Clinical trial results:
Mechanisms of action in exposure therapy:
Decoding the neural basis of fear extinction and its pharmacological modulation in patients with panic disorder

Summary

EudraCT number	2010-023044-32
Trial protocol	DE
Global end of trial date	31 March 2014

Results information

Result version number	v1 (current)
This version publication date	01 March 2022
First version publication date	01 March 2022

Trial information

Trial identification

Sponsor protocol code	DCS-fMRIPanik

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Charité - Universitätsmedizin Berlin
Sponsor organisation address	Charitéplatz 1, Berlin, Germany, 10117
Public contact	Prof. Dr. Andreas Ströhle Klinik für Psychiatrie und Psychotherapie Campus Charité Mitte, Charité - Universitätsmedizin Berlin, 030 450517034, andreas.stroehle@charite.de
Scientific contact	Koordinierungszentrum für klinische Studien der Charité KKS Charité Augustenburger Platz 1 13353 , Charité - Universitätsmedizin Berlin, 030 450 553 875, regulatory-kks@charite.de

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	31 March 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Changes in neuronal activation patterns of the three measurements of time in the "Extinction Circuit" (eg amygdala, hippocampus, medial prefrontal cortex)

Protection of trial subjects:

Please see subject disposition

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 February 2012
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	Germany: 37
Worldwide total number of subjects	37
EEA total number of subjects	37

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)	37
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

advertisemnts in newspapers, internet and the ambulance were used during a recruitment period of 18 months

Pre-assignment

Screening details:

Height, Weight, Bloodpressure, Pulse, ECG, psychiatric Examination, Blood Examination, Clinical Chemistry, Pregnancy Test, DrugScreening, urinanalysis
Clinical Scales: Composite International Diagnostic Interview (CIDI/DIA-X); Hamilton Anxiety Rating (HAMA); SIGH-A Interviewform; Clinical Global Impression Panic Scale (CGIpanic); ....

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	DCS-Group

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Seromycin
Investigational medicinal product code	SUB06863MIG
Other name	CYCLOSERINE
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Participants received an
oral dose of 50 mg of DCS (reformulated from 250 mg capsules, Seromycin®, USA) 1 h before extinction on Day 2.

Arm title	Placebo-Group

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Participants received an
oral dose of 50 mg of Placebo 1 h before extinction on day 2

Number of subjects in period 1	DCS-Group	Placebo-Group
Started	20	17
Completed	20	17

Baseline characteristics

Reporting groups	
Reporting group title	DCS-Group
Reporting group description: -	
Reporting group title	Placebo-Group
Reporting group description: -	

Reporting group values	DCS-Group	Placebo-Group	Total
Number of subjects	20	17	37
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)	20	17	37
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	25.87	27.82	
standard deviation	± 5.67	± 5.24	-
Gender categorical Units: Subjects			
Female	9	7	16
Male	11	10	21
Smoking status Units: Subjects			
smoker	7	5	12
non-smoker	12	11	23
no information	1	1	2
Neuroticism Units: Score			
arithmetic mean	1.58	1.56	
standard deviation	± 0.36	± 0.26	-
Anxiety Sensitivity Index Units: Score			
arithmetic mean	8.75	8.69	
standard deviation	± 6.33	± 5.4	-
Trail making test TMT A Units: Score			
arithmetic mean	22.80	23.93	
standard deviation	± 6.00	± 5.71	-
Trail making test TMT B			

Units: Score			
arithmetic mean	46.85	50.47	
standard deviation	± 11.14	± 13.57	-
Regensburg Verbal Fluency Test - P words			
Units: Score			
arithmetic mean	11.15	13.53	
standard deviation	± 3.80	± 3.56	-
Regensburg Verbal Fluency Test - K words			
Units: Score			
arithmetic mean	14.95	15.27	
standard deviation	± 3.14	± 4.74	-
Range of numbers - forward			
Units: Score			
arithmetic mean	8.60	8.80	
standard deviation	± 1.85	± 1.20	-
Range of numbers - backwards			
Units: Score			
arithmetic mean	8.25	8.53	
standard deviation	± 1.88	± 2.32	-

End points

End points reporting groups

Reporting group title	DCS-Group
Reporting group description: -	
Reporting group title	Placebo-Group
Reporting group description: -	

Primary: fMRI shows DCS effects on return of Fear in the amygdala Region

End point title	fMRI shows DCS effects on return of Fear in the amygdala Region

End point description:

placebo compared to DCS subjects showed
significant increases in differential BOLD (Blood-Oxygen-
Level-Dependent) responses in the left
amygdala (MNI peak at [x: −24, y: 2) and
left posterior hippocampus (MNI peak at [x: −33, y: −34, z: −8]) from extinction learning to recall.
For more information see Fig. 3

End point type	Primary

End point timeframe:

2 Days

End point values	DCS-Group	Placebo-Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	17		
Units: Score				
arithmetic mean (standard deviation)				
extinction cs+	0.3 (± 0.1)	-0.13 (± 0.1)		
extinction cs-	-0.10 (± 0.1)	0.05 (± 0.1)		
recall cs+	-0.3 (± 0.1)	0.18 (± 0.1)		
recall cs-	0.1 (± 0.1)	-0.10 (± 0.1)		

Attachments (see zip file)	behavioral and neural measures of ROF/Dok1.docx

Statistical analyses

Statistical analysis title	Behavioral and psychophysiological measures

Statistical analysis description:

All analyses
included study site as a covariate and were performed using R
software (v3.4.3; [38]).Conditioning effects in valence and arousal
ratings were analyzed in separate repeated measures ANCOVAs
(rmANCOVA) with within-subject factors cue (CS+/CS−) and time
(pre-/post-acquisition on day 1).

Comparison groups	DCS-Group v Placebo-Group

Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05 [1]
Method	ANCOVA

Notes:

[1] - Our analyses focused on predefined regions of interest (ROIs) using small volume correction (SVC) at p < 0.05 FWE-corrected, specifically, insula, dACC, amygdala, hippocampus and vmPFC

Secondary: DCS prevented the return of fear in arousal ratings

End point title	DCS prevented the return of fear in arousal ratings

End point description:

Participants receiving placebo but not DCS experienced a generalized ROF in arousal ratings, mainly driven by increases towards the CS+ from post-extinction to pre-recall.

End point type	Secondary

End point timeframe:

2days

End point values	DCS-Group	Placebo-Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	17		
Units: Score				
arithmetic mean (standard deviation)				
post extinction cs+	1.9 (± 0.1)	2.2 (± 0.1)		
post extinction cs-	1.7 (± 0.1)	1.9 (± 0.1)		
pre recall cs+	1.8 (± 0.1)	2.8 (± 0.1)		
pre recall cs-	1.7 (± 0.1)	2 (± 0.1)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: immediately within 24 hours	
Assessment type	Systematic

Dictionary used	
Dictionary name	Direktive 2001/20 EG
Dictionary version	4-Apr-2001

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: No adverse event were reported.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28512009

http://www.ncbi.nlm.nih.gov/pubmed/31634897