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: active drug	
Reporting group title	Placebo
Reporting group description: non-active placebo	
Subject analysis set title	Baseline
Subject analysis set type	Full analysis
Subject analysis set description: 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: 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

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

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.

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

Notes: