# Clinical trial results:
# The effect of a single-dose of d-cycloserine on the basic effects of cognitive-behaviour therapy for panic disorder - a randomized placebo-controlled trial

## Summary

| | |
|---|---|
| EudraCT number | 2012-003191-39 |
| Trial protocol | GB |
| Global end of trial date | 27 September 2017 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 17 July 2019 |
| First version publication date | 17 July 2019 |
| Summary attachment (see zip file) | Study summary (Eudract summary Reinecke.pdf) |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | 12/SC/0686- version 5 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01680107 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | University of Oxford |
| Sponsor organisation address | Churchill Drive, Oxford, United Kingdom, OX3 7GB |
| Public contact | Heather House, Clinical Trials and Research Governance Research Services, ctrg@admin.ox.ac.uk |
| Scientific contact | Dr Andrea Reinecke, Department of Psychiatry, andrea.reinecke@psych.ox.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 | 20 September 2018 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 27 September 2017 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

Does the combination of a single-session of cognitive-behaviour therapy (CBT) with the cognitive enhancer d-cycloserine (compared to placebo) lead to greater reduction in threat bias (computerised behavioural reaction tasks) on the day after treatment?

Protection of trial subjects:

Fifty per cent of patients were randomised to taking the drug d-cycloserine which can cause CNS manifested side effects such as headaches, drowsiness or tremor. However, such effects are usually not seen when using single doses and doses below 500mg (see Summary of Product Characteristics), and DCS has had MHRA market authorisation for more than 15 years (license number King Pharmaceuticals: 143850005). Participants were monitored closely by a physician after drug intake, and if judged to be at any risk, or if they did not wish to continue, were withdrawn from the study (no cases of withdrawal for that reason) . Moreover, they received an emergency phone number at the end of the Treatment Visit to be able to get in touch with one the researchers 24hrs after drug intake.
Also, patients were required to be in an MRI scanner. For most subjects, MRI is a safe, non-invasive imaging technique. However, as the scanner consists of a powerful magnet, it may attract certain metallic objects, leading to several situations in which it may be unsafe to scan a subject (e.g. metal implant). All subjects were therefore screened prior to being scanned, following the Oxford Centre for Clinical Magnetic Resonance Research standard operating procedure for safety screening . In the case of an incidental finding of a suspected brain abnormality, the Principal Investigator would alert the OCMR/FMRIB Contact Radiographer who, if appropriate (i.e. not a simple artefact) would independently inform a dedicated local hospital NHS consultant clinician. They would in turn obtain the opinion of the Contact Radiologist, and decide on the appropriate course of action, which might involve contact with the individual at the earliest opportunity and possible further investigation. This would all take place within the NHS framework and in communication with the volunteer’s GP. Subjects are informed of this standard procedure for incidental findings.

Background therapy:

Single-session cogniitve behaviour therapy, exposure-based.
Two hours after capsule intake (d-cycloserine or placebo), participants received a single session of CBT. To achieve a high level of standardization in treatment delivery, the CBT session followed a strict protocol (Reinecke et al., Biol Psych 2013; Salkovskis et al., 1999), including written delivery of the treatment rationale and 15 mins exposure to an individually relevant moderately agoraphobic situation chosen out of a pool of standard situations (e.g. being in a small cleaning closet). In particular, the role of safety seeking behaviour (i.e. behaviours to quickly reduce anxiety, e.g. leaving the situation early, sitting down) in the maintenance of the disorder was explained (e.g. I haven't had a heart attack because I have left on time.), and how dropping safety behaviour during exposure to fear-provoking symptoms and situations would help to effectively reduce anxiety (e.g. Even if I jump up and down in a crowded supermarket when my heart starts racing I won't have a heart attack.). Patient and therapist then agreed on exposure to an individually threatening situation while dropping all safety behaviour. A Standard Operating Procedure document for CBT delivery was in place at the start of the study.

Evidence for comparator:

Placebo as a standard comparator in active drug trials

| | |
|---|---|
| Actual start date of recruitment | 01 January 2013 |
| 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: 33 |
| Worldwide total number of subjects | 33 |
| EEA total number of subjects | 33 |

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) | 32 |
| From 65 to 84 years | 1 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Recruitment from the general public, through advertisements in newspapers, anxiety groups and websites, through radio advertisements, and through posters and flyers in GP practices, psychological outpatient clinics and counselling services, universities and other public places.

### Pre-assignment

Screening details:

Via email or phone, assessing age, medication during the last 6 weeks and psychological treatment in the past, serious physical illnesses, pregnancy, MRI contraindications, type of anxiety.

### Period 1

| | |
|---|---|
| Period 1 title | Baseline |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Assessor |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | D-cycloserine |

Arm description: -

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | d-cycloserine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, soft |
| Routes of administration | Oral use |

Dosage and administration details:

250 mg single dose, oral

| | |
|---|---|
| **Arm title** | Placebo |

Arm description: -

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | microcrystalline cellulose |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, soft |
| Routes of administration | Oral use |

Dosage and administration details:

oral single dose

| **Number of subjects in period 1** | D-cycloserine | Placebo |
|---|---|---|
| Started | 17 | 16 |
| Completed | 17 | 16 |

| **Period 2** | |
|---|---|
| Period 2 title | Outcome: Next-day, 1-M, 6-M |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Assessor |

| **Arms** | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | D-cycloserine |

Arm description:
active drug

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | d-cycloserine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, soft |
| Routes of administration | Oral use |

Dosage and administration details:
250 mg single dose, oral

| **Arm title** | Placebo |
|---|---|

Arm description:
non-active placebo

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | microcrystalline cellulose |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, soft |
| Routes of administration | Oral use |

Dosage and administration details:
oral single dose

| **Number of subjects in period 2** | D-cycloserine | Placebo |
|---|---|---|
| Started | 17 | 16 |
| Completed | 17 | 16 |

## Baseline characteristics

## End points

| End points reporting groups | |
|---|---|
| Reporting group title | D-cycloserine |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |
| Reporting group title | D-cycloserine |
| Reporting group description:<br>active drug | |
| Reporting group title | Placebo |
| Reporting group description:<br>non-active placebo | |
| Subject analysis set title | Baseline |
| Subject analysis set type | Full analysis |
| Subject analysis set description:<br>baseline data in the two arms | |

| Primary: threat bias dot probe | |
|---|---|
| End point title | threat bias dot probe |
| End point description: | |
| End point type | Primary |
| End point timeframe:<br>Next-day testing | |

| End point values | D-cycloserine | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 17 | 16 | | |
| Units: dot probe effect | | | | |
| arithmetic mean (standard deviation) | 2.1 (± 17.2) | 21.3 (± 30.8) | | |

### Statistical analyses

| Statistical analysis title | Next-day threat bias |
|---|---|
| Comparison groups | D-cycloserine v Placebo |
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.042 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -19 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -38.04 |
| upper limit | 0.14 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 9.3 |

| **Secondary: amygdala response** | |
|---|---|
| End point title | amygdala response |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Next-day | |

| **End point values** | D-cycloserine | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 | 14 | | |
| Units: BOLD % signal change | | | | |
| arithmetic mean (standard deviation) | -0.08 (± 0.35) | 0.25 (± 0.27) | | |

**Statistical analyses**

| **Statistical analysis title** | amygdala response |
|---|---|
| Comparison groups | Placebo v D-cycloserine |
| Number of subjects included in analysis | 27 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.023 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.61 |
| upper limit | -0.03 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.14 |

## Secondary: 1-M recovery rates

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|---|---|
| End point title | 1-M recovery rates |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

1-M follow-up

| End point values | D-cycloserine | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16 | 15 | | |
| Units: patients | 12 | 4 | | |

### Statistical analyses

| Statistical analysis title | recovery rates 1-M FU |
|---|---|
| Comparison groups | D-cycloserine v Placebo |
| Number of subjects included in analysis | 31 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.015 |
| Method | Chi-squared corrected |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 2.55 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.16 |
| upper limit | 5.61 |
| Variability estimate | Standard error of the mean |

## Adverse events

### Adverse events information[1]

Timeframe for reporting adverse events:

All SAEs had to be reported to the sponsor within 24 hours of discovery or notification of the event. No such events occured throughout the study.

| | |
|---|---|
| Assessment type | Non-systematic |

### Dictionary used

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|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 21 |

Frequency threshold for reporting non-serious adverse events: 0 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: There have been no adverse events seen in this study, probably due to the nature of this study (only a single dose of a drug or placebo).

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 31 January 2013 | prior to trial start: study drug turns out not to be red-white but red-grey, therefore change of placebo capsules to red-grey as well, allows full blinding. |
| 12 September 2013 | recruitment strategy is extended to radio advertisement |
| 25 May 2017 | be able to look at 'genes associated with emotional processing' rather than 'serotonin transporter gene' only |

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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| early termination leading to small number of subjects (although in line with amended pwoer analysis) |

Notes: