall:

- be 18 years of age or older
- meet the DSM-IV TR criteria for the diagnosis of opioid dependence (304.00) as confirmed by the Mini-International Neuropsychiatric Interview (MINI)
- Enrolled in opioid maintenance treatment (OMT) in the Norwegian national OMT program 'LAR'. For patients who complete & submit their LAR application while in a controlled environment, the investigator may complete enrolment data collection while awaiting response on LAR admission. For patients in the non-medicated comparison group, this criterion will be waived.
- reside temporarily and for a minimum of 7 (seven) days in either of the following controlled environments:
  a) an inpatient treatment facility for opioid dependent patients (detoxification, short-term, or residential/long-term) or
  b) in a prison or penal facility administered by the criminal justice system.

  To be designated as a controlled environment, a restriction of access to substances of abuse at admission and during the stay must be enforced (e.g. biometric samples, personnel observation) and any such use associated with sanctions (e.g. reinforced care)
- planned discharge from the controlled environment is due within 30 days after Visit 1

3.1.3 Twelve-week randomised treatment period (Visit 2 to Visit 13)

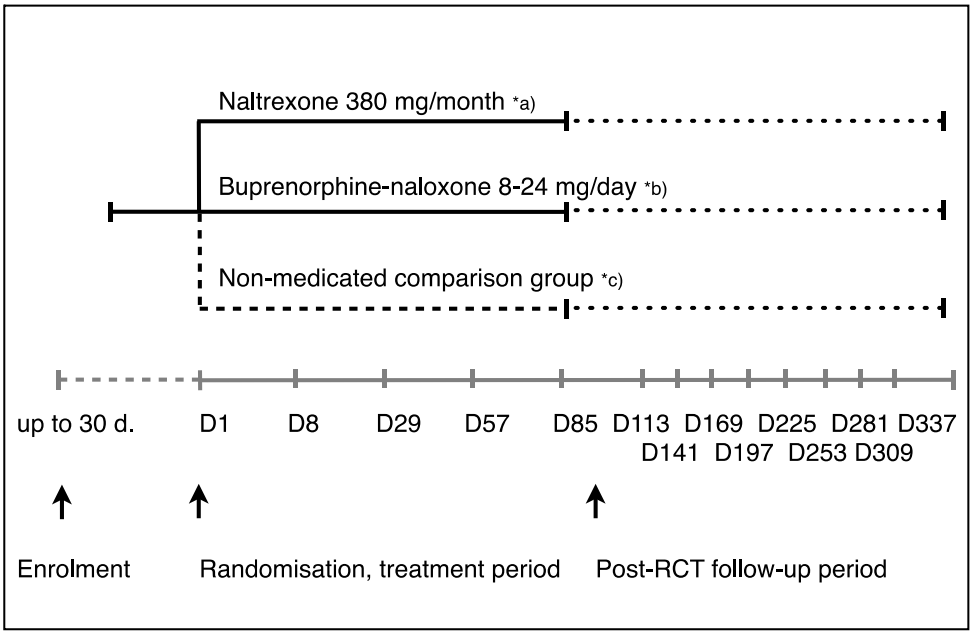
Eligible patients will be randomised during Visit 2 to one of two treatment arms: XR-NTX 380 mg/month or buprenorphine-naloxone 8-24 mg/day as add-on treatment to ongoing addiction treatment. Participants randomized to XR-NTX will need to complete detoxification from any opioid agonist (including any buprenorphine or methadone) and remain in a controlled environment for a minimum of 72 hours before the XR-NTX induction procedure (see below) is initiated. All participants will be referred to weekly counselling in cooperation with their current general or treating physician (e.g. prison medical service).

Patients not willing to enter these treatment arms but who satisfy remaining criteria for inclusion will be offered inclusion into a non-randomized, non-medicated group with quarterly assessment and follow up for up to 48 weeks according to the schedule in Table 1.

3.1.4 Thirty-six-week non-randomised treatment period (Visit 14 to Visit 23)

After completing 12-Week follow-up (Visit 13), participants may choose whether to continue or change their study medication, with monthly follow-up based on psychometric data until Week 48 (Visit 23). Shortly after Week 48 or the last feasible follow-up has been completed for all participants entering any arm of the study, the Norwegian Mortality Registry and Norwegian Cause of Death Registry will be contacted for collection of mortality data. Similarly, the Norwegian Registries on Prescriptions, Criminal Offences, OMT, and the Patient Registry will be contacted for data on recovery-related secondary variables before and during the study.

Figure 1. Study summary flowchart



[a.] Detoxification completed before monthly intramuscular administration on days 1,29,57 and up to day 309.
[b] Uptitration to a level of satisfactory response before discharge: 4-8 mg/day at days 1-2, 8-12 mg/day at day 3-4, and any further increase up to maximum 24 mg/day from Day 5 and throughout the study in accordance with the National OMT 'LAR' guidelines.
[c] Volunteers without pharmacological treatment or randomization to such treatment.

978 **Table 1a) Study plan and procedures 12-week randomized study period**

Task / Week no.	*Pre*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*
Inclusion/excl crit.	x												
Blood pressure	x												
Height, weight	x												
Physician examination	x												
Blood health screen	x												
Urine drug screen	x												
Pregnancy test	x												
Allocation	x												
Induction	x												
Concomitant meds.	x				x				x				x
Adverse events - active screening					x				x				x
XR-NTX admin. w/ naloxone test (XR-NTX group only)	x				x				x				x
Europ-ASI	x				x				x				x
Timeline follow-back					x				x				x
MINI 6.0 Incl/excl	x												
MINI 6.0 part J2	x				x				x				x
ISI	x				x				x				x
Socrates 8-D	x				x				x				x
SCL-25	x				x				x				x
TSWLS	x				x				x				x
VAS	x				x				x				x
Saliva sample (drugs, NTX)		x	x	x	x	x	x	x	x	x	x	x	x
Optional blood sample (drugs, NTX)		(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)

979

Table 1b) Study plan and procedures 36-week post-RCT phase (4-week follow-up

Task / Week no.	12	16	20	24	28	32	36	40	48
Choice of study medication	x	x	x	x	x	x	x	x	x
Concomitant meds.	x	x	x	x	x	x	x	x	x
Adverse events - active screening	x	x	x	x	x	x	x	x	x
XR-NTX admin. w/ naloxone test (XR-NTX group only)	x	x	x	x	x	x	x	x	x
Europ-ASI w/TLFB	x	x	x	x	x	x	x	x	x
& MINI 6.0 part J2	x	x	x	x	x	x	x	x	x
ISI	x	x	x	x	x	x	x	x	x
Socrates 8-D	x	x	x	x	x	x	x	x	x
SCL-25	x	x	x	x	x	x	x	x	x
TSWLS	x	x	x	x	x	x	x	x	x
VAS	x	x	x	x	x	x	x	x	x
Saliva sample (drugs, NTX)									
Optional blood sample (drugs, NTX)									
End-of-study (EOS) for all participants									x

989 **Table 1c) Study plan and procedures, non-medicated control patients**

Task / Week no.	*Pre*	*12*	*24*	*36*	*48*
Inclusion/excl. crit.	x				
Blood pressure	x				
Height, weight	x				
Physician examination	x				
Blood health screen	x				
Urine drug screen	x				
Pregnancy test					
Group inclusion	x				
Choice of study medication					
Concomitant meds.					
Adverse events - active screening	x	x	x	x	x
Europ-ASI	x	x	x	x	x
MINI 6.0	x	x	x	x	x
ISI	x	x	x	x	x
Socrates 8-D	x	x	x	x	x
SCL-25	x	x	x	x	x
TSWLS	x	x	x	x	x
VAS	x	x	x	x	x
Saliva sample (drugs, NTX)					
Optional blood sample (drugs, NTX)					
End-of-study (EOS) for all participants					x

990

3.1.5 Unscheduled visits

Patients can return at any time if their condition warrants medical attention.

3.2 Rationale and risk/benefit assessment

3.2.1 Rationale for study design, doses, and control groups

This study is designed as a randomized, open-label evaluation of the clinical effectiveness and safety of XR-NTX in a context of conventional treatment of opioid dependence. The rationale for this study is based upon positive results from a number of smaller studies demonstrating an adequate treatment effectiveness for XR-NTX in opioid dependent patients across different treatment settings (see Section 1).

The study is designed to compare the relapse-preventing effect of XR-NTX with other conventional treatment modalities in patients or inmates who are in a controlled environment and about to enter the high-risk scenario of discharge. For this study, two treatment groups and one non-randomized comparison group will be utilised:

- XR-NTX 380 mg/month
- buprenorphine-naloxone tablets 8-24 mg/day
- non-randomized, non-medicated comparison

3.2.2 Risk/benefit and ethical assessment

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH-GCP, and applicable regulatory requirements.

The final CSP, including the final versions of the written informed consent forms (ICF), must be approved by the regional ethics committee (REC) in Norway, for compliance with the Declaration of Helsinki and ICH-GCP.

Progress reports and notifications of serious unexpected drug reactions will be provided to the REC according regulations and guidelines. The Principal Investigator(s) must also provide the REC with any reports of SAEs from the study site. In addition, study drug manufacturers will be notified of SAEs and any relevant patient characteristics and contact with authorities.

3.3 Selection of study population

3.3.1 Study selection record

Investigator(s) must keep a record of patients who were considered for enrolment but were never enrolled, i.e. a patient screening log. Each clinic or criminal justice facility will also be requested to provide a reliable estimate on the number of eligible and non-eligible individuals in their facility during the period the study was open to recruitment. This information is necessary to establish that the patient population was selected without bias.

3.3.2 Inclusion criteria

For inclusion into the trial, each patient is required to fulfill all of the following criteria:

1. Capable of understanding and complying with the protocol, and sign the informed consent document
2. Be 18 years of age or older
3. Has a current diagnosis of opioid dependence, based on the criteria of the DSM-IV-TR
4. Is voluntarily seeking treatment for opioid dependence in a treatment or criminal justice setting
5. Completing a stay in a controlled environment with restricted access to substances of abuse with a minimum duration of 7 (seven) days.
6. Is enrolled in the Norwegian national opioid maintenance treatment program 'LAR' before discharge from a controlled environment (waived for volunteers in the non-medication comparison group).
7. If female and of childbearing potential, must agree to use an acceptable method of contraception for the duration of the study

3.3.3 Exclusion Criteria

For the purpose of assuring patients' safety and minimizing confounding variables, any of the following is regarded as a criterion for exclusion from the trial:

1. Pregnancy (ie, positive urine and/or serum pregnancy test) and/or currently breastfeeding
2. Clinically significant medical condition or observed abnormalities (including: severe hepatic (Child-Turcotte-Pugh level C) or renal failure, clinically significant symptoms of progressive Acquired Immunodeficiency Syndrome (AIDS))
3. Severe psychiatric disorder (including: current or recurrent affective disorders with suicidal behavior, psychotic disorders)
4. Use of any excluded medication at screening or anticipated/required use during the study period (including: requiring treatment with opioid medications other than study drugs)
5. Known intolerance and/or hypersensitivity to naltrexone, carboxymethylcellulose, or polylactide-co-polymers (PLG) or any other components of the diluent, as well as known hypersensitivity or intolerance to buprenorphine or naloxone or any of the Suboxone additives. Acute alcoholism or serious respiratory debilitation.

6. Any finding that in the view of the PI would compromise the patient's ability to fulfill the protocol visit schedule or visit requirements
7. Employment by Alkermes or Reckitt-Benckiser (permanent, temporary contract worker, or designee responsible for the conduct of the study) or immediate family of an Alkermes or Reckitt-Benckiser employee

At Visit 1 'inclusion', Inclusion criteria number 1-4 and Exclusion criteria 3 as listed above must be verified. At or before Visit 2 'randomisation,' Inclusion criteria 5-7 and Exclusion criteria 1,2, 4-7 above must be verified.

3.3.4 Interactions with study medications

Should any prescribed medications interact with buprenorphine-naloxone study medication, the dosage will be adjusted.

3.3.5 Restrictions

There are no restrictions on patients participating in this study with regard to smoking, physical activity, etc. See Section 3.6 for restricted medication and treatments.

3.3.6 Discontinuation of patients from treatment or assessment

3.3.6.1 Criteria for discontinuation / End of Study

Patients may be discontinued from study treatment and assessments at any time. If possible, it is recommended that the PI be consulted before discontinuation. Specific reasons for discontinuing a patient from this study are:

- Voluntary discontinuation by the patient who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment
- Safety reasons as judged by the investigator, particularly:
  - A clinically significant or serious adverse event (SAE) that would not be consistent with continuation in the study, as determined by the investigator or the patient
  - Two consecutive blood tests showing neutrophil counts <1
  - If the patient's hepatic status deteriorates to a Child-Turcotte-Pugh level 'C' state and this is deemed related to study participation by the investigator
  - An imminent risk of suicide, based on the investigator's judgement
  - Accidents or disease developments making palliative care with opioid agonists necessary, as evaluated by the investigator or patient

- Severe non-compliance to CSP as judged by the investigator
- Incorrect enrolment of the patient (i.e. the patient does not meet the required inclusion/exclusion criteria).
- Development of a condition included in the exclusion criteria. If possible, it is recommended that the Principal Investigator (PI) be contacted before discontinuation
- Use of concomitant medication prohibited by the CSP, as described in Section 3.6.
- The patient is unable to tolerate the assigned dose of medication
- The patient becomes pregnant
- The patient is lost to follow-up
- The study is terminated by the University of Oslo, Regulatory authorities, or the REC

3.3.6.2 Procedures for discontinuation

Patients who discontinue on their own accord should always be asked about the reason(s) for their discontinuation and the presence of any AEs. If possible, they should be seen and assessed by an investigator(s). AEs should be followed up; questionnaires and any investigational products should be returned by the patient.

If a patient is seen by the investigator, all assessments required at the final study visit will be conducted, whenever possible, and should be recorded on the Case Report Form (CRF). The category in the CRF specifying the reason for discontinuation as 'Other' should only be used when no other category is satisfactory.

Any patient who withdraws and has clinically significant abnormal results for any safety assessments should be followed up at appropriate intervals, as determined by the investigator, until the abnormality resolves or until, in the investigator's opinion, the condition has become stable and is unlikely to change further or the investigator has lost contact with the patient.

Participants who volunteered for receiving study drug but drop out before receiving medication without formal withdrawal of consent may be designated as a participant in the non-medicated group after evaluation of dropout circumstances by the Principal Investigator.

3.4 Treatments

3.4.1 Identity of investigational product and comparators

The allocated treatment group for the 12-week randomized period is openly communicated to the participant following randomisation.

Table 2 Investigational products

Drug	Manufacturer	Strength	Presentation
XR-NTX	Alkermes Inc.	380 mg	Injectable suspension
Buprenorphine-naloxone	Reckitt-Benckiser Inc.	8-24 mg	Sublingual resorbilets

Buprenorphine-naloxone resorbilets may contain lactose, which may cause discomfort in lactose-intolerant individuals (see Appendix B).

3.4.2 Doses and treatment regimens

XR-NTX patients receive an intramuscular injection of a naltrexone-polymer mixture into the gluteus following enrolment and randomisation, preferably within a minimum of 2 and a maximum of 5 days before discharge and after a minimum of 72 hours has passed after last intake of any opioid agonist (morphine, heroin, methadone, buprenorphine, codeine etc.). A small test dose (2-4 mg) of the short-acting opioid antagonist naloxone will be administered before injection of XR-NTX in order to reduce the risk of inducing prolonged withdrawal. If naloxone induces an increase in withdrawal symptoms (i.e. sweating, gastrointestinal cramps, yawning) to a level not acceptable to the investigator or patient, injection of the next naloxone test dose should be delayed by a buffer period of at least 24 hours depending on severity of withdrawal. The naloxone challenge and the subsequent 380 mg XR-NTX will then be repeated on days 29 and 58, and at monthly intervals during the follow-up period (days 85 to 337) depending upon patient preference and investigator approval. Cases of prolonged or continued withdrawal beyond 7 days after last intake of an opioid agonist may indicate intolerance to naloxone/naltrexone and/or motivational problems with antagonist treatment. These patients may warrant discontinuation from the study by the investigator.

Buprenorphine-naloxone will be initiated in a controlled environment if possible and dispensed daily in accordance with local OMT (Norwegian: LAR) regimens. The tablets should be taken sublingually by placing them under the tongue. All buprenorphine-naloxone patients will start on their medication by receiving 4-8 mg/day dose for days 1-2, 8-16 mg days 3-4. Target dose is 16 mg / day, with minimum dose being 8 mg/day and maximum dosage 24 mg/day. During days 5-12, the dosage may be adjusted in accordance with this and existing LAR guidelines (See Table 3).

From day 85 onwards to day 337 post-randomisation, participants will be allowed to choose their study medication. For participants who wish to change from buprenorphine-naloxone to XR-NTX, and/or participants with a regular (>3 days/week) heroin use, a detoxification and

discontinuation of medication for at least three days in a controlled environment will be required before commencing XR-NTX treatment. The induction procedure with naloxone challenge should be used as described above. Participants who wish to commence or continue treatment with buprenorphine should be able to do so by continuing to receive treatment in Norway's National OMT programme (LAR) at study inclusion.

Table 3 Titration of investigational product & comparator

Treatment group / Day	Naltrexone 380 mg/month	Buprenorphine-naloxone 8-24 mg/day	Non-medication comparison
Day 1-2	1 x 2 mg naloxone 1 x 380 mg XR-NTX / month	4 - 8 mg buprenorphine-naloxone / day	n.a.
Day 3-4	-	8 - 16 mg buprenorphine-naloxone	n.a.
Day 5 onwards		8 – 24 mg/day according to response	
Day 85/week 12 and every 4 weeks until day 337/week 48	1 x 2 mg naloxone & 1 x 380 mg XR-NTX / month	As day 5 onwards (above) or initiate switch to XR-NTX according to patient's wishes commencing day 85	n.a.

3.4.3 Labelling

Principle investigator will provide NTX (Vivitrol®) to the study sites. Labelling of the investigational product will be conducted in compliance with labelling instructions from the Norwegian Medicines Agency (NOMA), the National Coordinating Investigator (PI), and Apotekproduksjon AS (Farma Holding).

3.4.4 Storage

All investigational products must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage and shipment conditions are specified on the investigational product label and in the IB. All documents of significant value to the trial will be stored for a minimum of 15 years after the conclusion of the trial in accordance with existing guidelines. Storage can be extended beyond 15 years if regulations require.

3.4.5 Accountability

The investigator is responsible for establishing routines for correct handling of investigational product, to ensure that:

- The investigator correctly receives deliveries of such product from the principal investigator or designated institution, including pharmacy.

- Accurate records are maintained, accounting for the receipt of the investigational product and for the disposition of the product

- Investigational product is to be handled and stored safely, properly and in agreement with the given storage instructions

- The investigational product is to be prescribed only by the investigator or by a person authorised to do so by the Principal Investigator

- Under no circumstances will the investigator allow the investigational products to be used for other purposes than for this study

- When dispensing investigational product to patients, this must be noted in the dispensing record. Information recorded includes identification of the patient to whom the product is dispensed, name of the product, strength and quantity dispensed, date of dispensing, batch number and durability. This record must be kept in addition to any drug accountability information recorded in the CRF on the patient's source chart

- The study participants will not themselves handle investigational products. Vivitrol will be injected by investigational staff. Suboxone will be dispensed daily.

- The patient must return all unused investigational products to the investigator. However, in this study such a routine will not be applicable.

3.5 Method of assigning patients to treatment groups

After written informed consent has been obtained the patient will be assigned an Enrolment Code (site and patient specific).

Patient eligibility will be established before treatment randomisation. Patients will be randomised strictly sequentially, as patients are eligible for randomisation. If a patient discontinues from the study, the patient number will not be reused, and the patient will not be allowed to re-enter the study. Patients will not be allowed to enrol twice in the study.

The randomisation will be in consecutive order and site specific. A randomisation schedule will be prepared by the Clinical Research department at the Oslo University Hospital that utilizes electronic data entry to randomize patients in a block manner by centre and setting. The randomisation list will be generated using a computer based randomisation system, internally developed and validated.

Eligible patients who wish to participate in the pharmacotherapy comparison will be randomised in balanced blocks to receive XR-NTX 380 mg/month or buprenorphine-naloxone 8-24 mg/day in a 1:1 ratio.

If a patient enrolment or randomisation number is allocated incorrectly, the Principal Investigator should be notified immediately. Subsequent patient enrolment or randomisation numbers should be allocated according to the original allocation sequence. If a randomisation number is allocated incorrectly, no attempt should be made to change the treatment.

3.6 Pre-study, concomitant and post-study medication(s)

Other medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator(s) in accordance with the precautions and interactions listed for each medication in Appendix B: Additional Safety Information. The administration of all prescribed medications including investigational products and medications in use within 30 days of randomisation will be recorded in the appropriate sections of the CRF. Only medications prescribed for general (e.g. daily) use will be registered; medications prescribed for special circumstances, e.g. to induce withdrawal and/or reduce withdrawal symptoms during detoxification, will not be registered.

Women who enter the study with an intrauterine device in place, using oral contraceptives, or using injectable or implantable hormonal agents designed to prevent pregnancy may continue these treatments throughout the study. The University of Oslo or other main study site will reimburse any expenses associated with continuation or initiation of contraceptives or refer the participant to a health service providing such treatment free of charge to the target group.

Patients on methadone who are allocated to buprenorphine-naloxone will need to transfer to the new medication in accordance with local guidelines. Methadone patients allocated to XR-NTX will be required to discontinue methadone treatment, detoxify and undergo naloxone challenge before commencing XR-NTX treatment following procedures described above (Section 3.4.2).

Patients who elect to participate in follow-up but decline being randomized to any of the study medications are free to receive the medical treatment deemed suitable by their treating physician (e.g. GP, hospital). Thus the restrictions mentioned in Table 4 and 5 apply mainly to patients who consent to be randomized to one of the two study drugs (XR-NTX or buprenorphine-naloxone).

Patients requiring daily palliative care with opioid agonists should implement and evaluate a transfer to non-opioid medication in collaboration with their treating physician and the investigator before enrolling into the trial.

After study completion, or discontinuation, the patient should be treated according to normal practice.

Table 4 Prohibited pre-study medications and treatments

Medication or Treatment	Time period
Opioid agonist medications for pain, acute or chronic	4 days prior to randomisation
Naltrexone.	2 days prior to inclusion
Electroconvulsive therapy (ECT)	28 days prior to randomisation

Medication and treatments that are specifically prohibited or restricted during the study are listed in Table 5.

Table 5 Concomitant medications and treatments that are prohibited, allowed with restrictions, or permitted during the study

Use category	Type of medication	Details
Prohibited	Mu-opioid agonists	Including but not limited to methadone, morphine, buprenorphine (non-study prescribed), heroin, codeine, petidine, fentanyl.
	Non-study naltrexone	Includes any medication containing naltrexone other than study drugs administered according to the CSP
Permitted with restrictions	Antidepressant	One antidepressant where dosage should be stable at enrolment and remain at the same dose throughout the study. The following antidepressants are allowed: Amitryptyline, bupropion, citralopram, duloxetine, escitralopram, fluoxetine, paroxetine, sertraline, venlafaxine
Permitted	Non-psychoactive medications, including over-the-counter medications, which are required to treat illness or complaints that occur during the study	May be used at the discretion of the investigator or the patient's treating- or general physician (GP)
	Other medications which are considered necessary for the patient's safety and well-being	May be given at the discretion of the investigator(s) or the patient's treating or general physician (GP). Includes medication and devices for contraception.

3.7 Treatment compliance

Compliance will be discussed at each study visit and assessed based on reported diversion of study medication. Patients judged to be non-compliant may continue in the study, but should be counselled on the importance of taking their study medication as prescribed. Patients who are repeatedly or severely non-compliant may, at the investigator's discretion, be discontinued, see Section 3.3.6.

3.8 Psychosocial treatment and care recommended to all participants

The Norwegian model for socialized medicine ensures that a basic set of services is provided to all citizens, with extra services provided for targeted groups like the physically or mentally disabled, psychiatric patients, or people with drug dependence. The basic services guaranteed by federal legislation includes among others:

- Medical care by the GP or at any relevant hospital
- Free medication and specialized addiction counselling when an expense threshold of about 1900 NKR is exceeded. This includes expenses for e.g. HIV/AIDS and Hep-C medication
- Covering of medication and counselling expenses below the above threshold for those with a clear need for the intervention but who are unable to pay
- Housing with caretaking at the level appropriate for the individual
- Low-threshold health services including (among others) health check-ups by outreach physicians, outreach counselling services, low-threshold OMT programmes with buprenorphine-naloxone, needle exchanges, injection rooms
- Case management is highly recommended for patients in the addiction population
- Free OMT with agonist medication of their choice (methadone, buprenorphine, or buprenorphine-naloxone) in the National LAR program. Program enrolment includes reinforced rights to counselling, housing, and case management
- Free access to inpatient addiction treatment services including detoxification and long-term rehabilitation, subject to availability when applying for treatment at a specific treatment facility
- Free in-prison addiction treatment services in several prisons, with transitional residence (halfway-house type) before release

The general physician (GP) is considered the main coordinating body of all health services for permanent residents of Norway. The GP thus has special privileges to refer to specialized addiction treatment like psychotherapy or OMT. In the present study, the GPs of all participants will be contacted for information regarding participation in the study with a recommendation that their patient is referred to once-weekly counselling/psychotherapy and case management as soon as possible.

4. MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES

4.1 Primary variable

The primary variables are

a) the differences between medication groups in proportion of opioid-free oral fluid samples from randomisation to Week 12

b) differences in post-discharge mortality between medicated and non-medicated groups

c) retention (see page 4)

Outcome variable a) is used as the basis for the sample size calculation found in Section 6.5.

4.2 Screening and demographic measurements

Written informed consent must be provided before conducting any study specified procedures. The following data will be collected at enrolment (Visit 1; see also Table 1):

- Informed consent (original, signed ICF is source data)
- Inclusion and exclusion criteria
- Date of birth, sex, race and ethnicity
- DSM-IV diagnosis of opioid dependence (304.00) as confirmed by the MINI
- Relevant prior and concomitant medication
- Height and weight
- Psychiatric measurements (MINI)

4.3 Patient-Reported Outcomes (PRO)

The methods for collecting PRO data are presented below. The data will be collected in the appropriate sections of the CRF.

Table 6 shows how the PRO variables of this study relate to the study objectives and outcomes. The schedule of each assessment in time is listed in Table 1.

Table 6 Patient-reported outcomes objectives and variables relating to each objective

Objective	Variable
Secondary objective	**Secondary variable**
To evaluate how XR-NTX compared to buprenorphine-naloxone or no study medication affects quality of life of patients with opioid dependence	Change from randomisation to each monthly assessment on Temporal Satisfaction With Life score
To evaluate how XR-NTX compared to buprenorphine-naloxone or no study medication affects abstinence motivation or cognition	Change from randomisation to Week 12 on Socrates 8D score
To evaluate how XR-NTX compared to buprenorphine-naloxone or no study medication improves sleep quality in patients with opioid dependence	Change from randomisation to each monthly assessment on Insomnia Severity Index score
To evaluate XR-NTX compared to buprenorphine-naloxone or no study medication on heroin-related craving	Change from randomisation to each monthly assessment on a Visual Analogue Scale
To assess the subjective effects of opioid intake in XR-NTX treatment compared to buprenorphine-naloxone or no study medication	Between-group differences in Visual Analogue Scale (VAS) ratings of opioid agonist effects

Appropriate procedures for minimising bias and enhancing compliance will be followed throughout the study. The investigator and/or delegate at each site will be responsible for the PRO evaluation and a standardised procedure for the administration of the PRO questionnaires will be applied. The patients will complete the questionnaires independently, so that the responses reflect the patient's perception and views rather than those of family, friends, staff or others.

Each centre will have a designated quiet space in the clinic for patients to complete the questionnaires at each visit. The questionnaires should be completed prior to other examinations, before there are substantial professional encounters with transmission of information, such as disease status. Such information may influence the answers that patients provide on questionnaires. The order of administration of questionnaires will be: VAS, Socrates 8D, TSWLS, SCL-25 and the ISI.

A University of Oslo representative will be trained to evaluate the quality of the PRO assessments and alert sites to possible problems in this component of the clinical study.

4.3.1 The Temporal Satisfaction With Life Scale (TSWLS)

4.3.1.1 Methods of assessment

The TSWLS will be completed at scheduled visits during the study by each patient. The instrument has been developed to measure differences in degree of enjoyment and satisfaction (117). The short form used in this study has 5 items, comprising the 'present' items of the original instrument. Higher scores on the 1-7 Likert scale for each item (range of total score: 5-35) indicate better subjective quality of life. The instrument is sensitive to change over time following treatment. It has been found to have high internal consistency, test-retest reliability, and concurrent validity in a wide range of patients, non-patients, cultures, and settings.

4.3.1.2 Derivation or calculation of outcome variable (TSWLS)

The TSWLS total score is derived by summing scores on item 1-5 for a minimum score of 5 and a maximum score of 35. For all TSWLS scores, calculations can be made both on basis of change from randomization and/or direct study group comparisons.

4.3.2 Insomnia Severity Index (ISI)

4.3.2.1 Methods of assessment

The ISI (118) will be completed at scheduled visits during the study by each patient. The 5-item scale is a reliable, valid and standardised screening measure of sleep difficulties. The patient rates each problem-related item on a 0-4 Likert scale.

4.3.2.2 Derivation or calculation of outcome variable (ISI)

The 5 self-rated items will be used to gain a sense of the extent of sleeping difficulties in each participant group. The patient rates each problem-related item on a 0-4 Likert scale. The ISI global score is calculated as the sum of the 5 items. Clinical cut-offs exist that have been validated in sleep-problem populations. The changes from randomisation will be calculated as the visit score minus the randomisation score. Between-group differences at any study point or between-group changes may be calculated.

4.3.3 Stages of Change Readiness and Treatment Eagerness Scale – Drugs (SOCRATES-8D)

4.3.3.1 Methods of assessment

The Socrates-8D will be completed at scheduled visits during the study by each patient. The Socrates-8D is a self-administered instrument to measure recognition of drug problems and willingness to change in illicit drug users (119). The 19 items of the Socrates-8D are used to measure three dimensions of abstinence motivation: a) Recognition of addiction problems b) Ambivalence towards improvement c) Taking steps towards improvement. All 19 items in the Socrates-8d are scored on a 5-point scale. Higher scores on all items indicate higher abstinence motivation.

4.3.3.2 Derivation or calculation of outcome variable (Socrates-8D)

Socrates 8-D sub-scales include recognition, ambivalence, and taking steps. A Socrates 19-item total score will be calculated. Higher scores indicate a higher level of abstinence motivation. The change from randomisation will be calculated as the visit score minus the randomisation score. Between-group differences or differential developments in Socrates 8D scores will be calculated at any assessment.

4.3.4 Heroin effect, craving, & treatment satisfaction (VAS)

4.3.4.1 Methods of assessment

The VAS will be completed at scheduled visits during the study by each patient. This Visual Analogue Scale consists of several 0-100 mm items that are self-administered to measure a) craving for heroin b) effect of any opioid agonists used during treatment c) the extent to which patients are satisfied with their current treatment and would recommend it to a friend. The craving item is derived from previous investigations (76, 77) finding that a rating of the statement 'I need heroin' seems to have a higher extent of validity than other formulations. The items reporting on heroin effects are derived from a previous study challenging naltrexone blockade with increasing dosages of morphine or placebo (120). Although VAS are becoming more frequent, the scoring by making a mark on a 0-100 line will need to be demonstrated in order to ensure that the patient fully comprehends VAS.

4.3.4.2 Derivation or calculation of outcome variable (VAS)

The outcomes from the VAS sheet will be analysed separately: craving, treatment satisfaction, propensity to recommend current treatment, and opioid/heroin effects. Each of the items on the VAS sheet can be analysed separately as independent variables. Thematically related variables may also be combined for analyses as appropriate. The change from randomisation will be calculated as the visit score minus the randomisation score. Between-group differences or differential developments in VAS scores can be calculated for any assessment.

4.3.5 Hopkins' Symptom Checklist 25 (SCL-25)

The SCL-25 will be completed at scheduled visits during the study by each patient. The Symptom Checklist 25 (121) is a self-administered instrument to measure severity of mental distress. The 25 items of the SCL-25 are scored on a 4-point scale and summed to calculate total score of distress. The items include 15 depression-related items and 10 anxiety-related items, which can be scored separately. Higher scores on all items indicate a higher level of distress, and a higher score on each subscale indicates a higher level of depression and anxiety respectively. The SCL-25 preserves the depression and anxiety items from the original 90-item Hopkins' Symptom Checklist.

4.3.5.1 Derivation or calculation of outcome variable (SCL-25)

The outcomes from the SCL-25 will be analysed as a total score (range: 25 - 100) and/or subscale scores for depression and/or anxiety. Each score (total, depression, anxiety) can be analysed separately as independent variables. The change from randomisation will be

calculated as the visit score minus the randomisation score. Between-group differences or differential developments in SCL scores can be calculated for any assessment.

4.4 Health Economic measurements and variables.

This is not applicable for the current study.

4.5 Pharmacokinetic measurements and variables

For timing of individual pharmacokinetic samples, refer to the study plan (Table 1) specific to this CSP. Biological samples are collected in two types of settings with different procedures: Inclusion blood samples and pregnancy tests are collected and analyzed in the controlled environment (inpatient clinic, prison) according to standard procedures on site. The second setting occurs when patients are discharged from their controlled environment and are tested on a weekly basis during Week 1-12 (see Table 3); saliva samples are used to collect information on recent drug use and naltrexone levels, ideally with a blood sample (5 mg) taken simultaneously to validate the saliva naltrexone analysis. The samples should be properly taken, handled, labelled and shipped in accordance with the instructions provided. The methods for collection of biological samples and derivation of pharmacokinetic variables are presented below in Sections 4.5.1 and 4.5.2.

4.5.1 Determination of drug concentration in biological samples

The following sample handling procedures must be followed to avoid jeopardising the subsequent determination of both study drug and any psychotropic drug or selected metabolite concentrations in human plasma or oral fluid. All samples will be taken using aseptic technique. Samples taken at follow-up for measurement of drug and metabolite concentrations will be analysed using fully validated bioanalytical methods by The Norwegian Institute of Public Health, Division of Forensic Toxicology and Substance Abuse. The methods used will be detailed in the clinical study report (CSR).

4.5.1.1 Collection of biological samples

For biological samples collected at inclusion/randomization, standard on-site clinical procedures will be utilized. Pre-medication (e.g. inclusion/exclusion criteria) samples at or preceding Visit 1 & 2 are collected in an inpatient or prison setting an analysed according to local standards & procedures. Biological samples at follow-up (from Week 1 onwards following discharge from controlled environment) may be collected at any PI-approved location (e.g. GP office, outpatient clinic, local hospital, pharmacy). Routine follow-up samples will be collected and shipped in a uniform manner at all study sites in accordance with instructions provided by the FHI, who receive, store and analyse the samples in accordance with national guidelines. Oral fluid samples are collected using kits provided by the PI in collaboration with the FHI and are mandatory for all randomized participants during

weeks 1-12 of the study. A scratchcard incentive may be offered to participants following each oral fluid sample in order to reduce the likelihood of noncompliance. Venous blood samples (5 mL) will be collected from a subset of volunteer patients alongside the oral fluid samples in order to verify the oral fluid analyses. Using aseptic technique, a venous blood sample will be collected from a forearm vein (or other vein) into a 5-mL EDTA evacuated blood collection tube at visits specified in table 1. When sampling from veins is not possible, capillary blood may be used instead; this must be noted in the CRF and on the Specimen Shipment Form. Blood and oral fluid samples will be collected, labelled and shipped as detailed below and further directed by the PI in collaboration with the FHI.

For samples taken at the discretion of the investigator or treating physician to investigate AEs on an as-needed basis, the necessary analyses and procedures will be determined on-site. The PI may be consulted regarding AE analyses, and must be consulted if extra analyses from the FHI are considered necessary.

4.5.1.2 Labelling of pharmacokinetic samples

The labels for the polypropylene tubes should be wrapped with transparent tape (or laminate supplied with the label) to ensure that the labels remain attached to tubes during processing and shipment. The labels must maintain their integrity despite being in contact with moisture. The labels should not be obscured or extend over the tube, and no additional labels should be attached to the sample tube. Labels used for inclusion & AE analyses on-site will adhere to site standards for labelling of clinical samples. Labels for follow-up samples will be prepared and supplied by the designated laboratory at the Norwegian Institute of Public Health (FHI) for all tubes and containers used to collect oral fluid. Samples will be collected locally, sealed and shipped by mail with a Specimen Shipment Form to the FHI. Only FHI-supplied envelopes and Specimen Shipment Forms should be used for the oral fluid – and blood samples collected during this phase of the trial. Each FHI label will include a bar code corresponding to a designated column on the Specimen Shipment Form.

The randomisation number, time of last dose, time of any concomitant psychotropic drugs, date and time of sample collection will also be recorded on the appropriate CRF.

4.5.1.3 Shipping of pharmacokinetic samples

As the samples collected are utilized as part of the participants' clinical treatment, the Specimen Shipment Form includes patients' personal data, name and medical license ID # of the investigating physician/investigator, as well as boxes specifying sample matrix (e.g. saliva, blood), date, time and comments. Enrolment samples follow local site conventions with regard to shipment, analysis, and inclusion of results in medical records/EPJ.

All shipments of diagnostic or potentially infectious substances should be made in accordance with all applicable regulations. It is the responsibility of the investigational site to ensure that each specimen is classified, packaged, labelled, marked, and documented in compliance with all applicable regulations.

See Table 9 for the total amount of blood to be drawn from each subject throughout the study.

4.5.2 Drug concentration measurements, and derivation or calculation of pharmacokinetic parameters

Samples for measurement of drug and metabolite concentrations will be analysed using fully validated bioanalytical methods including MS-MS "fingerprint" technology. The methods used will be detailed in the clinical study report (CSR).

4.6 Effectiveness measurement and variables

The following effectiveness scales are utilised in this study and will be rated by the investigator or delegate, according to the schedule of events in Table 1, Section 3.

To ensure consistency throughout the study, all site personnel administering the Europ-ASI will receive training in conducting these assessments and must be approved by the PI before they take part in this study by inter-rater reliability tests. To reduce scoring variability, it is recommended that the same rater conduct all assessments for a given patient for a specific scale.

Europ-ASI, TLFB, and MINI will be integrated into one interview whenever possible in order to minimize the test burden on participants.

In the event that the primary site rater is not available, a designated back-up rater may perform the rating. The back-up rater must meet the same qualifications as the primary rater and be authorised by the Principal Investigator to conduct the ratings.

The scores in each of the scales will be recorded on the appropriate sections of the CRF. Signs and symptoms revealed and recorded during the ratings should only be reported as AEs if they fulfil the criteria for a SAE or are the reason for discontinuation from treatment with the investigational product.

The methods for collecting effectiveness data are described below. The shorter effectiveness rating scales are integrated into the larger structured interview Europ-ASI when possible (pending approval from the Norwegian Europ-ASI Certification Authority).

4.6.1 Oral fluid/saliva samples as outcome measures

The outcome from the oral fluid samples will be measured as dichotomous outcomes, e.g. above or below a clinically significant threshold or the level of detection (LOD) for each substance. The primary outcome is the number of opioid-free oral fluid samples during Weeks 1-4, 5-8, 9-12, or 1-12: The number of oral fluid samples negative for non-study opioids or their metabolites will be subtracted from the total number of samples (n=12) to yield a proportion of negative samples. Other substances may be analysed as secondary outcomes in a similar manner. For XR-NTX patients, analyses will include measurements of levels of

naltrexone or metabolites that will be compared to the expected dosage trajectory and/or blood samples taken concurrently with one or more saliva samples.

Between-group differences at any assessment, as well as within- or between-group change from randomisation to each assessment may be calculated.

4.6.2 Addiction Severity Index, European Version (Europ-ASI)

4.6.2.1 Methods of assessment

The Europ-ASI version 5 is a 40-90 minute structured interview that assesses demographics, physical health, work & education, substance use & treatment, criminal activity, and social functioning (122). History on these topics is assessed during the first Europ-ASI interview, administered at inclusion, while follow-up interviews (monthly for participants receiving medication) will assess present functioning only. Pending approval by the Norwegian Europ-ASI Certification Authority, the Europ-ASI will be modified to integrate other relevant instruments when possible. The main types of outcome assessments for the different outcomes in the sections of the Europ-ASI are: a) days of last 30 days (range: 0-30) b) frequency of use where 0 = no use, 1 = used 1-3 times per month, 2 = used 1 – 3 times per week, and 3 = daily almost daily use (range: 0-3) c) number of months occurrence of the outcome in question during the total number of months in the last observation period (in this study a range of 0-3, 0-12, or 0-1) d) dichotomous outcomes (0/1).

Each rater administering the Europ-ASI must receive training and certification on the use of the Europ-ASI and must be approved by the PI before they take part in the study.

4.6.2.2 Derivation or calculation of outcome variable (Europ-ASI)

Although it is possible to calculate a total or composite score from the Europ-ASI, single item scores or section composite scores will be preferred. For any relevant outcome from the Europ-ASI, between-group differences at any assessment and within- or between-group change from randomisation to each assessment may be calculated.

4.6.3 Mini Neuropsychiatric Interview (MINI)

4.6.3.1 Methods of assessment

The MINI is a structured screening interview for DSM-IV diagnoses (123). As an outcome measure in the present study, only section L from the MINI will be used to assess whether participants satisfy criteria for opioid dependence as a dichotomous outcome (Yes/No) when three criteria or more are satisfied. In addition, scores may be calculated for this study based on number of criteria satisfied (range: none to seven criteria).

The study design requires that follow-up assessments of opioid dependence criteria modify the time window of assessment - from the original DSM-IV criteria of any occurrence during the past 12 months to the study period in question (e.g. previous month or previous 3 months).

4.6.3.2 Derivation or calculation of outcome variable (MINI)

The MINI section L score for opioid dependence will be calculated as a) satisfying or not satisfying 3 or more of the 7 criteria for DSM-IV opioid dependence and/or b) number of criteria satisfied (range: 0-7).

For fulfilment of opioid dependence criteria on the MINI, between-group differences at any assessment and within- or between-group change from randomisation to each assessment may be calculated.

4.6.4 Time-Line Follow-Back (TLFB)

4.6.4.1 Methods of assessment

TLFB is a data collection method aimed at maximizing the accuracy of retrospective interview data (124): the patient is asked to remember on which days a specific substance was used today, yesterday, the day before that etc. By cueing the patient in this way, satisfactory levels of reliability and validity can be achieved, permitting an approximate of any variations in timing of substance use within a given time period in addition to its frequency.
TLFB will be used to assess participants' substance use during the follow-up period at monthly intervals, yielding ranges of 0-30 days' of use for alcohol (heavy (>3 week for intoxication) and any use), opioids, benzodiazepines, other sedatives, amphetamines, cocaine, cannabis, and other drugs.

4.6.4.2 Derivation or calculation of outcome variable (TLFB)

For TLFB data on substance use, between-group differences at any assessment and within- or between-group change from randomisation to each assessment may be calculated. In addition, frequency or presence/absence of use of one or more specific substances during different periods of the study may be calculated.

4.6.5 Registry data for mortality, morbidity, medical treatment, recidivism, prescription medications

Relevant registries (see Table 3) will be consulted after Week 48 on the frequency and/or type of registered outcome data during the study and (except mortality) up to one year before randomisation.

4.6.5.1 Derivation or calculation of outcome variable (registries)

For registry data on mortality, morbidity, recidivism, medical treatment, or prescription medications, between-group differences at any assessment and within- or between-group change from randomisation to each assessment may be calculated. In addition, frequency or presence/absence of use of one or more specific substances during different periods of the study may be calculated. Change from the year before to the year during treatment or the year following treatment may be calculated.

4.7 Safety measurements and adverse events as outcomes

In addition to being used for safety monitoring (see Section 10: Safety Assessments) adverse events (including AEs, SAEs & SUSARs) are outcomes that may differ between study groups.

Table 7 shows how the safety variables of this study relate to the study objectives.

Table 7 Safety objectives and variables relating to each objective

Objective	Variable
To evaluate the safety and tolerability of XR-NTX compared to buprenorphine-naloxone or no study medication in the treatment of patients with opoid dependence	Incidence of adverse events (AEs) Incidence of AEs leading to withdrawal Incidence of AEs of special interest (overdose) Proportion of patients reporting suicidal intent on the Europ-ASI at any time after randomisation or an AE of suicidality/suicidal ideation/suicide attempts/suicide completion (see Section 4.6)

Safety and tolerability outcomes will be evaluated using mainly descriptive statistical methods. The methods for collecting safety data are described in Section 9.

Other Significant Adverse Events (OAE)

Significant AEs of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from study treatment, will be classified as OAEs. OAEs will be identified by the investigators and if applicable also by the Study Team Physician during the evaluation of safety data for the CSR. Examples of these are marked laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment. For each OAE, a narrative may be written and included in the CSR.

4.7.4 Laboratory safety measurements and variables

4.7.4.1 Methods of assessment

Blood specimens will be collected for laboratory analysis according to Table 1. A designated laboratory will process these samples and results will be reported back to the clinic.

All samples should be taken by adequately trained study personnel, and performed and handled in accordance with given instructions. Results on all safety laboratory values will be reported to the Study site within three days after the analyses by the designated laboratory. The investigator should make an assessment of the available results with regard to clinically significant abnormalities. Up-to-date reference ranges will be provided during the study and laboratory results will be compared to the laboratory standard normal ranges and flagged if they are outside the normal range. The investigator or designee should make an assessment of the available results with regard to clinically significant abnormalities. The paper copy should be signed and retained at the site as source data for laboratory variables. Results can also be stored in the patient's EPJ on site for future reference.

Laboratory tests can be repeated if assessment at enrolment is abnormal and deemed clinically significant by the investigator. Results must be reviewed prior to randomisation to ensure patient meets eligibility requirements.

Table 8 Laboratory measurements

Haematology	Clinical chemistry	Urinalysis
B-Haemoglobin	S-Creatinine	U-Glucose
B-Haemoglobin glycosylated (HbA1c)	S-Bilirubin, total	U-Blood
B-Hematocrit	S-Alkaline phosphatise	U-Protein
B-Erythrocyte count	S-Alanine aminotransferase (ALT)	U-Leukocytes
B-Leukocyte count	S-Aspartate aminotransferase (AST)	UTS for substances of abuse
B-Leukocyte differential count	S-Potassium	Pregnancy test
B-Platelet count	S-Sodium	
	S-Calcium (Bicarbonate)	

B=whole blood; S=serum; P=plasma; U=urine [a] Serum pregnancy test are conducted at enrolment.

All enrolment laboratory assessments must be completed before randomisation takes place.

Volumes of blood samples to be taken are described in Table 9.

Urine samples

Urinalysis (blood, protein and leukocytes), including a UTS for substances of abuse, will be performed at enrolment and results available before randomization (Visit 2). Substances of abuse included in the screening are: amphetamines, barbiturates, cannabinoids, cocaine, benzodiazepines, and opioids. The UTS is part of a general assessment for the presence of

substance abuse disorders. The initial UTS is often expected to be positive, meaning patients will not be excluded from the study on the basis of a positive UTS.

Management of neutropenia

CBC including WBC differential count will be performed for all patients. CBC with a WBC differential should also be performed at any time a patient presents with a fever, pharyngitis (sore throat), or other signs and symptoms of infection. Patients should be instructed to seek medical care if they develop symptoms of infection such as fever and/or pharyngitis and mucous membrane ulceration. If signs and symptoms of the low neutrophil count are present, e.g., infection, these should be recorded as an AE. If a patient has a neutrophil count of $<1.0 \times 10^9$/L, the test should be repeated according to local procedures. If the second neutrophil count remains $<1.0 \times 10^9$/L, the patient should be discontinued from treatment with the study medication due to AE, see Section 3.3.6. The AE should be recorded as "Neutrophil count decreased". These patients should be monitored weekly with a CBC and a WBC differential until their counts recover. While experiencing neutropenia, patients should avoid invasive procedures such as dental work, rectal exams or enemas, exposure to people who are obviously ill, and exposure to fresh fruits, vegetables, or flowers. If a patient develops fever or symptoms of infection, he/she should contact his or her physician and acquire a CBC with differential immediately.

4.7.4.2 Derivation or calculation of outcome variables

For all laboratory variables, descriptive statistics will present change in laboratory measurements over the study period. Enrolment assessment will be considered baseline for all laboratory analyses where follow-up samples have been taken to analyse AEs, while for follow-up assessments (FHI analyses) the sample collected during Week 1 following discharge will be considered baseline.

Changes from baseline to subsequent visits will be calculated as the visit value minus the enrolment value. Changes from baseline to subsequent visits will be summarised for each variable and treatment group. Laboratory test results will also be compared to the laboratory reference ranges and the values that are outside the applicable reference range will be flagged as high (H) or low (L). Treatment emergent laboratory changes identified by comparing results or changes from baseline to standard extended reference ranges will be flagged at the patient and test level.

4.7.5 Vital signs and physical examination

4.7.5.1 Methods of assessment

A physical examination, height weight, and vital signs, including sitting blood pressure and pulse, will be measured according to table 1. A physician will conduct the complete physical examination at the enrolment visit.

Weight will be measured in kilograms (kg). During the weight assessment, the patient should be wearing light clothes and no shoes. The same scale should be used for all site assessments. Height will be measured in centimetres (cm).

4.8 Volume of blood sampling and handling of biological samples

The total volume of blood that will be drawn from each patient in this study is as follows:

Table 9 Volume of blood to be drawn from each patient at enrolment / Pre-inclusion phase (inpatient) (Visit 1-2, Day -30 to 0, Week -4 to 0)

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry[a, b]	5	2	10
	Haematology[b]	4	1	4
TOTAL			4	24

[a] Sampling for lipids are included in the clinical chemistry volume.
[b] May be repeated if needed, at the discretion of the investigator.

The maximum total volume will not exceed 50 mL (inclusive of repeated tests).

The designated laboratory will provide detailed instructions of all laboratory procedures, handling and shipment of laboratory samples before the study start. The samples should be properly taken, handled, labelled and shipped in accordance with the instructions provided by the designated laboratory (e.g. on-site or FHI instructions).

At follow-up, sites and participants will be encouraged to provide FHI with a 5-10 ml blood sample (1-2 tubes) with each oral fluid sample in order to assist FHI validation of naltrexone medication measurements in oral fluid. Providing blood for these samples is not mandatory for participants, but beneficial to confirm the reliability of analyses of medication levels. For blood samples taken for this purpose, labelling, shipment procedures and - equipment are identical to that of the mandatory oral fluid samples. This procedure is described in 4.5.

4.8.1 Analysis of biological samples

For biological samples collected at inclusion/randomization, the samples will be analysed at the hospital laboratory according to local procedures on site. For biological samples collected at follow-up (e.g. post inclusion, randomization & discharge from controlled environment), procedures from FHI will be adhered to. For samples taken at the discretion of the investigator or treating physician to investigate AEs on an as-needed basis, the necessary analyses and procedures will be determined on-site. The investigator may be consulted regarding AE analyses, and must be consulted if extra analyses from the FHI are considered necessary.

4.8.1.1 Clinical chemistry samples

The analyte stability limits defined by the designated laboratory will be applied to all analyses performed on behalf of the project owner / principal investigator. The designated laboratory will not analyse samples that fall outside these stability limits. Analytical data will not be

reported if found to have been derived from a sample that fell outside these stability limits. The designated laboratory will inform the PI of the stability limits relevant to this study before the first patient gives informed consent to take part in the study.

5. DATA MANAGEMENT

Data will be entered in the CRFs at the investigational site. Trained study personnel will be responsible for entering data on the observations, tests and assessments according to the CRF instructions. The CRF instructions will also provide the study site with data entry instructions. When data have been entered and reviewed / edited by a CRO, the site investigator will be notified and sign the CRF copy, and data will be locked to prevent further editing. A copy of the CRF will be provided to the investigational site after the study database has been locked and will be archived at the investigational site.

Data checks will be run and data validation performed by the National Coordinating Investigator (PI), delegate, or CRO. The investigator should answer any queries arising from such checks during the whole study including the clean-file process.

AEs will be classified according to the terminology of the CTCAE, see Section 9. Concomitant medications will be classified according to the Anatomical Therapeutic Chemical (ATC) system and the Committee of Proprietary Medicinal Products (CPMP) route of administration dictionary.

Data will be cleaned on a regular basis by a designated partner. Clean file for the final database will be declared by the principal investigator after all data have been set to clean. Prior to declaring clean file, all decisions on the evaluability of the data from each patient must have been made and documented.

The Data Management Plan (DMP) will provide information on data flow, timelines and all data management activities planned for the study, including responsibilities for the personnel involved in the processes. CROs will be used for handling clinical assessments and laboratory data and the results will be sent to a designated partner as SPSS or – compatible datasets.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

6.1 Statistical evaluation - general aspects

A comprehensive Statistical Analysis Plan (SAP) will be prepared and finalised prior to database lock. The final version of the SAP will be attached as an appendix to the clean file document.

6.2 Description of outcome variables in relation to objectives and hypotheses

6.2.1 Primary objective, hypotheses, and outcome variables

The primary objective of this study is to evaluate the effectiveness of XR-NTX 380 mg/month versus buprenorphine-naloxone 8-24 mg/day as part of "treatment as usual", assessed by the number of opioid free oral fluid samples during the treatment period from randomization to Week 12.

The primary hypotheses are as follows:

- XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in the mean number of oral fluid samples negative for opioid agonists (other than study drug) or their metabolites from randomization until Week 12.

- XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in increasing self-reported abstinence from illicit (e.g. non-study) opioids measured as number of days abstinent on time-line follow-back

- XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in retention in treatment at Week 12 as measured by comparing the number of patients left and/or calculating the proportion of patients retained in each group.

- XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in reducing the number of patients qualifying for an Opioid Dependence Diagnosis on the DSM-IV TR (304.00 except the 12-month criteria) as measured using the MINI.

- Any study drug (XR-NTX 380 mg/month or buprenorphine-naloxone 8-24 mg/day) is superior to no study drug on preventing mortality as measured by the number of patients deceased from randomisation until Week 48 according to Norway's National Mortality Registry.

6.2.2 Secondary objectives, hypotheses, and outcome variables

6.2.2.1 Secondary objective of particular interest

A secondary objective of particular interest is to evaluate if XR-NTX (380 mg/month) reduces heroin craving compared to or buprenorphine-naloxone (8-24 mg/day). The secondary hypotheses are as follows:

– XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in reducing craving for heroin from randomisation to each monthly assessment until Week 12 as measured on a visual analogue scale (VAS).

6.2.2.2 Other secondary objectives: Effectiveness

Another secondary objective of this study is to evaluate the effectiveness of XR-NTX versus buprenorphine-naloxone, or both of these drugs versus no study drugs, within or between clinical and criminal justice settings. The secondary hypotheses are as follows:

- Any study drug (XR-NTX 380 mg/month or buprenorphine-naloxone 8-24mg/day) will be superior to no study drug on:

  - Morbidity at 48 Weeks post randomization/inclusion as measured by data from the Norwegian Patient's Registry.

  - Criminal re-offending as measured by the number of offences registered at Week 48 in Norway's National Criminal Offense Registry and/or self-report.

  - XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in increasing Quality of Life from randomisation until Week 12 as measured using the Temporal Satisfaction With Life Scale.

- XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in reducing non-opioid substance use as measured by the number of oral fluid samples positive for illicit, non-opioid substances or their metabolites from Week 1-12 in the study or in self-reported use of (or abstinence from) non-opioid substances including cocaine, amphetamines, benzodiazepines, alcohol, cannabis, and hallucinogenic drugs (e.g. LSD, MDMA, GHB).

- XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in reducing drug-related needle use as measured by the number of days needle use reported from randomization to Week 12 on time-line follow-back.

- XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in reducing income from illicit sales of drugs as assessed by the change from randomisation to Week 12 in self-reported days with such income and/or the total amount of income from these sources in Norwegian Kroner (NKR; 10 NKR = approximately 1,7 US $). The Europ-ASI will be used for this outcome.

- XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in reducing frequency of injecting drug use as assessed by the change from randomisation to Week 12 in self-reported days with such use and/or the total use of needles in days during each month on the Europ-ASI.

- XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in reducing frequency blood-borne disease risk behaviours as assessed by the change from randomisation to Week 12 in self-reported needle use habits for each month on the Europ-ASI.

A secondary objective of this study is to evaluate if XR-NTX in the clinical and/or criminal justice settings affects motivation for abstinence compared to buprenorphine-naloxone and/or non-randomized controls by assessing the change from randomisation to Week 12 in self-reported abstinence motivation on the total or subscale levels of the Stages of Change Readiness and Treatment Eagerness Scale Drugs (SOCRATES 8D). The secondary hypotheses are:

- XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in increasing motivation for abstinence at Week 12 as measured by Total score on the SOCRATES 8D.

- XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in increasing recognition of addiction problems at Week 12 as measured by increased scores on the recognition subscale on the SOCRATES 8D.

- XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in increasing the reported effort towards abstinence at Week 12 as measured by the Taking Steps subscale on the SOCRATES 8D.

- XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in increasing motivation for abstinence at Week 12 as measured by a reduction on the ambivalence subscale of the SOCRATES 8D.

6.2.2.3 Other secondary objectives: Quality of Life

A secondary objective of this study is to evaluate if XR-NTX (380 mg/month) improves quality of life of patients with Opioid Dependence, compared to buprenorphine-naloxone or no study medication. The hypothesis regarding TSWLS total score, a secondary variable of particular interest, is specified in 6.2.2.2. The other secondary quality of life hypothesis is:

- XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in increasing the TSWLS overall quality of life score from randomisation to Week 12.

A secondary objective of this study is to evaluate if XR-NTX (380 mg/month) improves satisfaction with medication compared to buprenorphine-naloxone or no study medication. The secondary hypothesis is as follows:

- XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in increasing the VAS satisfaction with medication score at Week 12.

6.2.2.4 Other secondary objectives: Safety

A secondary objective of this study is to evaluate the safety and tolerability of XR-NTX compared to buprenorphine-naloxone and/or non-randomised controls in the treatment of patients with Opioid Dependence. The following assessments will be performed:

- Incidence of AEs (including AEs leading to discontinuation or study withdrawal)
- Incidence of AEs of special interest (overdose)
- Incidence of AEs related to insomnia as measured on the ISI
- Evaluation of changes from baseline in relapse rates, severity of substance use, and treatment attrition
- Incidence of patients reporting increase in suicidal intent or attempts on the Europ-ASI at any time after randomisation or an AE related to suicidality.

6.2.2.5 Other secondary objectives: Pharmacokinetics

- As the pharmacokinetic data of the study drugs are well-known, the collection of pharmacokinetic data will be limited to detecting the presence of naltrexone in XR-NTX patients using weekly oral fluid samples from randomisation to Week 12. A pre-defined threshold based on previous studies will be used to detect levels above or below the estimated minimum therapeutic plasma level of naltrexone (1 ng/mL). Blood samples will be collected alongside saliva samples from a subset of volunteer patients when possible and shipped to the FHI.

6.2.2.6 Other secondary objectives: Other registry data

A secondary objective of this study is to evaluate the recovery-relevant outcomes of medical treatment including hospitalization, recidivism, prescribed medications, counselling and OMT during XR-NTX compared to buprenorphine-naloxone and/or non-randomised controls in the treatment of patients with Opioid Dependence. The following assessments may be performed:

- Number of prescriptions as total number or by subtype (e.g. mental health, anti-retrovirals, etc)
- Number of counselling sessions or treatment periods
- Number and types of hospitalisations for which medical reasons
- Treatment episodes in the National OMT Program outside the scope of the study and medication type (e.g. methadone, buprenorphine)
- Recidivism (type and numbers of criminal offences)
- Death during the study or after end of study

6.3 Description of analysis sets

All data analyses, both primary and secondary, will be performed using at least one of the following analysis sets:

- The safety population will include all randomised patients who took at least one dose of study medication, classified according to the treatment actually received.
- The intention-to-treat (ITT) population will include all patients who were included and randomised to a treatment, regardless of whether first treatment dose was received or not. This population includes all drop-outs regardless of duration of participation.
- The modified intention-to-treat (MITT) population (Full Analysis Set) will include all randomised patients, classified according to randomised treatment, who received at least one dose of study treatment and who have at least one valid assessment after randomisation. Data from the MITT population will be used for analysis of the effectiveness objectives.
- The per-protocol (PP) population, a subset of the MITT population, will include patients who completed the study treatment with no major protocol violations or deviations affecting effectiveness. Data from this population will be used as a consistency check for analysis of the primary objective.

6.4 Method of statistical analysis

6.4.1 General aspects

Missing data will be imputed using a Last Observation Carried Forward (LOCF) approach. Patients with post randomisation data will have their last study assessment carried forward as the final assessment for analyses. These will serve as accurate estimates since the patients could be expected to get better over time. Analyses on Observed Cases (OC) will be performed to study the robustness of the results.

Baseline values, collected at randomisation or enrolment, will be defined as the last non-missing value prior to receiving first dose of study treatment.

Descriptive statistics including frequency tables (including n, mean, median, standard deviation, minimum and maximum for continuous variables and n, frequency and percentage for categorical values) and graphs will be provided for all variables, as well as for the changes from baseline within each treatment and the differences between the treatment groups at each visit, for both OC and LOCF, as appropriate.

For simplicity, the treatment groups will hereafter be referred to as XR-NTX 380 mg, buprenorphine-naloxone 8-24 mg, and non-medicated; however, all treatment groups may also have ongoing follow-up “as usual”.

6.4.2 Multiplicity

For the confirmative strategy, a step-wise sequential testing procedure will be used for handling multiple comparisons such that the overall significance level of 0.05 is preserved. First the primary outcome variable the number of opoid free saliva samples from randomisation to Week 12 will be tested for the naltrexone versus the suboxone group.

All statistical tests will be two-sided with a significance level of 5%, i.e. α=0.05 unless otherwise specified. Secondary analyses will report nominal 5% levels of significance, but p-values will be displayed primarily to aid the interpretation of results. No adjustments for multiplicity will be made for these secondary analyses. Where appropriate, model-based point estimates will be presented together with their 95% confidence intervals. Unless otherwise stated the interest will separately focus on the treatment differences between the groups.

6.4.3 Primary variable

An analysis of variance (ANOVA) model for between-groups differences at Week 12 in the number of opioid-positive oral fluid samples will be used. Study drug groups (XR-NTX 380 mg/month or buprenorphine-naloxone 8-24 mg/day) will be compared, and also compared separately or collectively (as a ‘medication’ group) to participants not receiving any study drug. The model will include treatment, centre and setting as explanatory variables. Centre will be treated as a random effect while all other explanatory variables will be treated as fixed effects. Model-based point estimates, 95% confidence intervals and p-values will be reported.

Similar analyses will be performed for the primary objectives of opioid abstinence and opioid-free days at Week 12. Joint analyses of study groups across the two study settings may be performed. The change in opioid use or abstinence from randomisation to Week 12 will be presented by descriptive statistics. Models based on analysis of regression or mixed models may be utilized if statistical properties of the data (e.g. distribution) suggests this will provide a more accurate or correct result.

For the primary objectives of mortality, number of patients retained, and satisfying DSM-IV criteria for Opioid Dependence, a chi-square analysis will be used to assess the Odds Ratio (OR), and/or the Hazard Ratio (HR), Relative Risk (RR), and/or the Number Needed to Treat. In the main statistics, 95% confidence intervals and p-values will be reported.

For the confirmatory strategy, comprising the primary objective and the secondary objective in Section 6.4.4, adjustment for multiplicity will be handled according to Section 6.4.2.

6.4.4 Secondary variable of particular interest

A statistical analysis similar to the one described in Section 6.4.3 will be performed for the craving total score from randomisation to Week 12. Baseline total score will be used as a covariate in the model. Model-based point estimates, 95% confidence intervals and p-values will be reported. For the confirmatory strategy, comprising the primary objective and the secondary objectives of particular interest, adjustment for multiplicity will be handled according to Section 6.4.2.

6.4.5 Other secondary variables

6.4.5.1 Non-opioid substance use

The change in the non-opioid substance use from randomisation to each assessment will be analysed using a similar model to that described for the primary variable. The interest will separately focus on the treatment differences between each dose of XR-NTX injections (each month). All assessments will be reported as point estimates and 95% confidence intervals. P-values will only be reported for the Week 12 assessment (as described in Section 6.4.3).

Response and remission at Week 12, defined from whichever is reported earliest in the oral fluid samples and/or TLFB, will be analysed utilising logistic regression or ANOVA models. The models will include treatment, centre and setting as explanatory variables. The interest will separately focus on the treatment differences between XR-NTX, buprenorphine-naloxone and non-medicated patients. Model-based point estimates of odds ratios, corresponding 95% confidence intervals and p-values will be reported.

6.4.5.2 Visual Analogue Scales

Visual Analogue Scales (VAS) are used to assess the secondary objectives of heroin craving and satisfaction with treatment. The between-groups differences in VAS total scores at Week 12 will be analysed using an a similar model to that described under the primary analysis. Baseline VAS score may be used as a covariate in the model. The interest will separately focus on the treatment differences between each study group (XR-NTX, buprenorphine-

naloxone, or no study drug). Model point estimates, 95% confidence intervals and p-values will be reported.

The change in VAS score and sleep disturbance factor score from randomisation to Week 12 may be presented by descriptive statistics.

6.4.5.3 SOCRATES-8D

The between-groups differences in the SOCRATES 8D score at Week 6 will be analysed using an ANOVA model, following the same conventions as the primary analysis. Baseline SOCRATES score may be used as a covariate in the model. The interest will separately focus on the treatment differences between the study groups (XR-NTX, buprenorphine-naloxone, or no study drug). Model-based point estimates, 95% confidence intervals and p-values will be reported. SOCRATES subscales will be analysed in a similar manner.

6.4.5.4 Registry data on morbidity, prescriptions and criminal offences

The registered occurrences on each participant in the National Norwegian Registries on Criminal Records, Hospitalizations and Prescriptions from randomisation to Week 48 will be analysed using an ANOVA model, following the same conventions as the primary analysis. Baseline reported hospitalizations, criminal offences, or prescriptions may be used as a covariate in the model. The interest will separately focus on the treatment differences between each dose of XR-NTX and other study groups (buprenorphine-naloxone and no study drug). All assessments will have model-based point estimates and 95% confidence intervals reported.

6.4.5.5 TSWLS

Change in TSWLS total score from randomisation to week 12 is a secondary variable of particular interest and the analysis is discussed in Section 6.4.4. The changes in TSWLS overall quality of life from randomisation to Week 12 will be presented by descriptive statistics.

6.4.6 Safety analyses

6.4.6.1 Physical examinations, laboratory assessments, and vital signs

All laboratory test results and vital signs results will be summarised using descriptive statistics each time collected for raw numbers and change from randomisation/ enrolment.

For laboratory assessments and vital signs number and proportion of patients with clinically important values emerging during treatment phase will be presented for each treatment arm. In addition, for laboratory values shift tables with the number and proportion of patients in each category (below normal, normal and above normal) at end of treatment by baseline category will be presented.

6.4.6.2 Adverse events

AEs that lead to premature withdrawal of patients from treatment with investigational product will be tabulated for each treatment group. Descriptive statistics of incidence rates will be used to evaluate AEs (including SAEs, AEs leading to withdrawal, overdose and deaths if any), and reasons for study early withdrawal.

Selected CTCAE terms will be aggregated to look at AEs of special interest. The areas of special interest will include substance-induced overdose as reported by the patient on Europ-ASI or as recorded in registry databases (Mortality registry, Cause of Death registry). The CTCAE terms will be specified in the SAP.

6.4.6.3 Waist circumference

Not applicable for this study

6.4.6.4 ISI

Change in the ISI total score from randomisation to each assessment may be summarised with descriptive statistics and analysed similar to the primary objective.

6.4.6.5 SCL-25

The changes in SCL-25 from randomisation to Week 12 may be presented by descriptive statistics whether or not the change is found to be statistically significant.

6.4.6.6 Suicidality

The proportion of patients reporting suicidal intent on the Europ-ASI or an AE related to suicidality at any time after randomisation will be presented with descriptive statistics (i.e., percent and number of patients). Patients already fulfilling these criteria at randomisation will not be included in this table. AEs will be presented as a special grouping of AEs in the same manner as other special groups of AEs previously described.

If a sufficient number of suicidality-related events are recorded, analysis of suicidality will be performed using a suicidality classification system similar to the one established by Columbia University.

6.4.7 Pharmacokinetics

The presence of naltrexone and 6-beta naltrexol in XR-NTX patients will be monitored using weekly oral fluid samples from randomisation to Week 12. A pre-defined threshold based on previous studies will be used to detect levels above or below the estimated minimum therapeutic plasma level of naltrexone (1 ng/mL). Analyses of pharmacokinetic data will only be conducted on data from patients who provide valid oral fluid samples from randomisation to Week 12. Voluntarily collected blood samples may be used to validate oral fluid data on pharmacokinetics. Findings will be reported descriptively. Pharmacokinetic data may be used as a basis for analysis of primary or secondary outcomes.

6.5 Determination of sample size

The sample size calculation in this exploratory study was done to model the event that XR-NTX demonstrates superior effectiveness over buprenorphine-naloxone with respect to the primary outcome variable, differences in opioid-negative oral fluid samples from randomisation to Week 12 – a total of 12 oral fluid samples. The lack of precedent for the study in the literature means that parameters in the sample size determination are based on studies with a different design than the present study (see Section 1: Introduction). Nonetheless, their similarities with the present study mean they constitute the best available basis for sample size determination.

The minimum sample size was estimated by assuming that participants receiving XR-NTX will achieve opioid-negative samples on a mean of 7 out of the total 12 samples, while participants receiving buprenorphine-naloxone will deliver a mean of 4 opioid-negative samples. The estimates assume a 95% significance level ($p<.05$) and a standard deviation of 3 in both medication groups. A power (beta) set to 90%, a sample size of 17 patients/medication arm will be sufficient, or n=34 total. Missing samples will be counted as positive in an ITT-manner.

Sample size calculations were based on information from previous studies of buprenorphine-naloxone showing attrition of about 50% in the first months following discharge from criminal justice settings. Attrition in the naltrexone group is based on previous studies with sustained release naltrexone in Norwegian settings showing only about 5% attrition.

Target sample size was calculated based on the assumption that one or several parameters will deviate from the above estimated values. To exemplify such deviations any adjustment could be made to any parameter (e.g. decreased power, less attrition in groups); in the present calculation of target sample size a hypothesized increase in the standard deviation of the mean number of opioid-negative samples from the above 3 (s.d.: 3) to 4 (s.d.: 4). Retaining the other parameters from the minimum-size calculation, this yields a sample size of n=36 per medication group. When worst-case assumptions are made corresponding to an average of 20% of outcomes being somehow lost or corrupted (e.g. sample contamination from as yet unknown reasons), target sample size is adjusted to n=45 per medication group, or n=90 for two groups. In addition, there are two settings in which the trial is anticipated to be conducted: clinical treatment and criminal justice settings respectively. Although participants from different settings may be combined for statistical power in a final analysis, it is the ambition of the study to recruit n=90 in each of these two settings, or n=180 total.

For mortality outcomes, 12-month mortality is assumed to reach 4 deaths per 1000 patient-years in the medication groups, while the non-medication groups is assumed to reach a mean of 40 per 1000 p.y. Assuming a 95% significance level ($p<.05$) and a 10% chance of committing a Type II error (beta: 90), the sample size needed to attain significance will be n=45 in each group, or n=90 total. As this outcome consists of registry-based data collection across settings, adjustments for contamination or attrition have not been conducted.

The target sample size for the study is thus n=220, based on the n=180 calculated for medication groups and n=45 volunteering for non-medicated participation. The precise target figure may be adjusted during the study, and the group comparisons made may be adjusted after data collection.

Table 10 Minimum sample size for the RCT

Parameter	As specified
Power	90%
Anticipated difference to be detected compared to control	3
Standard deviation	3
Significance level (p)	0.05
Sample size (evaluable)	17 patients/arm

6.6 Interim analyses

No interim analyses are planned. Regular analyses will be performed 1) after completion of the randomized trial, and 2) separate analyses performed for the non-randomized part of the study. In addition, more regular analyses may be performed following the conclusion of the trial, in particular (but not restricted to) after collection of data from national registries / databases.

6.7 Data and safety monitoring board

No data and safety monitoring board will be set up for this study. Internal review of ongoing safety issues will be handled by the study team.

7. STUDY MANAGEMENT

7.1 Monitoring

The study is conducted in accordance with ICH-GCP and is subject to monitoring confirm GCP compliance.

Before the first patient is randomized into the study, a representative of the study team will visit the investigational study site to:

- determine the adequacy of the facilities
- discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to CSP adherence. This will be documented in a Clinical Study Agreement (CSA) between the principal Investigator and the site investigator(s)
- discuss where data regarded as source data will be recorded, e.g., medical records, CRF and associated documents. This will be documented in a CSA between Principle Investigator and the site investigator(s)

During the study, a monitor from the Regional Clinical Trial Support Team for the relevant regional health authority will have regular contacts with the study site, including visits to:

- provide information and support to the investigator(s)
- confirm that facilities remain acceptable
- confirm that the investigational team is adhering to the CSP, that data are being accurately recorded in the CRFs, and that investigational product accountability checks are being performed
- perform a source data verification (SDV), that is a comparison of the data in the CRFs with the patient's medical records at the treatment or justice facility and other records relevant to the study. This will require direct access to all original records for each patient (e.g., clinic charts).

The monitor or another study team representative will be available between visits if the investigator(s) or other member of the study staff need information and advice. A contract detailing the outcomes, endpoints, and number of inspections will be signed by the National Coordinating Investigator (PI) or delegate and the monitoring service before inclusion commences.

7.2 Audits and inspections

A member of the study group or a regulatory authority may visit the centre to perform audits or inspections, including SDV. The purpose of a study group member audit is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the CSP, Good Clinical Practice (GCP), and any applicable regulatory requirements. The investigator should contact the Principal investigator immediately if contacted by a regulatory agency about an inspection at his or her centre.

7.3 Training of staff

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff). He will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

To ensure consistency throughout the study, all site personnel administering rating scales and assessments will receive training in conducting these assessments. Certification on training will be required for Europ-ASI only. There will be training and information on all study related processes at the start meeting and at local initiation and monitoring meetings. The study group will supply more detailed instructions to site personnel as necessary before and during the study. To reduce scoring variability, it is recommended that the same rater conduct all assessments for a given patient for a specific scale.

Information about training and certification of study personnel on assessments is given in the sections describing these assessments, see Sections 4.3 and 4.6.

Before the first patient is entered into the study, the investigational staff will have an opportunity to discuss the procedures associated with the collection of blood samples and prospective and registry data with members of the study group. The ethical considerations and the importance of the informed consent process will be made clear. The requirements for the collections of the patients' samples will also be made clear.

7.4 Changes to the protocol

If it is necessary for the CSP to be amended, the amendment or a new version of the CSP (Amended CSP) must be reapproved by the REC and the Norwegian Medicines Agency if major changes to study design (e.g. new medications, different comparison groups) have been made compared to the originally approved protocol version. Minor revisions (e.g. administrative, re-structuring of existing content) do not require re-approval. Local requirements must be followed.

The principle investigator will distribute amendments and Amended CSP, if applicable, to each Investigator(s), who in turn is responsible for the distribution of these documents to the

staff at his or her centre. The distribution of these documents to the regulatory authority will be handled according to local practice.

7.5 Study agreements

The Investigator(s) at each centre must comply with all the terms, conditions, and obligations of the CSA for this study. In the event of any inconsistency between this CSP and the CSA, the CSP shall prevail.

7.6 Study timetable and end of study

Before a patient's enrolment in the study and any study-related procedures are undertaken the following should be fulfilled:

- A signed CSP and other agreements between the Principal Investigator and the study Site.
- An approval of the study by the Regional Ethical Committee (REC)
- An approval of the study by the regulatory authority.

The study will start as soon as all pre-study activities are completed and the regulatory authorities and Ethical Committee have approved the CSP. Planned study start is August 2012. Recruitment is expected to last for 2 years or until all patients are included. Recruitment will be competitive between centres. If a study sites does not manage to recruit the agreed number of patients within the given timeline, the Principle Investigator may decide to close the site. Estimated date of the last patient completing is September 2015. End of study is defined as Database Lock, (estimated as September 2015) which is the time point after which no patient will be exposed to study related activities.

8. ETHICS

8.1 Ethics review

The PI will provide IECs and Investigators with safety updates/reports according to local requirements.

The final CSP, including the final version of the ICF, must be approved or given a favourable opinion in writing by the REC as appropriate.

The Principal Investigator is responsible for informing the REC of any amendment to the CSP in accordance with local requirements.

Notifications of serious and unexpected adverse drug reactions will be provided to regulatory authority according to regulations and guidelines.

8.2 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH-GCP and the applicable regulatory requirements.

8.3 Informed consent

The Investigator(s) at each centre will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any procedure specifically for the study, including the following:

- Withholding or discontinuation of treatment
- Collection of blood and urine samples
- Completion of rating scales and/or questionnaires
- Physical examination

The Investigator(s) must store the original, signed ICF. A copy of the signed ICF should be given to the patient.

8.4 Patient data protection and storage

The Master ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, patients will authorise the collection, use and disclosure of their study data by the Investigator and by those persons who need that information for the purposes of the study.

The Master ICF will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer processed by the study group will be identified by randomisation code / study code.

The Master ICF will also explain that for data verification purposes, a regulatory authority, the REC or Norwegian Medicines Agency may require direct access to parts of the clinical records relevant to the study, including patients' medical history.

All documents of significance for the trial will be kept and stored for at least 15 years following database lock by the sponsor in accordance with the national regulation of 30. October 2009. Other regulations may warrant storage beyond 15 years.

Clinical patient records and CRF are stored locally on site. Following database lock, local data will be stored in accordance with prevailing local and National guidelines.

9. SAFETY ASSESSMENTS

9.1 Definitions

The definitions of adverse events (AEs), serious adverse events (SAEs) and other significant adverse events (OAEs) are given below. It is of the utmost importance that all staff involved in the study is familiar with the content of this section. The Principal Investigator is responsible for ensuring that this is accomplished.

9.1.1 Adverse Event (AE)

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

9.1.2 Serious Adverse Event (SAE)

An SAE is an AE occurring during any study phase (i.e., run-in, treatment, wash-out, follow-up), and at any dose of the products used in this study that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the above listed outcomes

The causality of SAE (i.e. their relationship to study treatment) will be assessed by the investigator(s), who in completing the relevant CRF must answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by XR-NTX?” For further guidance on the definition of a SAE and a guide to the

interpretation of the causality question, see Appendix B. Note that SAEs that could be associated with any study procedure should also be reported. For such events the causal relationship is implied as "yes".

9.1.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Adverse Reaction: all untoward and unintended responses to an investigational medicinal product related to any dose administered. In this study, the investigational medicinal product is XR-NTX which is administered in one dosage only (380 mg) every 4 weeks.

Unexpected Adverse Reaction: an adverse reaction, the nature or severity of which is not consistent with the applicable product information (SPC or IB) for the investigational medicinal product (XR-NTX).

Suspected Unexpected Serious Adverse Reaction (SUSAR) is an Unexpected Adverse Reaction that fulfills any of the below criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Causes a congenital abnormality or birth defect in pregnant patients
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

9.2 Recording of adverse events

The AEs recorded in this study will be classified using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Only AEs that appear or worsen following administration of the first dose of study medication until the end of the RCT period (12 Weeks/85 days) and are rated level 2 (medical intervention indicated) or higher on the CTCAE will be registered.

AEs will be reported on the appropriate sections of the CRF, whether or not considered related to the investigational product. This will include AEs spontaneously reported by the patient and/or observed by the investigator(s) or centre staff. At each visit, the patient will be asked non-specific and addiction-related questions on somatic health status based on the Europ-ASI section C. Patients will also be instructed to volunteer AEs noted at any time during the study. Post study AEs will not be actively sought, but must be reported on the appropriate sections of the CRF when the investigator is made aware of them.

For each AE the following must be recorded on the CRF:

- Description of the event
- Start and stop date
- Whether it constitutes a SAE or not
- Action taken with regard to the study drugs
- If the AE caused the patient to discontinue the study
- Causality (relationship to investigational product)
- Outcome

9.2.1 Expected Adverse Events

The following events are commonly occurring in the opioid dependent population and will only be registered as AEs related to a patient's participation in the trial following careful assessment by the investigator, delegate and/or PI of their relationship to the investigational medicinal product in particular or study participation in general: Dependence, abuse or use of any illicit substance or alcohol; tissue damage, infections or related problems resulting from the patients' self-injection of illicit drugs, e.g. infection with hepatitis, HIV, or tissue infections surrounding the injection site; intoxication on any substance or withdrawal from such; acute medical or psychiatric events/disorders resulting from intoxication and/or withdrawal or interaction with persons suffering such effects: e.g. head or other trauma due to DUI, trauma or tissue damage due to violent interaction with law enforcement and/or intoxicated persons, acute psychiatric ward admission due to stimulant- or withdrawal-induced psychoses, manic behaviour due to intoxication, withdrawal-related depressive symptoms, etc.; infections, trauma or tissue damage due to long-term use of substances, e.g. symptoms of starvation or malnourishment due to substance use, STDs due to prostitution or rape or psychiatric disease, liver damage or Korsakoff's psychosis due to long-term heavy alcohol use, abnormal weight loss or hair loss due to neglect of food intake, and any other condition overrepresented in the drug using demographic as determined by the investigator.

The investigator determines if the patients' symptoms are coherent with any of the above causes or should be registered as a study-related AE. Cases of doubt should be resolved by discussion with the site investigator, National Coordinating Investigator (PI) or delegate. Symptoms that fail to register as a study-related AE may still be registered as study outcomes and should be treated according to standard medical practice. Death due to substance overdose (OD) shall be registered as an SAE and reported to the regulatory authorities via the PI in accordance with current regulatory guidelines.

A full list of the AEs that are expected based on previous experience with the study drug can be found in Appendix B. In summary, common AEs are injection site reactions like buttock pain, while swelling, hardness, blisters, redness, abcesses, and tissue death surrounding the injection site are less common. AEs likely attributable to the naltrexone component in XR-

NTX include nausea, vomiting, muscle cramps, dizziness, sedation, decreased appetite, and an allergic form of pneumonia. Hepatic enzyme abnormalities have sometimes been observed when extreme doses of naltrexone have been used or the patient's hepatic health is severely reduced compared to normal levels.

9.2.2 Diagnosis

If a diagnosis of the patient's condition has been made, then the diagnosis should be recorded as the SAE or the AE if it warrants medical intervention (see Section 9.2). In instances of well-recognised symptoms, they can be recorded as the commonly used diagnosis (e.g., fever, runny nose, and cough can be recorded as "flu"). However, if a diagnosis of the patient's condition has not been made, or if the individual symptoms are not well recognised, then the individual symptoms should be recorded separately.

9.2.3 Causality

A causality assessment must be recorded for all AEs. The CRF asks the question, "In your medical judgement, is there a reasonable possibility that the event may have been caused by the investigational product XR-NTX?" If there is valid reason, once sources of common AEs seem unlikely (see Section 9.2.1) for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then this should be answered "yes". Otherwise, if no valid reason exists for suggesting a possible relationship, then this should be answered "no". If more than one AE is identified, a causality assessment must be made for each AE. For further guidance, see Appendix B.

9.2.4 Abnormal laboratory tests/vital signs

Individual CSP mandated laboratory and other safety-related test results should not be recorded as AEs unless they fulfil the criteria for a SAE or lead to discontinuation of treatment with study medication, see Section 3.3.6. These test results will be evaluated in the overall safety analysis. However, if an abnormal laboratory or other safety-related test result is associated with clinical signs or symptoms, the sign or symptom should be recorded as an AE while the associated test result is recorded in the appropriate CRF section.

9.2.5 Rating scales/patient-reported outcomes

Signs and symptoms revealed and recorded during the rating of any of the scales and inventories used in the study should not be reported as AEs, unless they fulfil a criterion for a SAE or lead to discontinuation of study treatment, see Section 3.3.6. An evaluation of the findings from the rating scales will be performed in the overall analysis.

However, if information about an AE on any PRO instrument is elicited, this may be recorded on the AE - CRF page following investigations as described in Section 9.2 of this CSP. If such an AE fulfils the definition of a SAE, it should be reported as described in Section 9.3.

9.2.6 Adverse event of Special Interest – substance-related overdose

All AEs relating to overdose from alcohol and/or illicit drugs will be carefully monitored. These include fatal overdose, non-fatal overdose as reported on the Europ-ASI, events of overdose-related suicide attempts.

9.2.7 Follow-up of ongoing adverse events

All AEs and SAEs, including those that are ongoing at the end of the study or at discontinuation, will be followed up, recorded and treated (if possible) until resolution or until the Investigator decides that no further follow-up is necessary. The requirement to follow-up is not intended to delay database lock or production of the CSR. Both these activities should proceed as planned with ongoing AEs if necessary.

9.2.8 Overdose of study medication

For the purposes of this study, an overdose is defined as a dose exceeding 24 mg buprenorphine-naloxone per day or XR-NTX at 3-5 times normal dosage per month.

Should an overdose (accidental or deliberate) occur, it must be reported in accordance with the procedures described in Section 9.3 regardless of whether the overdose was associated with any symptom or not. All symptoms associated with the overdose should be reported as AEs provided they fulfil the criteria for AEs as described in this section.

9.3 Reporting of serious adverse events (SAE)

Investigators and other site personnel must inform the principal investigator of any SAE that occurs in the course of the study **within 48 hours** (no later than the end of the next business day) of when he or she becomes aware of it.

SAE information will be entered as a mail to the principal investigator and also reported to investigators in charge at the other study sites. The investigator is responsible for completing the CRF as soon as possible, and must also report follow-up information on SAEs.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to the principal investigator **within 48 hours** as described above.

National Coordinating Investigator (PI) shall immediately, and at the latest seven days after learning of an unexpected and serious adverse reaction (SUSAR) that is fatal or life-threatening, send a report to the authorities in all the EEA countries concerned. Thereafter, relevant information about the further course of events shall be given within eight days. SUSARs are reported by the National Coordinating Investigator (PI) submitting a copy of the CIOMS form attached in Appendix D of this CSP.

National Coordinating Investigator (PI) shall immediately, and at the latest 15 days after learning of an unexpected and serious adverse reaction (SUSAR) that is not fatal or life-threatening, send a report to the authorities in all the EEA countries concerned.

Sponsor shall inform all investigators of the investigational medicinal product in question of suspected unexpected serious adverse reactions (SUSARs).

The manufacturer of the study drug with which the participant was treated will also be notified by the Principal Investigator of the SAE and any contact with relevant regulatory authorities.

SAEs notifications to the manufacturer of VIVITROL © (Alkermes) should be submitted to the Dr. Safety fax line at +1 (617) 494-5202. SAEs that are considered SUSARs within the VIVITROL© group only should be submitted on a per case basis to Alkermes at the time CIOMS forms are submitted to the Norwegian Authorities. SAEs within the VIVITROL© group only that do not meet the criteria for expedited reporting can be submitted either on a per case basis and will be included as part of a quarterly progress report to Alkermes.

9.3.1 Outcome Death

If the reason for discontinuation from the study is death, the event causing death should be reported as a SAE. Mortality is greatly elevated among opioid users compared to the normal population due to increased exposure to several potentially lethal practices. Increased mortality relative to the normal population is therefore expected in the study sample, and careful assessment of the available evidence by the National Coordinating Investigator (PI) is necessary in order to accurately determine the cause of death in each individual case. Death itself should be reported as the outcome on the appropriate CRF. Where the death is due to a combination of conditions, the investigator must decide on the primary cause of death and assign discontinuation to the appropriate category. The appropriate sections of the CRF should be completed for all conditions and reported to the principal investigator. The report should contain information regarding the co-involvement of disease, if appropriate, and incorporate information regarding the primary and secondary causes of death.

9.4 Procedures in case of emergency, overdose or pregnancy

9.4.1 Emergency contact procedure

In the case of a medical emergency, any member of the study team may be contacted. Their contact details are detailed in **Clinical Study Protocol Supplement 1**: Study Team Contacts in the Event of Emergency Situations, Overdose or Pregnancy. This supplement will be inserted to face this page in all printed copies of the protocol.

9.4.2 Procedures in case of medical emergency

The Principal Investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and should be reported as such, see Section 9.3.**

9.4.3 Procedures in case of overdose

For the purposes of this study, an overdose is defined as a dose exceeding the number of tablets specified for each day. Overdose should be reported and recorded as follows:

- Use of study medication in doses in excess of that specified in the CSP should not be recorded in the CRFs as an AE of 'Overdose' unless there are associated symptoms or signs
- An overdose without associated symptoms should not be recorded as an AE in the CRFs.
- An overdose with associated non-serious AEs should be recorded as the AE diagnosis/symptoms on the relevant AE forms in the CRFs.
- An overdose with associated SAEs should be recorded as the SAE diagnosis/symptoms on the relevant AE forms in the CRFs. If symptoms meeting the criteria for a SAE have occurred in association with the overdose, the case must be reported as a SAE, see Section 6.4.6.2.
- In all instances, the overdose substance must be stated and an assessment whether the overdose was accidental or intentional should be recorded. If the overdose was a suicide attempt, this fact should be clearly stated, see Section 9.6.

9.5 Procedures in case of pregnancy

Should pregnancy occur during the study, treatment with investigational product should be stopped and the patient should be discontinued from the study.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported in the CRF.

Any complications during pregnancy should be recorded as AEs and may constitute SAE if they fulfil the specified criteria for a SAE.

9.6 Procedures in case of suicide attempt or suicide

Suicide or suicide attempt, irrespective of method, but in connection with the use of investigational product, should be reported as an AE or SAE in accordance with the definition provided in Section 4.7. The event should be identified as suicide or suicide attempt, and the method of the suicide or the suicide attempt, should be provided.

All events of suicidality will be recorded in the CRF. These include events of suicide attempts, suicide ideation, completed suicides, and suicidal behaviour. The last category includes behavioural AEs or SAEs in which the investigator cannot rule out underlying suicidal thinking, e.g., a motor vehicle accident, or behaving in a dangerous or unsafe way, and other self-injurious behaviours.

Any patient who, based on the investigator's judgement, poses an imminent risk of suicide should be discontinued from the study, see Section 3.3.6.1 and 3.3.6.2. All efforts should be taken to minimise the risk of suicide.

10. REFERENCES

1. Leshner AI. Addiction is a brain disease, and it matters. Science. 1997;278(5335):45-7.

2. Emcdda. The state of the drugs problem in Europe. Lisbon: European Monitoring Centre for Drugs and Drug Addiction2008.

3. Unodc. World Drug Report. Vienna: United Nations Office on Drugs and Crime2008.

4. Who. Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence 2009.

5. Gowing L, Farrell M, Ali R, White JM. Alpha2-adrenergic agonists for the management of opioid withdrawal. Cochrane Database SystRev. 2009(2):CD002024.

6. Gowing L, Ali R, White JM. Buprenorphine for the management of opioid withdrawal. GowingLinda, AliRobert, WhiteJasonMBuprenorphineforthe managementof opioidwithdrawalCochraneDatabaseof SystematicReviews: Reviews2009Issue3 JohnWiley& Sons, LtdChichester, UK DOI: 101002/14651858CD002025pub4. 2009.

7. Unnithan S, Gossop M, Strang J. Factors associated with relapse among opiate addicts in an out-patient detoxification programme. BrJ Psychiatry. 1992;161:654-7.

8. Chutuape MA, Jasinski DR, Fingerhood MI, Stitzer ML. One-, three-, and six-month outcomes after brief inpatient opioid detoxification. American Journal of Drug and Alcohol Abuse. 2001;27(1):19-44.

9. Strang J, McCambridge J, Best D, Beswick T, Bearn J, Rees S, et al. Loss of tolerance and overdose mortality after inpatient opiate detoxification: follow up study. BMJ. 2003;326(7396):959-60.

10. Simpson DD, Sells SB. Opioid Addiction and Treatment. Malabar, FL: Robert E. Krieger Publishing Co.; 1990.

11. Gossop M, Marsden J, Stewart D, Kidd T. The National Treatment Outcome Research Study (NTORS): 4-5 year follow-up results. Addiction. 2003;98(3):291-303.

12. Flynn PM, Joe GW, Broome KM, Simpson DD, Brown BS. Recovery from opioid addiction in DATOS. J Subst Abuse Treat. 2003 Oct;25(3):177-86.

13. Teesson M, Ross J, Darke S, Lynskey M, Ali R, Ritter A, et al. One year outcomes for heroin dependence: findings from the Australian Treatment Outcome Study (ATOS). Drug and Alcohol Dependence. 2006;83(2):174-80.

14. Ravndal E, Amundsen EJ. Mortality among drug users after discharge from inpatient treatment: An 8-year prospective study. Drug and Alcohol Dependence. 2009.

15. Ward J, Hall W, Mattick RP. Role of maintenance treatment in opioid dependence. Lancet. 1999;353(9148):221-6.

16. Buster MC, van Brussel GH, van den Brink W. An increase in overdose mortality during the first 2 weeks after entering or re-entering methadone treatment in Amsterdam. Addiction. 2002 Aug;97(8):993-1001.

17. Bao YP, Liu ZM, Epstein DH, Du C, Shi J, Lu L. A meta-analysis of retention in methadone maintenance by dose and dosing strategy. Am J Drug Alcohol Abuse. 2009;35(1):28-33.

18. Faggiano F, Vigna-Taglianti F, Versino E, Lemma P. Methadone maintenance at different dosages for opioid dependence. Cochrane Database Syst Rev. 2003(3):CD002208.

19. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. CochraneDatabaseSystRev. 2003(2):CD002209.

20. Amato L, Davoli M, Perucci A, Ferri M, Faggiano F, Mattick P. An overview of systematic reviews of the effectiveness of opiate maintenance therapies: available evidence to inform clinical practice and research. Journal of Substance Abuse Treatment. 2005;28(4):321-9.

21. Marsch LA. The efficacy of methadone maintenance interventions in reducing illicit opiate use, HIV risk behavior and criminality: a meta-analysis. Addiction. 1998;93(4):515-32.

22. Caplehorn JR, Dalton MS, Cluff MC, Petrenas AM. Retention in methadone maintenance and heroin addicts' risk of death. Addiction. 1994 Feb;89(2):203-9.

23. Gossop M, Marsden J, Stewart D, Treacy S. Outcomes after methadone maintenance and methadone reduction treatments: two-year follow-up results from the National Treatment Outcome Research Study. Drug Alcohol Depend. 2001 May 1;62(3):255-64.

24. Skeie I, Brekke M, Lindbaek M, Waal H. Somatic health among heroin addicts before and during opioid maintenance treatment: a retrospective cohort study. BMC Public Health. 2008;8:43.

25. Clausen T, Anchersen K, Waal H. Mortality prior to, during and after opioid maintenance treatment (OMT): a national prospective cross-registry study. Drug and Alcohol Dependence. 2008;94(1-3):151-7.

26. Magura S, Rosenblum A. Leaving methadone treatment: lessons learned, lessons forgotten, lessons ignored. Mount Sinai Journal of Medicine. 2001;68(1):62-74.

27. Ehret GB, Voide C, Gex-Fabry M, Chabert J, Shah D, Broers B, et al. Drug-induced long QT syndrome in injection drug users receiving methadone: high frequency in hospitalized patients and risk factors. Arch Intern Med. 2006 Jun 26;166(12):1280-7.

28. Maremmani I, Pacini M, Cesaroni C, Lovrecic M, Perugi G, Tagliamonte A. QTc interval prolongation in patients on long-term methadone maintenance therapy. Eur Addict Res. 2005;11(1):44-9.

29. Anchersen K, Clausen T, Gossop M, Hansteen V, Waal H. Prevalence and clinical relevance of corrected QT interval prolongation during methadone and buprenorphine treatment: a mortality assessment study. Addiction. 2009;104(6):993-9.

30. Walsh SL, Preston KL, Bigelow GE, Stitzer ML. Acute administration of buprenorphine in humans: partial agonist and blockade effects. JPharmacolExpTher. 1995;274(1):361-72.

31. Dollery C. Therapeutic Drugs. Toronto: Churchill Livingstone; 1999.

32. Lewis JW. Buprenorphine. Drug and Alcohol Dependence. 1985;14(3-4):363-72.

33. Johnson RE, Cone EJ, Henningfield JE, Fudala PJ. Use of buprenorphine in the treatment of opiate addiction. I. Physiologic and behavioral effects during a rapid dose induction. Clinical Pharmacology and Therapeutics. 1989;46(3):335-43.

34. Boysen K, Hertel S, Chraemmer-Jorgensen B, Risbo A, Poulsen NJ. Buprenorphine antagonism of ventilatory depression following fentanyl anaesthesia. Acta AnaesthesiolScand. 1988;32(6):490-2.

35. Kuhlman JJ, Jr., Lalani S, Magluilo J, Jr., Levine B, Darwin WD. Human pharmacokinetics of intravenous, sublingual, and buccal buprenorphine. JAnalToxicol. 1996;20(6):369-78.

36. Cone EJ, Dickerson S, Darwin WD, Fudala PJ, Johnson RE. Elevated drug saliva levels suggests a depot-like effect in subjects treated with sublingual buprenorphine. In: Harris L, editor.: The College on the Problems of Drug Dependence; 1991.

37. Ahmadi J, Babaee-Beigi M, Alishahi M, Maany I, Hidari T. Twelve-month maintenance treatment of opium-dependent patients. Journal of Substance Abuse Treatment. 2004;26(1):363-6.

38. Johnson RE, Eissenberg T, Stitzer ML, Strain EC, Liebson IA, Bigelow GE. A placebo controlled clinical trial of buprenorphine as a treatment for opioid dependence. Drug and Alcohol Dependence. 1995;40(1):17-25.

39. Kakko J, Svanborg KD, Kreek MJ, Heilig M. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. Lancet. 2003;361(9358):662-8.

40. Krook AL, Brors O, Dahlberg J, Grouff K, Magnus P, Roysamb E, et al. A placebo-controlled study of high dose buprenorphine in opiate dependents waiting for medication-assisted rehabilitation in Oslo, Norway. Addiction. 2002;97(5):533-42.

41. Ling W, Charuvastra C, Collins JF, Batki S, Brown LS, Jr., Kintaudi P, et al. Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial. Addiction. 1998;93(4):475-86.

42. Pani PP, Maremmani I, Pirastu R, Tagliamonte A, Gessa GL. Buprenorphine: a controlled clinical trial in the treatment of opioid dependence. Drug and Alcohol Dependence. 2000;60(1):39-50.

43. Schottenfeld RS, Chawarski MC, Pakes JR, Pantalon MV, Carroll KM, Kosten TR. Methadone versus buprenorphine with contingency management or performance feedback for cocaine and opioid dependence. American Journal of Psychiatry. 2005;162(2):340-9.

44. Uehlinger C, Deglon J, Livoti S, Petitjean S, Waldvogel D, Ladewig D. Comparison of buprenorphine and methadone in the treatment of opioid dependence. Swiss multicentre study. European Addiction Research. 1998;4 Suppl 1:13-8.

45. Ahmadi J. Methadone versus buprenorphine maintenance for the treatment of heroin-dependent outpatients. Journal of Substance Abuse Treatment. 2003;24(3):217-20.

46. Fischer G, Gombas W, Eder H, Jagsch R, Peternell A, Stuhlinger G, et al. Buprenorphine versus methadone maintenance for the treatment of opioid dependence. Addiction. 1999;94(9):1337-47.

47. Johnson RE, Jaffe JH, Fudala PJ. A controlled trial of buprenorphine treatment for opioid dependence. JAMA: The Journal of the American Medical Association. 1992;267(20):2750-5.

48. Kosten TR, Schottenfeld R, Ziedonis D, Falcioni J. Buprenorphine versus methadone maintenance for opioid dependence. Journal of Nervous and Mental Disease. 1993;181(6):358-64.

49. Ling W, Wesson DR, Charuvastra C, Klett CJ. A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. Archives of General Psychiatry. 1996;53(5):401-7.

50. Mattick RP, Ali R, White JM, O'Brien S, Wolk S, Danz C. Buprenorphine versus methadone maintenance therapy: a randomized double-blind trial with 405 opioid-dependent patients. Addiction. 2003;98(4):441-52.

51. Neri S, Bruno CM, Pulvirenti D, Malaguarnera M, Italiano C, Mauceri B, et al. Randomized clinical trial to compare the effects of methadone and buprenorphine on the immune system in drug abusers. Psychopharmacology (Berl). 2005;179(3):700-4.

52. Petitjean S, Stohler R, Deglon JJ, Livoti S, Waldvogel D, Uehlinger C, et al. Double-blind randomized trial of buprenorphine and methadone in opiate dependence. Drug and Alcohol Dependence. 2001;62(1):97-104.

53. Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Comparison of buprenorphine and methadone in the treatment of opioid dependence. American Journal of Psychiatry. 1994;151(7):1025-30.

54. Mattick RP, Kimber J, Breen C, Davoli M. Buprenophine maintenance versus placebo or methadone maintenance for opioid dependence (Review). Cochrane Database of Systematic Reviews. 2008(2).

55. Fatseas M, Auriacombe M. Why buprenorphine is so successful in treating opiate addiction in France. CurrPsychiatry Rep. 2007;9(5):358-64.

56. Thirion X, Lapierre V, Micallef J, Ronfle E, Masut A, Pradel V, et al. Buprenorphine prescription by general practitioners in a French region. Drug and Alcohol Dependence. 2002;65(2):197-204.

57. Auriacombe M, Fatseas M, Dubernet J, Daulouede JP, Tignol J. French field experience with buprenorphine. American Journal on Addictions. 2004;13 Suppl 1:S17-S28.

58. Bouchez J, Beauverie P, Touzeau D. Substitution with buprenorphine in methadone- and morphine sulfate-dependent patients. Preliminary results. European Addiction Research. 1998;4 Suppl 1:8-12.

59. Kayemba-Kay's S, Laclyde JP. Buprenorphine withdrawal syndrome in newborns: a report of 13 cases. Addiction. 2003;98(11):1599-604.

60. Bell J, Byron G, Gibson A, Morris A. A pilot study of buprenorphine-naloxone combination tablet (Suboxone) in treatment of opioid dependence. Drug and Alcohol Review. 2004;23(3):311-7.

61. Alho H, Sinclair D, Vuori E, Holopainen A. Abuse liability of buprenorphine-naloxone tablets in untreated IV drug users. Drug and Alcohol Dependence. 2007;88(1):75-8.

62. O'Brien CP, Greenstein RA, Mintz J, Woody GE. Clinical experience with naltrexone. American Journal of Drug and Alcohol Abuse. 1975;2(3-4):365-77.

63. Gonzalez JP, Brogden RN. Naltrexone. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of opioid dependence. Drugs. 1988;35(3):192-213.

64. Kunoe N, Lobmaier P, Vederhus JK, Hjerkinn B, Hegstad S, Gossop M, et al. Retention in naltrexone implant treatment for opioid dependence. Drug Alcohol Depend. 2010 Sep 1;111(1-2):166-9.

65. Narcotic Antagonists: Naltrexone progress report. In: Julius D, Renault P, editors.1976.

66. Washton AM, Pottash AC, Gold MS. Naltrexone in addicted business executives and physicians. Journal of Clinical Psychiatry. 1984;45(9 Pt 2):39-41.

67. Cornish JW, Metzger D, Woody GE, Wilson D, McLellan AT, Vandergrift B, et al. Naltrexone pharmacotherapy for opioid dependent federal probationers. Journal of Substance Abuse Treatment. 1997;14(6):529-34.

68. Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. Cochrane Database of Systematic Reviews. 2006;Issue 1(1).

69. Krupitsky EM, Zvartau EE, Masalov DV, Tsoi MV, Burakov AM, Egorova VY, et al. Naltrexone for heroin dependence treatment in St. Petersburg, Russia. Journal of Substance Abuse Treatment. 2004;26(4):285-94.

70. San L, Pomarol G, Peri JM, Olle JM, Cami J. Follow-up after a six-month maintenance period on naltrexone versus placebo in heroin addicts. BrJ Addict. 1991;86(8):983-90.

71. Shufman EN, Porat S, Witztum E, Gandacu D, Bar-Hamburger R, Ginath Y. The efficacy of naltrexone in preventing reabuse of heroin after detoxification. Biological Psychiatry. 1994;35(12):935-45.

72. Ladewig D. [Naltrexone--an effective aid in the psychosocial rehabilitation process of former opiate dependent patients]. TherUmsch. 1990;47(3):247-50.

73. Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. Cochrane Database Syst Rev. 2011;4:CD001333.

74. Willette RE. The development of sustained action preparations of narcotic antagonists. NIDA Research Monograph. 1978;19:333-9.

75. Lobmaier P, Kornor H, Kunoe N, Bjorndal A. Sustained-release naltrexone for opioid dependence. Cochrane Database of Systematic Reviews. 2008;Issue 2(2).

76. Comer SD, Sullivan MA, Yu E, Rothenberg JL, Kleber HD, Kampman K, et al. Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. Archives of General Psychiatry. 2006;63(2):210-8.

77. Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. Lancet. 2011 Apr 30;377(9776):1506-13.

78. Kunoe N, Lobmaier P, Vederhus JK, Hjerkinn B, Hegstad S, Gossop M, et al. Naltrexone implants after in-patient treatment for opioid dependence: randomised controlled trial. Br J Psychiatry. 2009;194(6):541-6.

79. Hulse GK, Morris N, Arnold-Reed D, Tait RJ. Improving clinical outcomes in treating heroin dependence: randomized, controlled trial of oral or implant naltrexone. Archives of General Psychiatry. 2009;66(10):1108-15.

80. O'Brien B, Cody C. Analgesia and sedation in the presence of a naltrexone implant: a novel pharmacological challenge. EurJ EmergMed. 2006;13(5):315-6.

81. Sinha R, Easton C. Substance abuse and criminality. Journal of the American Academy of Psychiatry and the Law Online. 1999;27(4):513-26.

82. Fazel S, Bains P, Doll H. Substance abuse and dependence in prisoners: a systematic review. Addiction. 2006;101(2):181-91.

83. Emcdda. Drugs and crime: a complex relationship. Lisbon: European Monitoring Centre for Drugs and Drug Addiction2007.

84. Mumola CJ, Karberg JC. Drug Use and Dependence, State and Federal Prisoners, 2004: U.S. Department of Justice Office of Justice Programs Bureau of Justice Statistics2006.

85. Friestad C, Hansen IL. Mental health problems among prison inmates: the effect of welfare deficencies, drug use and self-efficacy. Journal of Scandinavian Studies in Criminology and Crime Prevention. 2005;6:183-96.

86. Ødegård E. Drug and alcohol problems among Norwegian inmates. Nordisk alkohol- & narkotikatidskrift (NAT). 2008;25(3):21-37.

87. Plourde C, Brochu S. Drugs in prison: a break in the pathway. SubstUse Misuse. 2002;37(1):47-63.

88. Shewan D, Gemmell M, Davies JB. Prison as a Modifier of Drug Using Behaviour. Addiction Research & Theory. 1994;2(2):203-15.

89. Simpler AH, Langhinrichsen-Rohling J. Substance use in prison: How much occurs and is it associated with psychopathology? Addiction Research & Theory. 2005;13(5):503-11.

90. Dolan KA, Shearer J, White B, Zhou J, Kaldor J, Wodak AD. Four-year follow-up of imprisoned male heroin users and methadone treatment: mortality, re-incarceration and hepatitis C infection. Addiction. 2005;100(6):820-8.

91. Milloy MJ, Wood E, Small W, Tyndall M, Lai C, Montaner J, et al. Incarceration experiences in a cohort of active injection drug users. Drug Alcohol Rev. 2008:1-7.

92. Lines R, Jurgens R, Betteridge G, Stover H, Laticevschi D, Nelles J. Prison needle exchange: lessons from a comprehensive review of international evidence and experience. Montreal: Canadian HIV/AIDS Legal Network2006.

93. Kinlock TW, Battjes RJ, Schwartz RP. A novel opioid maintenance program for prisoners: preliminary findings. Journal of Substance Abuse Treatment. 2002;22(3):141-7.

94. Nurco DN, Hanlon TE, Kinlock TW. Recent research on the relationship between illicit drug use and crime. Behavioral Sciences & the Law. 1991;9(3):221-42.

95. Seaman SR, Brettle RP, Gore SM. Mortality from overdose among injecting drug users recently released from prison: database linkage study. British Medical Journal. 1998;316(7129):426-8.

96. Ødegård E, Amundsen EJ, Kielland KB, Kristoffersen R. The contribution of imprisonment and release to fatal overdose among a cohort of Norwegian drug abusers. Addiction Research & Theory. 2010;18(1):51-8.

97. Cropsey KL, Villalobos GC, St Clair CL. Pharmacotherapy treatment in substance-dependent correctional populations: a review. Substance use & misuse. 2005;40(13-14):1983-8.

98. Pearson FS, Lipton DS. A Meta-Analytic Review of the Effectiveness of Corrections-Based Treatments for Drug Abuse. The Prison Journal. 1999;79(4):384-410.

99. Perry A, Coulton S, Glanville J, Godfrey C, Lunn J, McDougall C, et al. Interventions for drug-using offenders in the courts, secure establishments and the community. Cochrane Database of Systematic Reviews. 2006;Issue 3(3).

100. Prendergast ML, Hall EA, Wexler HK, Melnick G, Cao Y. Amity Prison-Based Therapeutic Community: 5-Year Outcomes. The Prison Journal. 2004;84(1):36-60.

101. Johansen TH. Stifinner'n - en rus- og rehabiliteringsavdeling innenfor Oslo fengsel sett i lys av Lysgaards kollektivteori og Goffmans begrepsapparat: University of Oslo, Department of Sociology and Human Geography; 2005.

102. Lobmaier PP, Kunoe N, Gossop M, Katevoll T, Waal H. Naltrexone Implants Compared to Methadone: Outcomes Six Months after Prison Release. European Addiction Research. 2010;16(3):139-45.

103. Lobmaier PP, Kun+¸e N, Waal H. Treatment research in prison: Problems and solutions in a randomized trial. Addiction Research & Theory. 2010;18(1):1-13.

104. Shearer J, Wodak AD, Dolan KA. Evaluation of a prison-based naltrexone program. International Journal of Prisoner Health. 2007;3(3):214-24.

105. Brahen LS, Henderson RK, Capone T, Kordal N. Naltrexone treatment in a jail work-release program. Journal of Clinical Psychiatry. 1984;45(9 Pt 2):49-52.

106. Chan KY. The Singapore naltrexone community-based project for heroin addicts compared with drugfree community-based program: the first cohort. Journal of Clinical Forensic Medicine. 1996;3(2):87-92.

107. Binswanger IA, Stern MF, Deyo RA, Heagerty PJ, Cheadle A, Elmore JG, et al. Release from prison - a high risk of death for former inmates. New England Journal of Medicine. 2007;356(2):157-65.

108. Marzo JN, Rotily M, Meroueh F, Varastet M, Hunault C, Obradovic I, et al. Maintenance therapy and 3-year outcome of opioid-dependent prisoners: a prospective study in France (2003-06). Addiction. 2009;104(7):1233-40.

109. Dolan KA, Shearer J, Macdonald M, Mattick RP, Hall W, Wodak AD. A randomised controlled trial of methadone maintenance treatment versus wait list control in an Australian prison system. Drug and Alcohol Dependence. 2003;72(1):59-65.

110. Stover H, Hennebel LC, Casselman J. Substitution Treatment in European Prisons - A study of policies and practices of substitution treatment in prisons in 18 European countries: The European Network of Drug Services in Prison, Cranstoun Drug Services; 2004.

111. Larney S, Dolan K. A literature review of international implementation of opioid substitution treatment in prisons: equivalence of care? European Addiction Research. 2009;15(2):107-12.

112. Stallwitz A, Stover H. The impact of substitution treatment in prisons - a literature review. International Journal of Drug Policy. 2007;18(6):464-74.

113. Undp. Fighting climate change: Human solidarity in a divided world2009.

114. Dole VP, Robinson JW, Orraca J, Towns E, Searcy P, Caine E. Methadone treatment of randomly selected criminal addicts. NEnglJ Med. 1969;280(25):1372-5.

115. Tomasino V, Swanson AJ, Nolan J, Shuman HI. The Key Extended Entry Program (KEEP): a methadone treatment program for opiate-dependent inmates. Mount Sinai Journal of Medicine. 2001;68(1):14-20.

116. Kinlock TW, Gordon MS, Schwartz RP, Fitzgerald TT, O'Grady KE. A randomized clinical trial of methadone maintenance for prisoners: results at 12 months postrelease. J SubstAbuse Treat. 2009;37(3):277-85.

117. Pavot W, Diener E, Suh E. The Temporal Satisfaction With Life Scale. 1998.

118. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med. 2001 Jul;2(4):297-307.

119. Miller WR, Tonigan JS. Assessing drinkers' motivations for change: The Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES). Psychology of Addictive Behaviors. 1996;10(2):81-9.

120. Sullivan MA, Vosburg SK, Comer SD. Depot naltrexone: antagonism of the reinforcing, subjective, and physiological effects of heroin. Psychopharmacology (Berl). 2006;189(1):37-46.

121. Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory. BehavSci. 1974;19(1):1-15.

122. McLellan AT, Kushner H, Metzger D, Peters R, Smith I, Grissom G, et al. The Fifth Edition of the Addiction Severity Index. Journal of Substance Abuse Treatment. 1992;9(3):199-213.

123. Sheehan DV. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. The Journal of clinical psychiatry. 1998;59 Suppl 20:22-33.

124. Sobell LC, Sobell MB. Timeline follow-back: a technique for assessing self-reported alcohol consumption. In: Allen JP, Litten RZ, editors. Measuring Alcohol Consumption: Psychosocial and Biochemical Methods Totowa, NJ: Human Press; 1992. p. 41-72.

AMENDMENT 2 to Clinical Study Protocol for the study 'Optimal Prevention of Overdose Deaths and Opioid Relapse Following Discharge: A Multi-Center RCT (EudraCT Code 2011-002858-31) Edition 3C (June 12th 2012).

Date: Mar 21st 2013.

This amendment introduces two changes to the above mentioned CSP:

1) Replaces biological sampling of drug use using saliva / oral fluid samples with standard urine drug screen sampling.
2) Cancels plans to verify patients' naltrexone levels by comparing levels of naltrexone and 6-beta naltrexone in oral fluid and in voluntary blood samples.

This deletes or substitutes or changes the following sections of the aforementioned CSP:

TEXT EDITS – "ORAL FLUID" or "SALIVA" is substituted with "URINE" in:

Synopsis

p. 5: *"Abstinence from illicit opioids assessed by the absence of non-study opioid agonists or their metabolites in oral fluid and/or patient-reported use of such opioids during the first 12 weeks of the study"* is edited to read

"Abstinence from illicit opioids assessed by the absence of non-study opioid agonists or their metabolites in urine drug screens and/or patient-reported use of such opioids during the first 12 weeks of the study."

TABLE OF CONTENTS

p. 11: "Oral fluid/saliva samples as outcome measures …….. 56"

TABLE 1a)

p. 37: *"Saliva sample (drugs, NTX)"* is edited to *"Urine sample (drugs)"*

TABLE 1b)

p. 38: *"Saliva sample (drugs, NTX)"* is edited to *"Urine sample (drugs)"*

TABLE 1c)

p. 39: *"Saliva sample (drugs, NTX)"* is edited to *"Urine sample (drugs)"*

2.1. Primary objective

p. 30: *"…assessed by the number of opioid free oral fluid samples during the RCT period. Variables supporting the primary objective are:*

Between-group differences on opioid abstinence from randomisation to Week 12 as measured by proportion of weekly oral fluid samples positive for non- study opioid agonists or their metabolites" is edited to read

"…assessed by the number of opioid free urine drug screen samples during the RCT period. Variables supporting the primary objective are:

Between-group differences on opioid abstinence from randomisation to Week 12 as measured by proportion of weekly urine drug screen samples positive for non- study opioid agonists or their metabolites"

2.2 Secondary objective E2

p. 31: *"- the number of oral fluid samples positive for illicit, non-opioid substances or their metabolites from Week 1-12 in the study."* is edited to read *"- the number of urine drug screen*

samples positive for illicit, non-opioid substances or their metabolites from Week 1-12 in the study."

3.1. Overall study design and flow chart

p. 34: *"An evaluable patient is defined as a patient who received at least one dose of study treatment and who has one valid assessment at randomisation and at least one valid oral fluid or drug use self-report assessment after randomisation."* is edited to read "*An evaluable patient is defined as a patient who received at least one dose of study treatment and who has one valid assessment at randomisation and at least one valid urine drug test or drug use self-report assessment after randomisation."*

p. 34: *"a) Number of weekly oral fluid samples (range 1-12) negative for opioids or their metabolites.."* is edited to read *"a) Number of weekly urine drug screen samples (range 1-12) negative for opioids or their metabolites.."*

4.1. Primary variable

p. 50: *"a) the differences between medication groups in proportion of opioid-free oral fluid samples from randomization to Week 12"* is edited to read *"a) the differences between medication groups in proportion of opioid-free urine drug screen samples from randomization to Week 12"*

4.5 Pharmacokinetic measurements and variables

p. 54: *"saliva samples are used to collect information on recent drug use and naltrexone levels, ideally with a blood sample (5 mg) taken simultaneously to validate the saliva naltrexone analysis."* is edited to read *"urine samples are used to collect information on recent drug use."*

4.6.1 Oral fluid/saliva measures as variables

p.56-57: *"The outcome from the oral fluid samples will be measured as dichotomous outcomes, e.g. above or below a clinically significant threshold or the level of detection (LOD) for each substance. The primary outcome is the number of opioid-free oral fluid samples during Weeks 1-4, 5-8, 9-12, or 1-12: The number of oral fluid samples negative for non-study opioids or their metabolites will be subtracted from the total number of samples (n=12) to yield a proportion of negative samples. Other substances may be analysed as secondary outcomes in a similar manner. For XR-NTX patients, analyses will include measurements of levels of naltrexone or metabolites that will be compared to the expected dosage trajectory and/or blood samples taken concurrently with one or more saliva samples."* is edited to read

"The outcome from the urine drug screen samples will be measured as dichotomous outcomes, e.g. above or below a clinically significant threshold or the level of detection (LOD) for each substance. The primary outcome is the number of opioid-free urine drug screen samples during Weeks 1-4, 5-8, 9-12, or 1-12: The number of urine drug screen samples negative for non-study opioids or their metabolites will be subtracted from the total number of samples (n=12) to yield a proportion of negative samples. Other substances may be analysed as secondary outcomes in a similar manner."

6.2.1 Primary objective, hypotheses, and outcome variables

p. 64: *"The primary objective of this study is to evaluate the effectiveness of XR-NTX 380 mg/month versus buprenorphine-naloxone 8-24 mg/day as part of "treatment as usual", assessed by the number of opioid free oral fluid samples during the treatment period from randomization to Week 12.*

The primary hypotheses are as follows:

- *XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in the mean number of oral fluid samples negative for opioid agonists (other than study drug) or their metabolites from randomization until Week 12."* is edited to read
"The primary objective of this study is to evaluate the effectiveness of XR-NTX 380 mg/month versus buprenorphine-naloxone 8-24 mg/day as part of "treatment as usual", assessed by the number of opioid free urine drug samples during the treatment period from randomization to Week 12.
The primary hypotheses are as follows:
- *XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in the mean number of urine drug screen samples negative for opioid agonists (other than study drug) or their metabolites from randomization until Week 12."*

6.2.2. Other secondary objectives: Effectiveness

p. 65: *"XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in reducing non-opioid substance use as measured by the number of oral fluid samples positive for illicit, non-opioid substances or their metabolites from Week 1-12 in the study or in self-reported use of (or abstinence from) non-opioid substances including cocaine, amphetamines, benzodiazepines, alcohol, cannabis, and hallucinogenic drugs (e.g. LSD, MDMA, GHB)."* is edited to read
"XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in reducing non-opioid substance use as measured by the number of urine drug samples positive for illicit, non-opioid substances or their metabolites from Week 1-12 in the study or in self-reported use of (or abstinence from) non-opioid substances including cocaine, amphetamines, benzodiazepines, alcohol, cannabis, and hallucinogenic drugs (e.g. LSD, MDMA, GHB)."

6.4.2 Multiplicity

p. 69: *"First the primary outcome variable the number of opoid free saliva samples from randomisation to Week 12 will be tested for the naltrexone versus the suboxone group."* is edited to read
"First the primary outcome variable the number of opoid free urine samples from randomisation to Week 12 will be tested for the naltrexone versus the suboxone group."

6.4.3 Primary variable

p. 69: *"An analysis of variance (ANOVA) model for between-groups differences at Week 12 in the number of opioid-positive oral fluid samples will be used."* is edited to read *"An analysis of variance (ANOVA) model for between-groups differences at Week 12 in the number of opioid-positive urine drug screen samples will be used."*

6.4.5.1 Non-opioid substance use

p. 70: *"Response and remission at Week 12, defined from whichever is reported earliest in the oral fluid samples and/or TLFB, will be analysed utilising logistic regression or ANOVA models."* is edited to read *"Response and remission at Week 12, defined from whichever is reported earliest in the urine drug samples and/or TLFB, will be analysed utilising logistic regression or ANOVA models."*

6.5 Determination of sample size

p. 73: *"The sample size calculation in this exploratory study was done to model the event that XR- NTX demonstrates superior effectiveness over buprenorphine-naloxone with respect to the primary outcome variable, differences in opioid-negative oral fluid samples from randomisation to Week 12 – a total of 12 oral fluid samples."*
is edited to read *"The sample size calculation in this exploratory study was done to model the*

event that XR- NTX demonstrates superior effectiveness over buprenorphine-naloxone with respect to the primary outcome variable, differences in opioid-negative urine drug samples from randomisation to Week 12 – a total of 12 urine drug samples."

DELETED – Sentences or sections with "ORAL FLUID" or "SALIVA" or detailing plans for pharmacokinetics testing or oral fluid sampling:
Synopsis

p. 6: **"- Pharmacokinetic**
"Patients with detectable quantities of study drug in oral fluid"

NOTE: ANY AND ALL TEXT IN THE FOLLOWING SECTIONS IS DELETED AND CONSIDERED NOT APPLICABLE TO THIS STUDY:

4.5. Pharmacokinetic measurements and variables including subsections 4.5 (4.5, 4.5.1, 4.5.1.1, 4.5.1.2, 4.5.1.3, 4.5.2) pp. 54 to pp 55
4.8 Volume of blood sampling and handling of biological samples
p. 62
p. 67: **6.2.2.5 Other secondary objectives: Pharmacokinetics**
p. 72: **6.4.7 Pharmacokinetics**

Oslo, Aug 26th 2013

Protocol amendment NO 4 to 'Optimal Prevention of Overdose Deaths and Opioid Relapse Following Discharge: A Multi-Center RCT' (EudraCT 2011-002858-31)

Changes introduced in this amendment and their rationale:

A. Patients who wish to switch to XR-NTX onwards will enter a washout-period of up to 2 weeks (14 days) following the Week 12 interview. The Washout period is introduced in order to prevent data from the buprenorphine-naloxone group (arm B) during the 12-Week RCT being biased by influence from detoxification-related events and symptoms, e.g. withdrawal symptoms. Patients wishing to commence XR-NTX after the 12-Week RCT will be advised to not commence detoxification until after the Week 12 visit & interview. Regular Week / Visit counts are paused during the Washout period and recommence once XR-NTX is administered at the end of detoxification.

B. Patients who experience 'force majeure' type events between randomization and administration of study medication are allowed five (n=5) extra working days aka 'grace days' during which they re-align themselves with this CSP and the instructions of site personnel. The grace days are introduced in order to not allow force majeure-type events to result in study drop-out during randomization and administration of study drug. Force majeure will be defined as any serious circumstance study personnel determine to be beyond the patient's control. E.g. death of a close relative, natural disasters, intermittent serious illness. Under special circumstances determined by the investigator, the number of grace days may be extended if deemed necessary to prevent patient drop-out. Week 1 will commence once the patient has received the first dose of study drug and has been discharged in a regular manner from a controlled environment.

Sections of the original CSP (version 3C) changed, modified, or annulled by amendment 4A:

Sections of the original CSP (version 3C) changed, modified, or annulled by amendment 4B:

Oslo, Aug 26th 2013

Protocol amendment NO 4 to 'Optimal Prevention of Overdose Deaths and Opioid Relapse Following Discharge: A Multi-Center RCT' (EudraCT 2011-002858-31)

Changes introduced in this amendment and their rationale:

A. Patients who wish to switch to XR-NTX onwards will enter a washout-period of up to 2 weeks (14 days) following the Week 12 interview. The Washout period is introduced in order to prevent data from the buprenorphine-naloxone group (arm B) during the 12-Week RCT being biased by influence from detoxification-related events and symptoms, e.g. withdrawal symptoms. Patients wishing to commence XR-NTX after the 12-Week RCT will be advised to not commence detoxification until after the Week 12 visit & interview. Regular Week / Visit counts are paused during the Washout period and recommence once XR-NTX is administered at the end of detoxification.

B. Patients who experience 'force majeure' type events between randomization and administration of study medication are allowed five (n=5) extra working days aka 'grace days' during which they re-align themselves with this CSP and the instructions of site personnel. The grace days are introduced in order to not allow force majeure-type events to result in study drop-out during randomization and administration of study drug. Force majeure will be defined as any serious circumstance study personnel determine to be beyond the patient's control. E.g. death of a close relative, natural disasters, intermittent serious illness. Under special circumstances determined by the investigator, the number of grace days may be extended if deemed necessary to prevent patient drop-out. Week 1 will commence once the patient has received the first dose of study drug and has been discharged in a regular manner from a controlled environment.

Sections of the original CSP (version 3C) changed, modified, or annulled by amendment 4A:

Sections of the original CSP (version 3C) changed, modified, or annulled by amendment 4B:

Oslo, Feb 10th 2015,

Amendment 7 to protocol 'Optimal Prevention of Overdose Deaths and Relapse following Discharge: A Multi-Center RCT': statistical modifications.

This amendment introduces modifications to the statistical analysis sections of the protocol in order for analyses to remain up-to-date with developments in statistical analysis since the original text was written in 2010.

This includes:

- Edits and adjustments to analyses to increase concordance with ICH-GCP Topic 9, Statistical analyses (EMEA, 2006), including non-inferiority hypotheses for primary outcomes (as the NTX-SBX study is a comparison with the current preferred / standard treatment)
- Ensuring compatibility between Section 5: Data Management and the current Data Management Plan
- Minor edits to urine test outcomes to ensure compliance with Cochrane Drugs & Alcohol Group criteria for urine drug test outcomes
- Analyses are edited to permit utilization of the statistical advances that have taken place in the years since drafting of the original protocol
- In statistical software, the open 'R' platform is increasingly popular in statistical analysis due to its versatility and community-driven, transparent development platform
- Corrections to the SOCRATES-8D analyses
- The CSP now provides more guidance on when to consult the Statistical Analysis Plan (SAP) for further guidance

The analyses of outcomes not mentioned in the original CSP but introduced in amendments will be subject to similar changes as those described here and in the Statistical Analysis Plan (SAP).

pp. 7 Summary - 'Statistical Methods'

The original version reads:

> "Descriptive statistics including frequency tables, graphs or scatterplots will be provided for all primary outcomes, as well as for the changes from baseline within each treatment and the differences between the treatment groups at each visit (Observed Cases (OC) and LOCF as appropriate)."

The revised version shall read:

"Descriptive statistics including frequency tables, graphs or scatterplots will be calculated for all primary outcomes, as well as for the changes from baseline within each treatment and the differences between the treatment groups at each visit (Observed Cases (OC) and LOCF as appropriate)."

The original version reads:

"Missing data will be imputed using a Last Observation Carried Forward (LOCF) approach."

The revised version shall read:

"Missing data will be imputed using a Last Observation Carried Forward (LOCF) approach or other method of imputation or modeling as appropriate."

The original version reads:

"The primary outcome variable will be analysed using an analysis of variance (ANOVA) or regression model as appropriate including treatment, study site and baseline frequency of opioid use as explanatory variables. Study site will be treated as a random effect while all other explanatory variables will be treated as fixed effects."

The revised version shall read:

"The primary outcome variable will be analysed using a Generalized Linear Mixed Model (GLMM) or Generalize Alinear Mixed Model (GAMM) as appropriate. Relevant background variables will be controlled for, including treatment, study site and baseline frequency of opioid use. Non-inferiority and superiority analyses will be performed.

The original version reads:

"Changes from randomisation to every assessment will be analysed similar to the primary objective."

The revised version shall read:

"Changes from randomisation to every assessment will be analysed similar to the primary objective as appropriate."

pp. 53, Section 4.3.3.2: Derivation or Calculation of outcome variable (Socrates-8D)

The original version reads:

"Socrates 8-D sub-scales include recognition, ambivalence, and taking steps. A Socrates 19- item total score will be calculated. Higher scores indicate a higher level of abstinence motivation. The change from randomisation will be calculated as the visit score minus the randomisation score. Between-group differences or differential developments in Socrates 8D scores will be calculated at any assessment."

The revised version shall read:

"Socrates 8-D sub-scales will be excluded from analyses due to lack of approved scientific validation of the Norwegian version."

pp. 63, Section 5: Data Management

The original version reads:

"When data have been entered and reviewed / edited by a CRO, the site investigator will be notified and sign the CRF copy, and data will be locked to prevent further editing."

The revised version shall read:

"When data have been entered and reviewed / edited, the investigator will be notified and sign the CRF copy, and data will be locked to prevent further editing."

The original version reads:

"Data will be cleaned on a regular basis by a designated partner. Clean file for the final database will be declared by the principal investigator after all data have been set to clean. Prior to declaring clean file, all decisions on the evaluability of the data from each patient must have been made and documented."

The revised version shall read:

"Data will be cleaned on a regular basis. Clean file for the final database will be declared by the principal investigator following entry of data from each major study phase, after all data have been set to clean. Prior to declaring clean file, all decisions on the evaluability of the data from each patient must have been made and documented."

The original version reads:

"CROs will be used for handling clinical assessments and laboratory data and the results will be sent to a designated partner as SPSS or – compatible datasets."

The revised version shall read:

"Clinical assessments and laboratory data will be handled in accordance with ICH-GCP, and the data file for the initial analysis of RCT phase data (randomization to Week 12) will be sent to a designated statistician; this initial data file will mask the names of medication groups with 'A' and 'B', respectively. Data files will be in a format compatible with modern statistical software, e.g R or SPSS."

pp. 64-67 Section 6.2. Description of Outcome Variables in relation to Objectives and Hypotheses

pp. 64, Section 6.2.1 Primary objectives, hypotheses and outcome variables

The original version reads:

"The primary objective of this study is to evaluate the effectiveness of XR-NTX 380 mg/month versus buprenorphine-naloxone 8-24 mg/day as part of "treatment as usual", assessed by the number of opioid free oral fluid samples during the treatment period from randomization to Week 12.

The primary hypotheses are as follows:

XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in the mean number of oral fluid samples negative for opioid agonists (other than study drug) or their metabolites from randomization until Week 12.

. XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in increasing self-reported abstinence from illicit (e.g. non-study) opioids measured as number of days abstinent on time-line follow-back
. XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in retention in treatment at Week 12 as measured by comparing the number of patients left and/or calculating the proportion of patients retained in each group.
. XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in reducing the number of patients qualifying for an Opioid Dependence Diagnosis on the DSM-IV TR (304.00 except the 12-month criteria) as measured using the MINI.
. Any study drug (XR-NTX 380 mg/month or buprenorphine-naloxone 8-24 mg/day) is superior to no study drug on preventing mortality as measured by the number of patients deceased from randomization until Week 48 according to Norway's National Mortality Registry."

The revised version shall read:

"The primary objective of this study is to evaluate the effectiveness of XR-NTX 380 mg/month versus daily buprenorphine-naloxone as part of "treatment as usual", assessed by the number of opioid-free urine drug tests (UDTs) during the treatment period from randomization to Week 12.

The primary hypotheses are as follows:

XR-NTX (380 mg/month) is noninferior or equally effective to daily buprenorphine-naloxone in the mean number of urine samples negative for opioid agonists (other than study drug) or their metabolites from randomization until Week 12.

. - XR-NTX (380 mg/month) noninferior or equally effective to daily buprenorphine-naloxone in increasing self-reported abstinence from illicit (e.g. non-study) opioids measured as number of days of use on time-line follow-back
. - XR-NTX (380 mg/month) is equally effective to daily buprenorphine-naloxone in retention in treatment at Week 12 as measured by comparing the number of patients left and/or calculating the proportion of patients retained in each group or other method of analysis as appropriate
. - XR-NTX (380 mg/month) is superior or equally effective to daily buprenorphine-naloxone in reducing the number of patients qualifying for an Opioid Dependence Diagnosis on the DSM-IV TR (304.00 except the 12-month criteria) as measured using the MINI.

.

. - If mortality proves viable for analysis, any study drug (XR-NTX 380 mg/month or daily buprenorphine-naloxone is superior to no study drug on preventing mortality as measured by the number of patients deceased from randomization until Week 48 according to Norway's National Mortality Registry."

pp. 65, Section 6.2.2 Secondary objectives, hypotheses and outcome variables
pp.64, Section 6.2.2.1 Secondary objective of particular interest

The original version reads:

"A secondary objective of particular interest is to evaluate if XR-NTX (380 mg/month) reduces heroin craving compared to or buprenorphine-naloxone (8-24 mg/day). The secondary hypotheses are as follows:

XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in reducing craving for heroin from 107andomization to each monthly assessment until Week 12 as measured on a visual analogue scale (VAS)."

The revised version shall read:

"A secondary objective of particular interest is to evaluate if XR-NTX (380 mg/month) reduces heroin craving as much as or more than daily medication with buprenorphine-naloxone. The secondary hypotheses are as follows:

XR-NTX (380 mg/month) is superior or equivalent to daily buprenorphine-naloxone in reducing craving for heroin from randomization to each monthly assessment until Week 12 as measured on a visual analogue scale (VAS)."

pp. 65, Section 6.2.2.2 Other secondary objectives: Effectiveness

The original version reads:

"Another secondary objective of this study is to evaluate the effectiveness of XR-NTX versus buprenorphine-naloxone, or both of these drugs versus no study drugs, within or between clinical and criminal justice settings. The secondary hypotheses are as follows:

Any study drug (XR-NTX 380 mg/month or daily buprenorphine-naloxone) will be superior to no study drug on:

- Morbidity at 48 Weeks post randomization/inclusion as measured by data from the Norwegian Patient's Registry.

- Criminal re-offending as measured by the number of offences registered at Week 48 in Norway's National Criminal Offense Registry and/or self-report.

- XR-NTX (380 mg/month) is superior or equal to buprenorphine-naloxone in increasing Quality of Life from randomization until Week 12 as measured using the Temporal Satisfaction With Life Scale.

- XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in reducing non-opioid substance use as measured by the number of oral fluid samples positive for illicit, non-opioid substances or their metabolites from Week 1-12 in the study or in self-reported use of (or abstinence from) non-opioid substances including cocaine, amphetamines,

- benzodiazepines, alcohol, cannabis, and hallucinogenic drugs (e.g. LSD, MDMA, GHB).

- XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in reducing drug-related needle use as measured by the number of days needle use reported from randomization to Week 12 on time-line follow-back.

- XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in reducing income from illicit sales of drugs as assessed by the change from randomization to Week 12 in self-reported days with such income and/or the total amount of income from these sources in Norwegian Kroner (NKR; 10 NKR = approximately 1,7 US $). The Europ-ASI will be used for this outcome.

. XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in reducing frequency of injecting drug use as assessed by the change from randomization to Week 12 in self-reported days with such use and/or the total use of needles in days during each month on the Europ-ASI.

. XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in reducing frequency blood-borne disease risk behaviours as assessed by the change from 108andomization to Week 12 in self-reported needle use habits for each month on the Europ-ASI.

A secondary objective of this study is to evaluate if XR-NTX in the clinical and/or criminal justice settings affects motivation for abstinence compared to buprenorphine-naloxone and/or non-randomized controls by assessing the change from 108andomization to Week 12 in self- reported abstinence motivation on the total or subscale levels of the Stages of Change Readiness and Treatment Eagerness Scale Drugs (SOCRATES 8D).

The secondary hypotheses are:

- XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in increasing motivation for abstinence at Week 12 as measured by Total score on the SOCRATES 8D.
- XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in increasing recognition of addiction problems at Week 12 as measured by increased scores on the recognition subscale on the SOCRATES 8D."

- XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in increasing the reported effort towards abstinence at Week 12 as measured by the Taking Steps subscale on the SOCRATES 8D.

- XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in increasing motivation for abstinence at Week 12 as measured by a reduction on the ambivalence subscale of the SOCRATES 8D."

The revised version shall read:

"The secondary objective of this study to evaluate the effectiveness of XR-NTX versus buprenorphine-naloxone, or both of these drugs versus no study drugs, within or between clinical and criminal justice settings, has been deleted from the protocol due to too low recruitment from criminal justice settings and a too low number of participants in the no-study drug group. Only comparisons between XR-NTX and buprenorphine-naloxone will be performed.

XR-NTX (380 mg/month) is superior or equivalent to daily buprenorphine-naloxone in increasing or stabilizing Quality of Life from randomization until Week 12 as measured using the Temporal Satisfaction With Life Scale.

- XR-NTX (380 mg/month) is superior or equivalent to daily buprenorphine-naloxone in reducing or stabilizing non-opioid substance use as measured by the number of urine drug tests (UDTs) positive for illicit, non-opioid substances or their metabolites from Week 1-12 in the study or in self-reported use of (or abstinence from) non-opioid substances including cocaine, amphetamines, benzodiazepines, alcohol, cannabis, and hallucinogenic drugs (e.g. LSD, MDMA, GHB).

- XR-NTX (380 mg/month) is superior or equivalent to daily buprenorphine-naloxone in reducing or stabilizing drug-related needle use as measured by the number of days needle use reported from randomization to Week 12 on time-line follow-back.

- XR-NTX (380 mg/month) is superior or equivalent to daily buprenorphine-naloxone in reducing income from illicit sales of drugs as assessed by the change from randomization to Week 12 in self-reported days with such income and/or the total amount of income from these sources in Norwegian Kroner (NKR; 10 NKR = approximately 1,7 US $). The Europ-ASI will be used for this outcome.

. XR-NTX (380 mg/month) is superior or equivalent to daily buprenorphine-naloxone in reducing or stabilizing frequency of injecting drug use as assessed by the change from randomization to Week 12 in self-reported days with such use and/or the total use of needles in days during each month on the Europ-ASI.

. XR-NTX (380 mg/month) is superior or equivalent to daily buprenorphine-naloxone in reducing or stabilizing blood-borne disease risk behaviours as assessed by the change from randomization to Week 12 in self-reported needle use habits for each month on the Europ-ASI.

.

A secondary objective of this study is to evaluate if XR-NTX in the clinical and/or criminal justice settings affects motivation for abstinence compared to buprenorphine-naloxone and/or non-randomized controls by assessing the change from randomization to Week 12 in self- reported abstinence motivation on the total or subscale levels of the Stages of Change Readiness and Treatment Eagerness Scale Drugs (SOCRATES 8D). Data on SOCRATES 8D is excluded from analyses due to lack of approved scientific validation of the Norwegian version."

pp. 66, Section 6.2.2.3 Other secondary objectives: Quality of Life

The original version reads:

"A secondary objective of this study is to evaluate if XR-NTX (380 mg/month) improves quality of life of patients with Opioid Dependence, compared to buprenorphine-naloxone or no study medication. The hypothesis regarding TSWLS total score, a secondary variable of particular interest, is specified in 6.2.2.2. The other secondary quality of life hypothesis is:

XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in increasing the TSWLS overall quality of life score from randomisation to Week 12."

The revised version shall read:

"A secondary objective of this study is to evaluate if XR-NTX (380 mg/month) improves or stabilizes quality of life of patients with Opioid Dependence, compared to buprenorphine-naloxone. The hypothesis regarding TSWLS total score, a secondary variable of particular interest, is specified in

6.2.2.2. The other secondary quality of life hypothesis is:

XR-NTX (380 mg/month) is superior or equivalent to daily buprenorphine-naloxone in increasing or stabilizing the TSWLS overall quality of life score from randomization to Week 12."

pp. 67, Section 6.2.2.3 (cont.) Other secondary objectives: Quality of Life

The original version reads:

"A secondary objective of this study is to evaluate if XR-NTX (380 mg/month) improves satisfaction with medication compared to buprenorphine-naloxone or no study medication. The secondary hypothesis is as follows:

XR-NTX (380 mg/month) is superior to buprenorphine-naloxone (8-24 mg/day) in increasing the VAS satisfaction with medication score at Week 12."

The revised version reads:

"A secondary objective of this study is to evaluate how satisfaction with XR-NTX (380 mg/month) compares to satisfaction with daily buprenorphine-naloxone. The secondary hypothesis is as follows:

XR-NTX (380 mg/month) is superior or equivalent to daily buprenorphine-naloxone in increasing or stabilizing the VAS satisfaction with medication score at Week 12."

Amendment 10 to CSP version 3C in the study 'Optimal Prevention of Overdose Deaths and Opioid Relapse Following Discharge: A Multi-Center RCT' (EudraCT: 2011-002858-31)

Oslo, Mar 8th 2016,

Definition of Adverse (AE) – and Serious Adverse Events (SAE)

The traditional definition of SAE states that any in-patient hospitalisation or prolongation of existing hospitalisation over night is registered as a Severe Adverse Event. This definition is satisfactory for non-addicted patient samples where hospitalisation signals a clear increase in severity. However, this may not be satisfactory in a high-risk population such as poly-drug using opioid users, who often mask somatic and psychiatric problems with substance use and are exposed to a higher incidence of health problems due to substance abuse, criminal involvement, lack of permanent residency and other problems. Research on the current standard treatment (and active comparator in this study) in Norway suggests that a stable reduction in illicit opioid use is followed by a transition in the utilization of health services from acute care for injectionrelated disease events to planned admissions for treatment of general somatic and mental health events (see [1]). The literature does not give reason to expect opioid users in treatment with extended-release naltrexone (XR-NTX; study drug in this study) to behave differently from this norm.

Thus in the lives of the majority of opioid users, admissions to hospital will often signify increased access to healthcare due to overall improvement or recovery from illicit drug use. Many of these admissions would not be consistent with the premise that a SAE signifies a worsening of the condition under investigation. This also applies to residential treatment or hospital-based care for mental health problems, addiction problems, and personality disorders.

In order for the registration of SAE to better reflect the occurrence of negative health events in opioid users in the study, this amendment revises the in-study definition of AEs and SAEs to comprise only acute admissions for unexpected health problems. Planned admissions will still be registered in Europ-ASI Chapter B – days in a controlled environment, Chapter C (somatic health problems and hospitalizations) or Chapter I (mental health hospitalizations).

The original protocol pp 79, section 9.1. reads:

9.1.1 Adverse Event (AE)

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product,

whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

9.1.2 Serious Adverse Event (SAE)

An SAE is an AE occurring during any study phase (i.e., run-in, treatment,wash-out, follow-up), and at any dose of the products used in this study that fulfils one or more of the following criteria:

- *Results in death*
- *Is immediately life-threatening*
- *Requires in-patient hospitalisation or prolongation of existing hospitalization*
- *Results in persistent or significant disability or incapacity*
- *Is a congenital abnormality or birth defect*
- *Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the above listed outcomes*

The causality of SAE (i.e. their relationship to study treatment) will be assessed by the investigator(s), who in completing the relevant CRF must answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by XR-NTX?"

For further guidance on the definition of a SAE and a guide to the interpretation of the causality question, see Appendix B. Note that SAEs that could be associated with any study procedure should also be reported. For such events the causal relationship is implied as "yes".

The revised text shall read:

9.1.1 Adverse Event (AE)

An AE is the development of unexpected or previously unknown undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including during run-in or washout periods, even if no study treatment has been administered.

9.1.2 Serious Adverse Event (SAE)

An SAE is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), and at any dose of the products used in this study that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening

- Requires unplanned or acute in-patient hospitalisation or unplanned prolongation of existing hospitalisation in a somatic, psychiatric or addiction ward
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the above listed outcomes

The causality of SAE (i.e. their relationship to study treatment) will be assessed by the investigator(s), who in completing the relevant CRF must answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by XR-NTX?" For further guidance on the definition of a SAE and a guide to the interpretation of the causality question, see Appendix B. Note that SAEs that could be associated with any study procedure should also be reported. For such events the causal relationship is implied as "yes". The exception to this is the admission to washout voluntary tapering of opioid drugs or medications following completion of the 12-Week RCT period.

Reference:

1. Skeie I, Brekke M, Gossop M, Lindbaek M, Reinertsen E, Thoresen M, Waal H: Changes in somatic disease incidents during opioid maintenance treatment: results from a Norwegian cohort study**.** *BMJ Open* 2011, **1**:e000130.

pp. 68, Section 6.3. Description of Analysis Sets

The original version reads:

> "The per-protocol (PP) population, a subset of the MITT population, will include patients who completed the study treatment with no major protocol violations or deviations affecting effectiveness. Data from this population will be used as a consistency check for analysis of the primary objective."

The revised version shall read:

> "The per-protocol (PP) population (aka Observed Cases (OC)), a subset of the MITT population, will include patients who completed the study treatment with no major protocol violations or deviations affecting effectiveness. Data from this population will be used as a consistency check for analysis of the primary objective."

pp. 69, 6.4. Method of Statistical Analysis
pp.69, 6.4.1 General aspects

The original version reads:

> "Missing data will be imputed using a Last Observation Carried Forward (LOCF) approach. Patients with post randomisation data will have their last study assessment carried forward as the final assessment for analyses. These will serve as accurate estimates since the patients could be expected to get better over time. Analyses on Observed Cases (OC) will be performed to study the robustness of the results.
>
> Baseline values, collected at randomisation or enrolment, will be defined as the last non- missing value prior to receiving first dose of study treatment."

The revised version shall read:

> "Missing data will be imputed using an appropriate imputation method, e.g. Last Observation Carried Forward (LOCF) and patients who lack such data have their pre-participation data carried forward (ITT analysis set). Patients with post randomisation data (MITT analysis set) will have their last study assessment carried forward as the final assessment for analyses,. Analyses on Observed Cases (OC) (Per Protocol analysis set) will also be performed to study the robustness of the results.
>
> Baseline values, collected at enrolment, will be defined as the last non- missing value prior to receiving first dose of study treatment."

The revised version shall add:

> "The Statistical Analysis Plan (SAP) may add additional guidance on statistical analyses and / or the adaptation of the contents of this Section to statistical analyses."

pp.69 Section 6.5 Multiplicity

The original version reads:

> "For the confirmative strategy, a step-wise sequential testing procedure will be used for handling multiple comparisons such that the overall significance level of 0.05 is preserved. First the primary outcome variable the number of opoid free saliva samples from randomisation to Week 12 will be tested for the naltrexone versus the suboxone group.
>
> All statistical tests will be two-sided with a significance level of 5%, i.e. α=0.05 unless otherwise specified. Secondary analyses will report nominal 5% levels of significance, but p- values will be displayed primarily to aid the interpretation of results. No adjustments for multiplicity will be made for these secondary analyses. Where appropriate, model-based point estimates will be presented together with their 95% confidence intervals. Unless otherwise stated the interest will separately focus on the treatment differences between the groups."

The revised version shall read:

> "For the confirmative strategy, a step-wise sequential testing procedure will be used for handling multiple comparisons such that the overall significance level of 0.05 is preserved. First the primary outcome variable the number of opoid free urine drug tests from Week 1 to Week 12 will be tested for the naltrexone versus the suboxone group.
>
> All statistical tests will be two-sided with a significance level of 5%, i.e. α=0.05 unless otherwise specified. Secondary analyses will report nominal 5% levels of significance, but p- values will be displayed primarily to aid the interpretation of results with adjustments for multiplicity made as appropriate. Where appropriate, model-based point estimates will be presented together with their 95% confidence intervals. Unless otherwise stated the interest will separately focus on the treatment differences or – similarities between the groups."

pp. 69, Section 6.4.3 Primary variable

> "An analysis of variance (ANOVA) model for between-groups differences at Week 12 in the number of opioid-positive oral fluid samples will be used. Study drug groups (XR-NTX 380 mg/month or buprenorphine-naloxone 8-24 mg/day) will be compared, and also compared separately or collectively (as a 'medication' group) to participants not receiving any study drug. The model will include treatment, centre and setting as explanatory variables. Centre will be treated as a random effect while all other explanatory variables will be treated as fixed effects. Model-based point estimates, 95% confidence intervals and p-values will be reported."

The revised version shall read:

> "An analysis of variance (ANOVA) model for between-groups differences at Week 12 in the number of opioid-positive urin fluid samples will be used. Study drug groups. The model will include treatment, centre and setting as explanatory variables. Centre will be treated as a random effect while all other explanatory variables will be treated as fixed effects. Model-based point estimates, 95% confidence intervals and p-values will be reported."

(Note: Mixed-models approaches are already mentioned in this Section at top paragraph, pp70, and comprise both General Linear – and Alinear Mixed Models).

pp. 73, Section 6.5: Determination of Sample Size

The original version reads:

> "The sample size calculation in this exploratory study was done to model the event that XR- NTX demonstrates superior effectiveness over buprenorphine-naloxone with respect to the primary outcome variable, differences in opioid-negative oral fluid samples from randomisation to Week 12 – a total of 12 oral fluid samples."

The revised version shall read:

> "The sample size calculations in this exploratory study was done to model the event that XR- NTX demonstrates superior or noninferior ffectiveness to buprenorphine-naloxone with respect to the primary outcome variables, including proportion opioid-negative urine samples from randomisation to Week 12 – a total of 12 urine drug tests."

The original version reads:

> "The minimum sample size was estimated by assuming that participants receiving XR-NTX will achieve opioid-negative samples on a mean of 7 out of the total 12 samples, while participants receiving buprenorphine-naloxone will deliver a mean of 4 opioid-negative samples. The estimates assume a 95% significance level ($p<.05$) and a standard deviation of 3 in both medication groups. A power (beta) set to 90%, a sample size of 17 patients/medication arm will be sufficient, or n=34 total. Missing samples will be counted as positive in an ITT- manner.
> Sample size calculations were based on information from previous studies of buprenorphine- naloxone showing attrition of about 50% in the first months following discharge from criminal justice settings. Attrition in the naltrexone group is based on previous studies with sustained release naltrexone in Norwegian settings showing only about 5% attrition."

The revised version shall add:

> "As the objective of this study is a comparison between novel - and the preferred / standard treatment, ICH-GCP suggests that power/sample estimates also be calculated for nonsuperiority scenarios. The Statistical Analysis Plan (SAP) will provide guidance on estimates for nonsuperiority analyses."

pp. 74, Section 6.6: Interim analyses

The original version reads:

> "No interim analyses are planned. Regular analyses will be performed 1) after completion of the randomized trial, and 2) separate analyses performed for the non-randomized part of the study. In addition, more regular analyses may be performed following the conclusion of the trial, in particular (but not restricted to) after collection of data from national registries / databases."

The revised version shall read:

> "No interim analyses are planned. Regular analyses will be performed 1) after completion of the randomized trial, and 2) separate analyses performed for the non-randomized part of the study. Regular

analyses may commence after 'Last Patient in', e.g. the last patient is included in the study as deemed appropriate by the Principal Investigator. In addition more regular analyses may be performed following the conclusion of the trial, in particular (but not restricted to) after collection of data from national registries / databases."

STATISTICAL ANALYSIS PLAN

for the clinical trial

'Optimal Prevention of Overdose Deaths and Opioid Relapse Following Discharge: A Multi-Center RCT'

Study code: NTX-204725-1

Protocol version: 3C with amendments

Version 1.0b February 2015

Table of Contents

INTRODUCTION TO THE NTX-SBX STATISTICAL ANALYSIS PLAN 3

Table 1. Overview of statistics-relevant information in the NTX-SBX study 3

NTX-SBX study design and investigatory status of outcomes in the study 4

Role of publications versus NTX-SBX guidance on analyses 4

PREPARATIONS OF DATA FOR ANALYSES 5

STATISTICAL PROCEDURES FOR THE DIFFERENT PHASES OF INVESTIGATION 5

Table 2. Planned statistical – and data management procedures the four phases of investigation 7

NON-INFERIORITY SCENARIOS 8

Non-inferiority analyses and - margins 8

Defining non-inferiority margins for opioid addiction outcomes 8

Table 3a. Non-inferiority margins and corresponding group size estimates for primary outcomes 9

Table 3b. Non-inferiority margins and corresponding group size estimates for secondary outcomes 9

ADVERSE EVENTS AND PATIENTS FLOW 10

APPENDIX TO THE STATISTICAL ANALYSIS PLAN (SAP): SUM SCORE CALCULATION FOR PATIENT-REPORTED OUTCOMES IN THE NTX-SBX STUDY 11

Symptom Checklist 25 (aka Hopkins' Symptom Checklist 25 or SCL-25) 11

The Stages of Change Eagerness and Readiness Scale (SOCRATES) 8D 11

Insomnia Severity Index 11

Temporal Satisfaction with Life Scale, 'Current' Items (TSWLS) 11

Visual Analogue Scales on Heroin use, craving, treatment satisfaction a.o. 11

Introduction to the NTX-SBX Statistical Analysis Plan

This section repeats and summarizes the statistical analysis information described in the study protocol and its ensuing amendments in order to improve ease-of-use of this Statistical Analysis Plan (SAP) as a template for the statistical analyses of data originating from the clinical trial 'Optimal Prevention of Overdose Deaths and Opioid Relapse Following Discharge: A Multi-Center RCT' (from here on referred to as 'the study' or 'the NTX-SBX study').

The role of the SAP is to complement and expand on statistics and data sections in the Clinical Study Protocol (CSP) with amendments. To improve guidance, some aspects of data management mentioned in the CSP and Data Management Plan (DMP) are repeated here.

Table 1 provides an overview of where to locate statistically relevant information in the NTX-SBX study documents.

Table 1. Overview of statistics-relevant information in the NTX-SBX study

Statistical Topic	**Clinical Study Protocol with Amendment 7**	**Statistical Analysis Plan (SAP)**	**Data Management Plan**
Hypotheses	Yes, Section 6.2 pp 64-69, Amd7 pp 4-9	No	No
Outcomes – descriptions and definitions	Yes, Section 4, pp 50-54, 56-69, Amd7 pp 2	No	No
Statistical Power analyses	Yes, Section 6.5. pp 73, Amd 7 p11	Yes – non-inferiority	No
Non-inferiority margins for outcomes	No	Yes	No
Analysis sets – descriptions	Yes, Section 6.3, pp. 68, Amd 7 p9	No	No
Study design & phases	Yes	Briefly	No
Procedures for preparation & handling of data	Yes, Section 5 pp 63, Amd7 p3	No	Yes
Statistical procedures and – analyses	Yes, Section 6.4.3, 6.5,	Yes, detailed guidance	No

NTX-SBX study design and investigatory status of outcomes in the study

Traditionally, scientific investigations of medical treatments are divided into two categories: Confirmatory studies are typically done with large samples in naturalistic settings with the emphasis of defining a finite set of hypotheses and analyses that must not be changed once data have been collected and the database has been locked from further editing; such changes or deviations from the SAP are considered post-hoc – editing hypotheses to fit the data - and are regarded with considerably less confidence than the pre-defined hypotheses and – analyses.

The other type of investigation is exploratory studies, where efficacy is usually given priority by emphasizing internal validity. In exploratory studies, the SAP serves as a guidance for statistical analyses, but deviation from pre-planned analyses are permitted and thus need not be considered 'post-hoc' in a statistical/philosophical sense (EMEA 2006: ICH Topic 9, Statistical analyses). For this reason, however, results from exploratory studies are not given the same significance as confirmatory studies.

The NTX-SBX study is an open-label exploratory comparison of extended release naltrexone with daily buprenorphine-naloxone for the treatment of opioid dependence. While a first-of-its-kind study, it has characteristics normally seen in confirmatory trials, e.g.: A 'naturalistic' setting with few restrictions on who are admitted into the study; an open-label design with free disclosure of study medication due to ethical concerns with placebo in testing opioid-blocking medication; use of medications whose characteristics have been investigated in other trials with users of illicit opioids. These characteristics emphasize external validity (aka generalizability).

Thus the SAP of the NTX-SBX study will consider analyses of adverse events to be of a confirmatory nature, while studies of effectiveness for primary and secondary outcomes will be regarded as exploratory.

Role of publications versus NTX-SBX guidance on analyses

In situations where Journal author guidelines or editor / referee opinion require or request statistical analyses or procedures other than those described in the CSP or SAP, the NTX-SBX National management or delegate will respond to the request and decide on the feasibility and applicability of the request.

Preparations of data for analyses

This section provides a brief summary of data management information found in the NTX-SBX protocol (CSP) and data management plan (DMP).

Once the last patient has been included in the study, data will be retrieved from the GCP-approved MedInsight database in a compatible format (SPSS, R, or similar) and inspected for errors.

Following data entry and – inspection of the last included patient, the database will be locked for further editing and considered final. If feasible, database lock will occur in stages corresponding to the end of data entry from each phase of investigation (see below).

RCT data (from inclusion Week 0 to Week 12 / Day 85) will have names of medication groups masked by the letters 'A' and 'B' before being made available to a designated statistician for analysis. The masking should be preserved until statistical analyses are considered final by the NTX-SBX National Management (PI and National Study Coordinator).

For composite scores (e.g. patient-reported outcomes (PROs) like forms and scales), total score and any subscale scores will have to be calculated based on the data file originating from MedInsight and added to the study data file for analysis. An appendix to this SAP will contain the necessary information for calculating the scores for each patient on the different study PROs.

Statistical procedures for the different phases of investigation

The NTX-SBX data will originate from four phases of investigation, of which only the first is randomized:

1) Inclusion until RCT Phase completion at 12 Week follow-up.

2) The Continuation Phase lasting from Weeks 13 until Week 48 Post Inclusion

3) The Prolongation phase (See Amendment 6, 'Prolong') lasting from Week 49 Post Inclusion and until Week 89 or beyond. Study Management have for ethical reasons elected to offer Study Medication to study participants who demonstrate willingness and ability to benefit from the medication for as long as feasible or until it is available through other legitimate sources.

4) Registry data Phase; patients have provided informed consent to retrieve their data from various national database registries. This opportunity may be conducted as part of long-term studies and / or other designs and comparisons, depending on scientific merit and available resources.

Note: Information on or from patients queried / screened about their interest in study participation may be compared to clinical data to address questions

regarding the link between interest in medication / participation and actual participation. As pre-consent data are not a part of this study, they will not be subject to further discussion in this SAP.

Table 2 (below) shows the planned statistical – and data management procedures applied to the data originating from the four phases of investigation in the NTX-SBX study.

Table 2. Planned statistical – and data management procedures the four phases of investigation

	RCT Phase	Continuation	Prolongation	Registry data
Week no.	0/1 – 12	13 – 48	49 – 89 +	- 52 – 52
'MedInsight' database data entry & retrieval	Yes	Yes	No	No
Masking of medication groups for analyses of primary outcomes	Yes	No	No / N.A.	N.A.
Designated Statistician to conduct analyses	Yes (primary outcomes / main article)	As needed / collaboration with lead author	As needed / collaboration with lead author	As needed / collaboration with lead author
Analysis sets	Yes: ITT & MITT/PP, others as appropriate	If applicable	If applicable	If applicable
Imputation or estimation of missing data	Yes LOCF for outcomes in ITT (where possible)	Optional	Optional	N.A.
Equivalence / non-inferiority testing	Yes, on primary outcomes where H1 is false, optional on other outcomes	N.A.	N.A.	Optional
Controlling for centre / site	Yes, for primary outcomes	If applicable	If applicable	If applicable
Controlling for multiplicity	Yes	If applicable	If applicable	If applicable
Adverse Events analyses	Yes	If applicable	If applicable	If applicable

Non-inferiority scenarios

Non-inferiority analyses and - margins

The ICH-GCP guidance on statistical analysis (aka 'Chapter 9') state that RCTs comparing a novel treatment with preferred treatment should have hypotheses, analysis plans and power estimates to analyze both statistically significant differences (aka 'superiority' / 'non-equality') and non-inferiority (aka 'equality', 'non-inferiority', etc; EMEA, 2006).

An estimate of non-inferiority requires a defined limit for the minimum clinically meaningful between-group difference for each outcome - e.g. what would be the minimum increment on each outcome required to be relevant or noticeable to treatment personnel and patients?

Defining non-inferiority margins for opioid addiction outcomes

The size or quality of the minimum significant difference (non-inferiority margin) varies with the characteristics of the outcome measure, of the study setting, and of the illness under investigation. E.g. consensus on what is the minimum clinically significant margin is likely reduced with continuous versus binary (or stepwise) measures, and is likely easier with brief, well-defined illnesses as opposed to chronic comprehensive disorders like opioid addiction.

Thus in the case of opioid addiction, the increment of a single measure would need to be sizeable to signify a clear, reliable step towards (or away from) recovery. We have therefore defined non-inferiority margins that are no smaller than 10%, and in some cases 20-25%. Outcomes may depend on measures designed to reflect an incremental burden of symptoms rather than separate well-defined states of recovery or illness. E.g. a 10% variation in drug use that occurs every day on a 30-day measure (range: 0-30) could be due to external factors like travel or an influenza infection limiting access to drugs. A 20-30% improvement, however, seems less controversial as a clear indicator of change. In similar manner, urine drug tests are based on immunoassay technologies with well-known limitations in reliability and validity; again, a larger number of tests (three or more) seem less controversial as an indicator of change.

Table 3 (Tab 3) shows the non-inferiority margins in the NTX-SBX study and estimates the necessary number of participants in each group needed to show non-inferiority given an alpha of 95% and beta of 80%. Note that the estimates are based on simple, means-based tests that assuming normal distribution for continuous variables and binary / non-linear tests for proportions; with different statistical procedures or breach of these assumptions, the power/margin size ratio may change. Estimates are also based on identical group values, something that is unlikely to occur in the NTX-SBX dataset; a larger number of participants may be needed for groups with differing values, and this number should increase the closer the difference is to the outcome-specific non-superiority margin.

Table 3a. Non-inferiority margins and corresponding group size estimates for primary outcomes

	Non-inferiority margin	Minimum group sample sizes (n)		Group values (examples)	
Primary outcome (range)		XR-NTX	BP-NLX	XR-NTX	BP-NLX
Proportion opioid-negative UDT's (0-1.0)	3 of 12 tests / 0.25 / 25%	N=45	N=45	8 of 12 / 0.66	8 of 12 / 0.66
Days abstinence from illicit opioids (0-85)	10 days / 11.7%	N=50	N=50	Mean 65 days (sd: 20)	Mean 65 days (sd: 20)
Completed RCT study (% of n)	20%	N=58	N=58	0.70	0.70
Opioid dependent (DSM-IV) (% of n / 0-1.0)	20% / 0.2	N=28	N=28	0.10 / 10%	0.10 / 10%

Table 3b. Non-inferiority margins and corresponding group size estimates for secondary outcomes

Secondary outcome (range)	Non-inferiority margin	Minimum group sample size (n)	Minimum group sample size (n)	Group value (example)	Group value (example)
Heroin Craving (0-10)	2.0	N=50	N=50	Mean 2.5, (s.d. 4.0)	Mean 2.5, (s.d. 4.0)
Days injecting drug use (0-85 days)	12 days	N=68	N=68	Mean 25 days (sd: 28)	Mean 25 days (sd: 28)
Quality of Life (5-35)	5 points	N=72	N=72	Mean 20 (sd: 12)	Mean 20 (sd: 12)
Days of amphetamine use (0-85)	14 days	N=57	N=57	Mean 20 days (sd: 30)	Mean 20 days (sd: 30)

Other secondary outcomes may have non-inferiority margins defined as needed by the NTX-SBX National Management once statistical analyses have commenced.

Adverse Events and Patient Flow

In accordance with the study protocol (CSP), Adverse Events and patient flow/retention will be analyzed using the most feasible non-continuous analysis – e.g. log-rank, Chi Square, Fischer's Exact Test or potentially Generalized Additive Mixed Model as appropriate.

Categorization of events

Adverse events may be categorized according to their seriousness, the symptoms presented, and the assumed relation to study medication.

Definitions of seriousness are provided in the CSP and ICH-GCP; in brief, only events requiring extra hospitalization, resulting in a life-threatening state or in death are categorized as Serious Adverse Events (SAEs). Less dramatic events requiring minor treatment interventions (e.g. symptomatic medication) are categorized and reported as Adverse Events. Unexpected life-threatening SAEs attributed to study medication are called Sudden Unexpected SAEs (SUSARS).

A separate category of adverse events in the NTX-SBX study will be established to reflect withdrawal syndrome states (e.g. diarrhea, vomiting, sweating). These events reflect the lack of experience of study personnel in inducing patients onto XR-NTX from strong opioid agonists like buprenorphine and methadone; this requires a longer detoxification and, ideally, opioid-free urine drug tests before XR-NTX is administered, but was not specified in the protocol. Thus these types of events should be identified (as they describe withdrawal symptoms following the first dose of XR-NTX) and may be presented separately from other adverse events in order to not confuse them with adverse events originating from the pharmacological properties of the study medication (XR-NTX).

Appendix to the Statistical Analysis Plan (SAP): Sum Score Calculation for Patient-Reported Outcomes in the NTX-SBX Study

Symptom Checklist 25 (aka Hopkins' Symptom Checklist 25 or SCL-25)

Total Score: Summarize all items (scale range 1-4)
Anxiety Subscale: Summarize items 1 – 10
Depression Subscale: Summarize items 11 – 25

Higher score on all items indicate greater number of symptoms of mental illness.

The Stages of Change Eagerness and Readiness Scale (SOCRATES) 8D

Excluded from analyses due to no adequate validation of the Norwegian version of the scale.

Insomnia Severity Index

Scale range 0-4 (5 steps)

Total score: Summarize scores for all seven items
Clinical categories exist for interpretation, and may be used for presentation purposes at the discretion of the Principal Investigator:

0-7: No clinically significant insomnia
8-14: Subthreshold insomnia
15-21: Clinical insomnia (moderate severity)
22-28: Clinical insomnia (severe)

Temporal Satisfaction with Life Scale, 'Current' Items (TSWLS)

Scale range 1-7.
Total score: Summarize all five items (range: 5-35)

Visual Analogue Scales on Heroin use, craving, treatment satisfaction a.o.

No composite scores – direct interpretation / description of the score on each item