



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

| | | | |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 | 0 / 24 (0.00%) 0 | 0 / 23 (0.00%) 0 |
| Flat affect subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 | 1 / 24 (4.17%) 1 | 0 / 23 (0.00%) 0 |
| Lethargy subjects affected / exposed occurrences (all) | 1 / 24 (4.17%) 3 | 0 / 24 (0.00%) 0 | 0 / 23 (0.00%) 0 |
| Loss of interest in activities subjects affected / exposed occurrences (all) | 1 / 24 (4.17%) 1 | 0 / 24 (0.00%) 0 | 0 / 23 (0.00%) 0 |
| Mood fluctuations subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 | 0 / 24 (0.00%) 0 | 1 / 23 (4.35%) 1 |
| Nervousness subjects affected / exposed occurrences (all) | 1 / 24 (4.17%) 1 | 0 / 24 (0.00%) 0 | 0 / 23 (0.00%) 0 |
| Passive suicidal thoughts subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 | 1 / 24 (4.17%) 1 | 0 / 23 (0.00%) 0 |
| Seizure during alcohol withdrawal subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 | 0 / 24 (0.00%) 0 | 0 / 23 (0.00%) 0 |
| Suicidal ideation subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 | 1 / 24 (4.17%) 1 | 0 / 23 (0.00%) 0 |
| Tearfulness subjects affected / exposed occurrences (all) | 2 / 24 (8.33%) 3 | 0 / 24 (0.00%) 0 | 0 / 23 (0.00%) 0 |
| Injury, poisoning and procedural complications Haematoma subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 | 1 / 24 (4.17%) 1 | 0 / 23 (0.00%) 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 occurrences (all) | 0 / 24 (0.00%) 0 | 1 / 24 (4.17%) 1 | 0 / 23 (0.00%) 0 |
| Cardiac disorders | | | |
| Tachycardia subjects affected / exposed occurrences (all) | 1 / 24 (4.17%) 1 | 0 / 24 (0.00%) 0 | 0 / 23 (0.00%) 0 |
| Hypotension subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 | 0 / 24 (0.00%) 0 | 1 / 23 (4.35%) 1 |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 2 / 24 (8.33%) 2 | 1 / 24 (4.17%) 1 | 2 / 23 (8.70%) 2 |
| Headache subjects affected / exposed occurrences (all) | 3 / 24 (12.50%) 6 | 4 / 24 (16.67%) 5 | 2 / 23 (8.70%) 2 |
| Impaired concentration subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 | 4 / 24 (16.67%) 6 | 1 / 23 (4.35%) 1 |
| Memory impairment subjects affected / exposed occurrences (all) | 1 / 24 (4.17%) 1 | 3 / 24 (12.50%) 3 | 0 / 23 (0.00%) 0 |
| Altered Time perception subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 | 0 / 24 (0.00%) 0 | 0 / 23 (0.00%) 0 |
| Bodily numbness subjects affected / exposed occurrences (all) | 1 / 24 (4.17%) 1 | 0 / 24 (0.00%) 0 | 0 / 23 (0.00%) 0 |
| Laceration to forehead due to fall during seizure subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 | 0 / 24 (0.00%) 0 | 0 / 23 (0.00%) 0 |
| Migraine subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 | 0 / 24 (0.00%) 0 | 0 / 23 (0.00%) 0 |
| Restless legs syndrome | | | |

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

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

Additional description: On both hands

| | | | |
|---|---------------------------|--|--|
| 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 occurrences (all) | 1 / 25 (4.00%) 1 | | |
| Surgical and medical procedures Arm pain subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | | |
| Dental implantation subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | | |
| Hernia repair subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | | |
| General disorders and administration site conditions | | | |

Additional description: Pain in arm were cannula was administered/ blood was taken from.

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

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

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

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

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

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

| | | | |
|-----------------------------|----------------|--|--|
| 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 | | |

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
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| 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. |

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| 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 indicators 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. |

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| 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 with 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 readministered 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. <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 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 |

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| 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.

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