Clinical trial results:
A phase II, randomised, double-blind, placebo- controlled, multi-site, parallel group clinical trial to examine ketamine as a pharmacological treatment for alcohol dependence in an alcohol dependent population.

Summary

EudraCT number	2015-000222-11
Trial protocol	GB
Global end of trial date	07 February 2020

Results information

Result version number	v1 (current)
This version publication date	01 May 2021
First version publication date	01 May 2021

Trial information

Trial identification

Sponsor protocol code	13/0253

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02649231
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Gower Street, London, United Kingdom, WC1E 6BT
Public contact	Samim Patel, University College London, samim.patel@ucl.ac.uk
Scientific contact	Celia Morgan, University College London, Celia.Morgan@exeter.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 February 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 February 2020
Global end of trial reached?	Yes
Global end of trial date	07 February 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1) To obtain preliminary data on whether ketamine is effective in promoting and prolonging abstinence in patients with severe alcohol use disorder following detoxification.

2) To assess safety and tolerability of ketamine in severe alcohol use disorder.

3) To make an early assessment on likely compliance to a combined ketamine and relapse prevention based cognitive behavioural therapy.

4) To obtain preliminary data as to whether ketamine alone is as effective as a combined ketamine and psychotherapy treatment.

Protection of trial subjects:

In-depth screening of physical and mental well-being and concurrent medication prescribed/ used in order to ensure any potential risks related to IMP reduced. Consultation with participant's GP about any potential risks. Number of participants kept as low as possible. Patient have an in depth discussion with medic and psychologist about the study drug and potential effects of the drug to prepare participants for the infusion. Constant monitoring of vitals during infusion. Infusions only administered by anaesthetists. Participants to be kept on study site after infusion until "street ready".

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 June 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 96
Worldwide total number of subjects	96
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	95
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was recruited on 22/09/2016 and the last on 23/07/2019. Patients were recruited in the UK, mainly in the Greater London Area and the south West of England

Pre-assignment

Screening details:

At the screening visit eligibility was determined by a medic, taking the patient's medical history, physical examination, mental health assessments, blood and urine analysis, and breath alcohol tests.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Ketamine, therapy

Arm description:

The active drug treatment (ketamine), and the active therapy treatment (therapy) were administered in this arm.

Arm type	Experimental
Investigational medicinal product name	Ketamine
Investigational medicinal product code	CAS number: 6740-88-1
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

3 x weekly infusions of IV ketamine hydrochloride at a dose of 0.8mg/kg over 40 mins.

Arm title	Ketamine, alcohol education

Arm description:

Active drug treatment (ketamine) and placebo therapy treatment (alcohol education) were administered in this arm.

Arm type	Experimental
Investigational medicinal product name	Ketamine
Investigational medicinal product code	CAS number: 6740-88-1
Other name	
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

3 x weekly infusions of IV ketamine hydrochloride (Ketalar®) at a dose of 0.8mg/kg over 40 mins.

Arm title	Saline, therapy

Arm description:

The placebo drug treatment (saline), and the active therapy treatment (therapy) were administered in this arm.

Arm type	Experimental

Investigational medicinal product name	Saline
Investigational medicinal product code	7647-14-5
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

3 x weekly infusion of placebo (0.9% saline over 40 minutes)

Arm title	Saline, alcohol education

Arm description:

The placebo drug treatment (saline), and the placebo therapy treatment (alcohol education) were administered in this arm.

Arm type	Placebo
Investigational medicinal product name	Saline
Investigational medicinal product code	7647-14-5
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

3 x weekly infusion of placebo (0.9% saline over 40 minutes)

Number of subjects in period 1	Ketamine, therapy	Ketamine, alcohol education	Saline, therapy
Started	24	24	23
Completed	20	21	21
Not completed	4	3	2
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	-	-	-
Lost to follow-up	2	1	1
Protocol deviation	2	1	1

Number of subjects in period 1	Saline, alcohol education
Started	25
Completed	23
Not completed	2
Consent withdrawn by subject	1
Adverse event, non-fatal	1
Lost to follow-up	-
Protocol deviation	-

Baseline characteristics

Reporting groups	
Reporting group title	Ketamine, therapy
Reporting group description:	
The active drug treatment (ketamine), and the active therapy treatment (therapy) were administered in this arm.	
Reporting group title	Ketamine, alcohol education
Reporting group description:	
Active drug treatment (ketamine) and placebo therapy treatment (alcohol education) were administered in this arm.	
Reporting group title	Saline, therapy
Reporting group description:	
The placebo drug treatment (saline), and the active therapy treatment (therapy) were administered in this arm.	
Reporting group title	Saline, alcohol education
Reporting group description:	
The placebo drug treatment (saline), and the placebo therapy treatment (alcohol education) were administered in this arm.	

Reporting group values	Ketamine, therapy	Ketamine, alcohol education	Saline, therapy
Number of subjects	24	24	23
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	24	24	23
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Participant age by treatment group at baseline			
Units: years			
arithmetic mean	45.2	40.5	47.0
standard deviation	± 8.7	± 11.1	± 11.8
Gender categorical			
Gender by treatment group at baseline.			
Units: Subjects			
Female	10	7	8
Male	14	17	15

Reporting group values	Saline, alcohol education	Total	
Number of subjects	25	96	

Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	24	95	
From 65-84 years	1	1	
85 years and over	0	0	
Age continuous			
Participant age by treatment group at baseline			
Units: years			
arithmetic mean	43.7		
standard deviation	± 10.2	-	
Gender categorical			
Gender by treatment group at baseline.			
Units: Subjects			
Female	10	35	
Male	15	61	

End points

End points reporting groups

Reporting group title	Ketamine, therapy
Reporting group description:	
The active drug treatment (ketamine), and the active therapy treatment (therapy) were administered in this arm.	
Reporting group title	Ketamine, alcohol education
Reporting group description:	
Active drug treatment (ketamine) and placebo therapy treatment (alcohol education) were administered in this arm.	
Reporting group title	Saline, therapy
Reporting group description:	
The placebo drug treatment (saline), and the active therapy treatment (therapy) were administered in this arm.	
Reporting group title	Saline, alcohol education
Reporting group description:	
The placebo drug treatment (saline), and the placebo therapy treatment (alcohol education) were administered in this arm.	

Primary: Alcohol relapse at 6 month

End point title	Alcohol relapse at 6 month
End point description:	
Odds for alcohol relapse were lower in the ketamine than the placebo group.	
End point type	Primary
End point timeframe:	
6 months follow-up	

End point values	Ketamine, therapy	Ketamine, alcohol education	Saline, therapy	Saline, alcohol education
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	24	23	25
Units: Number of participants who relapsed				
number (not applicable)	13	15	14	18

Statistical analyses

Statistical analysis title	Intention to treat analysis relapse
Statistical analysis description:	
Confirmed alcohol relapse by drug condition at 6 months using the Alcohol Timeline-Followback. Logistic regression modelling was used to compare the ketamine group with the placebo group (combined across therapy and alcohol education).	
Comparison groups	Ketamine, alcohol education v Saline, therapy v Saline, alcohol education v Ketamine, therapy

Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	1.75

Primary: Percentage days abstinent at 6 month

End point title	Percentage days abstinent at 6 month
End point description:	
Percentage days abstinent according to participants' timeline followback data.	
End point type	Primary
End point timeframe:	
6 months follow-up	

End point values	Ketamine, therapy	Ketamine, alcohol education	Saline, therapy	Saline, alcohol education
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	24	23	25
Units: Percentage days abstinent				
arithmetic mean (standard deviation)	86.4 (± 17.7)	82.5 (± 20.0)	78.3 (± 26.9)	70.7 (± 25.1)

Statistical analyses

Statistical analysis title	Intention to treat analysis % days abstinent

Statistical analysis description:

Linear regression modelling was used to compare the ketamine group with the placebo group (combined across therapy and psychoeducation). Only participants with a minimum of 159 days of completed drinking self-report data were included in the main ITT analysis as this was the shortest duration of time before any participant completed the 6 month (23-25 week) follow up in the study. Reporting time was capped at 180 days.

Comparison groups	Ketamine, therapy v Ketamine, alcohol education v Saline, therapy v Saline, alcohol education
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	10.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	19

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Screening visit (visit 1) to 6 month follow-up visit (visit 10).	
Adverse event reporting additional description:	
Participants were asked about any potential adverse events at the beginning of each visit.	
Assessment type	Systematic

Dictionary used	
Dictionary name	None specified
Dictionary version	N/A

Reporting groups	
Reporting group title	Ketamine, therapy
Reporting group description:	
The active drug treatment (ketamine), and the active therapy treatment (therapy) were administered in this arm.	
Reporting group title	Ketamine, alcohol education
Reporting group description:	
Active drug treatment (ketamine) and placebo therapy treatment (alcohol education) were administered in this arm.	
Reporting group title	Saline, therapy
Reporting group description:	
The placebo drug treatment (saline), and the active therapy treatment (therapy) were administered in this arm.	
Reporting group title	Saline, alcohol education
Reporting group description:	
The placebo drug treatment (saline), and the placebo therapy treatment (alcohol education) were administered in this arm.	

Serious adverse events	Ketamine, therapy	Ketamine, alcohol education	Saline, therapy
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	2 / 23 (8.70%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Brain hemorrhage			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fracture			

subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abdominal pain	Additional description: Abdominal pain secondary to spontaneous abortion		
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Alcohol intoxication			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Kidney infection			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Saline, alcohol education		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 25 (4.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Brain hemorrhage			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skull fracture			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			

Abdominal pain	Additional description: Abdominal pain secondary to spontaneous abortion		
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Alcohol intoxication			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Kidney infection			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Ketamine, therapy	Ketamine, alcohol education	Saline, therapy
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 24 (54.17%)	17 / 24 (70.83%)	16 / 23 (69.57%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 24 (4.17%)	2 / 24 (8.33%)	0 / 23 (0.00%)
occurrences (all)	1	2	0
Surgical and medical procedures			
Arm pain	Additional description: Pain in arm were cannula was administered/ blood was taken from.		
subjects affected / exposed	1 / 24 (4.17%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	2	1	0
Dental implantation			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Hernia repair			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	3 / 24 (12.50%)	6 / 24 (25.00%)	0 / 23 (0.00%)
occurrences (all)	3	10	0
Influenza			
subjects affected / exposed	1 / 24 (4.17%)	1 / 24 (4.17%)	1 / 23 (4.35%)
occurrences (all)	1	2	1
Insomnia			
subjects affected / exposed	2 / 24 (8.33%)	2 / 24 (8.33%)	2 / 23 (8.70%)
occurrences (all)	4	4	2
Mental confusion			
subjects affected / exposed	1 / 24 (4.17%)	2 / 24 (8.33%)	0 / 23 (0.00%)
occurrences (all)	1	2	0
Unsteadiness			
subjects affected / exposed	1 / 24 (4.17%)	2 / 24 (8.33%)	0 / 23 (0.00%)
occurrences (all)	2	2	0
Lack of coordination			
subjects affected / exposed	1 / 24 (4.17%)	2 / 24 (8.33%)	0 / 23 (0.00%)
occurrences (all)	1	2	0
Ankle pain			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences (all)	1	0	1
Chest pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Elbow pain			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Joint pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Knee pain			
subjects affected / exposed	1 / 24 (4.17%)	1 / 24 (4.17%)	1 / 23 (4.35%)
occurrences (all)	1	1	1
Stomach pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1

Toe pain			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Cannula (for infusion) blocked			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Feeling cold			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Fever			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Hot flush			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	2	0	0
Immune system disorders			
Allergic reaction insect bites			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Erection	Additional description: During infusion		
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Throat irritation			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	1 / 23 (4.35%)
occurrences (all)	0	1	1
Viral rhinitis			
subjects affected / exposed	1 / 24 (4.17%)	2 / 24 (8.33%)	2 / 23 (8.70%)
occurrences (all)	1	4	3
Bronchitis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1

Chest infection			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Coughing up blood			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Lower respiratory tract infection			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Nasal congestion			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 24 (8.33%)	1 / 24 (4.17%)	3 / 23 (13.04%)
occurrences (all)	3	1	3
Depressed mood			
subjects affected / exposed	4 / 24 (16.67%)	12 / 24 (50.00%)	7 / 23 (30.43%)
occurrences (all)	5	15	8
Anger			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	1 / 23 (4.35%)
occurrences (all)	0	1	1
Emotional distress during talking session			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Emotionally unstable			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Euphoric mood			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Feelings of altered realilty			

subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Flat affect			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Lethargy			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	3	0	0
Loss of interest in activities			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Mood fluctuations			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Nervousness			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Passive suicidal thoughts			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Seizure during alcohol withdrawal			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Suicidal ideation			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Tearfulness			
subjects affected / exposed	2 / 24 (8.33%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	3	0	0
Injury, poisoning and procedural complications			
Haematoma			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Anaesthetic shivers			

subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Broken thumb			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Cut heel	Additional description: Cause by SCRAM device		
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Cut finger			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Cut at wrist	Additional description: Accident		
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Scratch to forehead	Additional description: After fall		
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Finger fracture			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Hospitalisation due to morphine overdose			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Injured coccyx			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
IV cannula infiltration			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Sprained ankle			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Whiplash associated disorder			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1

Wrist sprain			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Hypotension			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 24 (8.33%)	1 / 24 (4.17%)	2 / 23 (8.70%)
occurrences (all)	2	1	2
Headache			
subjects affected / exposed	3 / 24 (12.50%)	4 / 24 (16.67%)	2 / 23 (8.70%)
occurrences (all)	6	5	2
Impaired concentration			
subjects affected / exposed	0 / 24 (0.00%)	4 / 24 (16.67%)	1 / 23 (4.35%)
occurrences (all)	0	6	1
Memory impairment			
subjects affected / exposed	1 / 24 (4.17%)	3 / 24 (12.50%)	0 / 23 (0.00%)
occurrences (all)	1	3	0
Altered Time perception			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Bodily numbness			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Laceration to forehead due to fall during seizure			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Restless legs syndrome			

subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	2	0	0
Vasovagal syncope			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
ALT and AST increase in blood test			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Chronic lymphocytic leukaemia diagnosis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Low folic acid			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Swollen glands			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Visual distortions			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	1 / 23 (4.35%)
occurrences (all)	0	1	1
Diarrhoea			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Thirst			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Loss of appetite			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Nausea			

subjects affected / exposed	1 / 24 (4.17%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	1	1	0
Vomiting			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Liver function test increased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Skin rash arm			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Skin rash leg			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Dry skin			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Skin irritation			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Two red bumps around eyes			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Cystitis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Haematuria			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	1 / 24 (4.17%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	1	1	0
Muscle pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Neck pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Shoulder pain			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Arthritis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Bursitis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Carpal tunnel syndrome			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Muscle strain thorax			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Strained gluteus maximus			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Stiff neck			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Tendonitis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1

Infections and infestations			
Herpes labialis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Finger infection			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Fungal infection	Additional description: On both hands		
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Mouth ulcer			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	1 / 23 (4.35%)
occurrences (all)	1	0	1
Oral candidiasis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Saline, alcohol education		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 25 (68.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Surgical and medical procedures			
Arm pain	Additional description: Pain in arm were cannula was administered/ blood was taken from.		
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Dental implantation			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Hernia repair			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
General disorders and administration site conditions			

Fatigue				
subjects affected / exposed	4 / 25 (16.00%)			
occurrences (all)	7			
Influenza				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences (all)	0			
Insomnia				
subjects affected / exposed	2 / 25 (8.00%)			
occurrences (all)	4			
Mental confusion				
subjects affected / exposed	2 / 25 (8.00%)			
occurrences (all)	3			
Unsteadiness				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences (all)	1			
Lack of coordination				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences (all)	0			
Ankle pain				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences (all)	1			
Chest pain				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences (all)	0			
Elbow pain				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences (all)	0			
Joint pain				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences (all)	1			
Knee pain				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences (all)	0			
Stomach pain				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences (all)	0			

Toe pain			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Cannula (for infusion) blocked			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Feeling cold			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Fever			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Hot flush			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Allergic reaction insect bites			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	2		
Erection	Additional description: During infusion		
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Throat irritation			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Viral rhinitis			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	4		
Bronchitis			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		

Chest infection			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Coughing up blood			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Lower respiratory tract infection			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Nasal congestion			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Depressed mood			
subjects affected / exposed	6 / 25 (24.00%)		
occurrences (all)	7		
Anger			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Emotional distress during talking session			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Emotionally unstable			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Euphoric mood			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Feelings of altered realilty			

subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Flat affect			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Lethargy			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Loss of interest in activities			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Mood fluctuations			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Nervousness			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Passive suicidal thoughts			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Seizure during alcohol withdrawal			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Suicidal ideation			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Tearfulness			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Haematoma			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	7		
Anaesthetic shivers			

subjects affected / exposed	0 / 25 (0.00%)			
occurrences (all)	0			
Broken thumb				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences (all)	0			
Cut heel	Additional description: Cause by SCRAM device			
subjects affected / exposed	0 / 25 (0.00%)			
occurrences (all)	0			
Cut finger				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences (all)	1			
Cut at wrist	Additional description: Accident			
subjects affected / exposed	0 / 25 (0.00%)			
occurrences (all)	0			
Scratch to forehead	Additional description: After fall			
subjects affected / exposed	0 / 25 (0.00%)			
occurrences (all)	0			
Finger fracture				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences (all)	1			
Hospitalisation due to morphine overdose				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences (all)	1			
Injured coccyx				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences (all)	1			
IV cannula infiltration				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences (all)	0			
Sprained ankle				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences (all)	0			
Whiplash associated disorder				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences (all)	0			

Wrist sprain			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Hypotension			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	8 / 25 (32.00%)		
occurrences (all)	15		
Impaired concentration			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	3		
Memory impairment			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Altered Time perception			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Bodily numbness			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Laceration to forehead due to fall during seizure			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Migraine			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	2		
Restless legs syndrome			

subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Vasovagal syncope			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
ALT and AST increase in blood test			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Chronic lymphocytic leukaemia diagnosis			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Low folic acid			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Swollen glands			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Eye disorders			
Visual distortions			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Thirst			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Loss of appetite			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Nausea			

subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Hepatobiliary disorders			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Liver function test increased			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Skin rash arm			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	5		
Skin rash leg			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Dry skin			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Skin irritation			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Two red bumps around eyes			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Renal and urinary disorders			
Cystitis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Haematuria			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			

Back pain				
subjects affected / exposed	2 / 25 (8.00%)			
occurrences (all)	3			
Muscle pain				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences (all)	0			
Neck pain				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences (all)	1			
Shoulder pain				
subjects affected / exposed	2 / 25 (8.00%)			
occurrences (all)	3			
Arthritis				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences (all)	0			
Bursitis				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences (all)	0			
Carpal tunnel syndrome				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences (all)	0			
Muscle strain thorax				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences (all)	0			
Strained gluteus maximus				
subjects affected / exposed	0 / 25 (0.00%)			
occurrences (all)	0			
Stiff neck				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences (all)	1			
Tendonitis				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences (all)	1			
Toothache				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences (all)	2			

Infections and infestations			
Herpes labialis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Finger infection			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Fungal infection	Additional description: On both hands		
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Mouth ulcer			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Oral candidiasis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 March 2016	The inclusion criteria clarifies only 'True Abstinence' is in regards to contraception in this trial is acceptable and to makes clear that periodic abstinence is not true abstinence
07 March 2016	The addition of Columbia Rating Severity Scale at screening visit as an additional assessment tool to exclude potentially suicidal patients
27 April 2016	Clarifications to the incl./excl. criteria of the protocol, specifically to correct the breathalyser reading to 0.00 to ensure participants cannot have consumed alcohol prior to participation.
27 April 2016	Explanation to the randomisation procedure, specifically pre-randomisation participants will be given a screening ID, whereas post-randomisation this will be updated and participants will be given a patient ID.
27 April 2016	Clarification that two blood samples will be collected for BDNF and Ketamine on infusion days.
27 April 2016	Explanation of the urine drug testing regarding which testing will be performed: to correct an error in the previous protocol as alcohol cannot be screened for by the urine test. The alcohol screen is from the breathalyser reading thus there are no additional tests made by this change. Not all urine tests will be carried out using dip tests, some will be carried out using a urine test cup, therefore this has been made clear in this amendment.
27 April 2016	The purpose of this amendment is to provide further clarification on the eligibility criteria to identify that participants only need to meet criteria within one DSM version not both. Additionally we are specifying that these criteria need to be present within the past 12 months.
27 April 2016	The purpose of this amendment is to clarify that a positive THC urine drug result is not grounds for exclusion. Occasional cannabis use is acceptable though cannabis dependence is grounds for exclusion. Cannabis dependence will be assessed using standardised dependence-related questions.
27 April 2016	The purpose of this amendment is to clarify that the SCID will be used to assess for psychosis as the SPC for ketamine cautions against use in individuals with a history or current diagnosis of psychosis. All other psychiatric diagnoses will be recorded based on self-report information or identification by their medical professional.
21 November 2016	We are increasing the upper age limit for the trial from 60 to 65 years to be in line with the working age. There is no extra implication of this clinically following discussion with study team anaesthetists and psychiatrists.
21 November 2016	We are making it easier for volunteers to meet criteria for an alcohol use disorder in that participants will only be required to have a minimum of a moderate alcohol use disorder as opposed to the original criteria which asked for a severe disorder.
21 November 2016	Benzodiazepines are used in community and inpatient alcohol detox and for sleep problems. They have a relatively long detection window in urine (up to 7 days for long-acting) so we are removing a positive urine benzodiazepine screen from the exclusion criteria at screening as we may erroneously exclude people who have just completed a detox. We will still exclude people with a diagnosis of benzodiazepine dependence.

21 November 2016	Both the Beck Depression Inventory-II and the Hamilton Depression rating Scale are reliable assessments of depression therefore we are including the HAMD here for completeness.
21 November 2016	We want to expand recruitment to include participants that have minimal depression on the BDI and HAM-D. We are already excluding participants who are using anti-depressants, to exclude people who are not depressed is reducing the pool of participants considerably and feel this change would aid recruitment without altering the safety of participants (as we are expanding to include those who are psychologically healthier). This would also not alter the scientific value of the trial as synaptogenesis has been observed in healthy mice following ketamine (Zunszain et al., 2013), thus we think ketamine would still work via its proposed treatment mechanism.
21 November 2016	We are clarifying this exclusion criteria to specify any relevant mental or physical health issues identified by a medically qualified personnel can be grounds for exclusion, specifically including a history of psychosis in the participant, however there is only a risk from a first degree relative if a diagnosis of schizophrenia has been given. There is a large co-morbidity between anxiety and both depression and alcohol use disorder and no clinical implications of including anxiety disorders (phobias, GAD, PTSD), as ketamine is also being trialled as a treatment of these in other settings (https://clinicaltrials.gov/ct2/show/NCT02083926).
21 November 2016	The original criteria is for participants to be willing and able to wear the SCRAM-X data collection bracelet for the duration of the trial, 6 months. However, we have found resistance to this criteria, the idea of wearing the device for 6 months as well as the stigma associated with such a bracelet. Other unforeseen events have also arisen, such as patients having to remove the bracelet to fly and issues with data download if neither a landline or mobile telephone reception is present in patients homes meaning researchers would have to attend patients homes to download the data. Criteria are now revised so that patients will wear the bracelet from screening to the end of active treatment (roughly 2 months). The TLFB, an index of self-reported alcohol consumption, as well as drink diaries, will be used to assess our primary outcome, the gold standard used in other clinical trials of alcoholism.
21 November 2016	Anxiolytics, sedatives and hypnotics (e.g. Librium) are often prescribed to help with alcohol detoxification and also sleep problems that are associated with alcohol dependence. Use of these drugs does not pose a risk alongside our ketamine administration, only when concurrently administered, therefore this criterion from the SPC is inappropriate for the use of ketamine in the manner in which we are using it during this trial. Halogenated anaesthetics are not taken as daily prescribed medications so this is an inappropriate criterion as pointed out by the REC committee during the original meeting. As part of screening procedures we check with the trial medical professionals (anaesthetist and psychiatrist) about all concomitant medications. Therefore it is more thorough and representative to include this criterion
21 November 2016	The original criteria indicated that any liver function test (listed in the protocol) result outside of 3 times the normal range would be grounds for exclusion from the trial. The reason for this being that liver damage is contraindicated in administration of ketamine. This criteria has been updated to specify three specific tests which should be used as indictors of liver damage and therefore grounds for exclusion (bilirubin, ALT and AST). Other listed LFTs provide markers of recent alcohol consumption but not liver impairment and so updating this criteria will not impact on patient safety and is more in line with criteria used in other trials (http://archpsyc.jamanetwork.com/article.aspx?articleid=2548275)
21 November 2016	It has become apparent after screening a number of patients that 'detoxifications' is ambiguous therefore we have added 'inpatient' to disambiguate this phrase. The criterion was included to exclude the very severe, higher risk of relapse and evidence suggest that these are those that have undertaken a very high number of inpatient detoxification programmes.

21 November 2016	We are expanding our recruitment to enlist the help of GPs to send invitations to participate to eligible patients across CCGs in the South West and London. The amendment to add these PICs has been approved (amendment number: 15/SW/0312/AM03 – PIC sites) Additionally, we have designed a recruitment flyer which can be given to staff working in PICs to help them when trying to identify potential participants and to aid discussion which such participants.
21 November 2016	The screening visit should originally have been within 14 days of the baseline visit. This has been updated so that visits could be 28 days apart. We will still endeavour to have these two visits within 14 days however this provides flexibility if participants have other commitments e.g. work, which get in the way of this specific timeline.
21 November 2016	A refresher screening session has been added to the protocol for those instances where more than 28 days elapses between screening and baseline visit. Such a situation might arise if participants relapse in between visits, yet is a participant becomes abstinent again and wishes to continue with the trial then we would like to provide the option for such a situation to occur. We are therefore defining the procedure for what would happen if such an event was to arise. All measures which could have changed in the elapsed timeframe and proposed to be readminstered to the participant.
27 April 2017	Further clarification to timepoints of data collection for the vital sign assessments on infusion days: vital signs will be continuously monitored through infusion but the eCRF will detail specific sets of readings at 3 time points, prior to infusion, after infusion and after recovery.
13 September 2017	Updated to provide clarity to several criteria which should be judged by medically qualified personnel. • How to determine previous or current dependence is outlined based on trial personnel discussions, i.e. including this within the GP letter and self-reported seeking of help for a drug problem. • Only clinically relevant neuropsychological difficulties should influence eligibility for the trial. • How to clarify what classes as a seizure has been added based on trial team discussions, i.e. they should be medically witnessed by an appropriate clinician and there should be documented evidence from an EEG or a history consistent with a diagnosis of epileptiform illness. • Current suicidal ideation should be considered relevant to eligibility which would require discussion between the clinical team.
13 September 2017	Clarification that any medications which are deemed to pose a risk when combined with ketamine can be grounds for exclusion from the trial, not just those medications listed.
13 September 2017	Clarification that a current diagnosis of the physical health conditions outlined would be grounds for exclusion if the risk benefit ratio was not in favour of giving ketamine by medically qualified personnel. Criteria updated: • Patients receiving thyroid replacement has been removed as this is a duplication of the criteria outlined in the medication section listing thyroid hormone treatment as an exclusion criteria. • Diabetes has been removed from this list as this was a requirement when participants were wearing the SCRAM-X bracelet for 6 months, however they now wear this only during active treatment (visits 1-8). The SCRAM bracelet is checked weekly at these visits and so this criterion is no longer relevant based on the current protocol. • Neurological condition/brain damage has been removed from this list as this is duplication as this is covered by points e and h in this criterion. • Clarification of what exactly presence of a head injury means

13 September 2017	Participants in the KARE trial are judged as 'street ready' by an anaesthetist after their infusion. However, it is not always possible to arrange for a responsible adult to collect a participant after a visit therefore wording has been added to indicate that if a responsible adult is not able to pick up the participant after the visit then transportation will be arranged for that participant.
13 September 2017	Updated definition of expected adverse event to reflect that this isn't a serious event as the classification of seriousness is used throughout this protocol to indicate how an adverse event should be reported. Expected AEs are reported in source whereas Unexpected AEs are reported in the eCRF as well as source.
13 September 2017	The protocol currently states that visits 3, 5 and 7 should always be one day after visits 2, 4 and 6 respectively, and that failure to attend one of these visits leads to exclusion from the trial. Every effort should be made to maintain this rule, however if a participant has a valid reason for being unable to attend one of these visits then some flexibility can be given, up to 5 days, to avoid exclusion. However, if a participant fails to attend this re-arranged appointment then they will be excluded from the trial.
04 April 2018	Update to reflect that the bracelet can be removed if deemed necessary by the study team.
04 April 2018	SCRAM-X bracelets cannot always be attached to participants at screening visit due to uncertainty around participant eligibility and difficulty in getting the bracelets back. Where possible a bracelet will be attached at screening, however anytime within the window of screening to baseline visit is acceptable.
04 April 2018	We will not exclude participants from the trial if they start taking anti-depressants during follow-up therefore we are clarifying that only during active treatment i.e. visit 2-8, would this be an issue for eligibility. This is being updated as ethically we don't feel that we can ask participants not to take anti-depressants during the follow up phase of this trial if they are deemed by a medical professional to be needed for the participant's mental health.
06 September 2018	Update to the protocol to allow re-consenting of patients by trial psychologists (including research assistants and postdoctoral research associates.
06 September 2018	Update for possibility to repeat some of the screening period assessments if initially they did not meet criteria for eligibility. Some of the eligibility criteria in this trial relate to physical variables which can change with time. If participants prior to randomisation are judged to be ineligible based on one such characteristic e.g. elevated blood pressure, elevated LFTs, BMI outside of protocol limits, or a positive urine drug test due to recreational use, they will be invited back to re-do one or more such tests to truly determine whether they should be excluded based on this characteristic. For example, blood pressure can be elevated by situational anxiety or recent alcohol withdrawal, both of which are not indicative of uncontrolled hypertension. If a participant came back and blood pressure was found to be within trial limits prior to randomisation then we would include this participant. Additionally, due to the nature of alcoholism LFTs can be elevated outside of protocol limits. However the liver regenerates when alcohol use is stopped. We will repeat LFTs and if significant improvement has been seen putting the participant within protocol limits then they would be included. If a participant is too overweight or underweight to participate then those who lose or gain weight respectively so that their BMI is within trial limits will be included in the trial. Participants who only recreationally take other substances, without any evidence of current or prior dependence, who test positive for a substance will be informed this is an exclusion factor and given the chance to repeat such tests at a later date. If found to be negative for such substances in the future then participants would be included in the study.
06 September 2018	Patient information sheet updated to reflect GDPR compatibility.
11 January 2019	Updates to the protocol to clarify the purpose of the breathalyser test in the study and the follow-up visit schedule for participants that are withdrawn/discontinued from treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

N/A

Notes: