Clinical trial results:
D-cycloserine augmented exposure therapy in patients with agoraphobia

Summary

EudraCT number	2011-001398-19
Trial protocol	DE
Global end of trial date	25 April 2014

Results information

Result version number	v1 (current)
This version publication date	14 May 2022
First version publication date	14 May 2022
Summary attachment (see zip file)	2018_LearnToForget-DoesPost-exposureAdministrationOfD-cycloserineEnhanceFearExtinctionInAgoraphobia (2018_LearnToForget-DoesPost-exposureAdministrationOfD-cycloserineEnhanceFearExtinctionInAgoraphobia.pdf)

Trial information

Trial identification

Sponsor protocol code	Exposition-DCS

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01928823
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Charité - Universitätsmedizin Berlin
Sponsor organisation address	Charitéplatz 1, Berlin, Germany, 10117
Public contact	Dipl.-Psych. Lena Pyrkosch, Charité - Universitätsmedizin Berlin Klinik für Psychiatrie und Psychotherapie, +49 30 450517214, lena.pyrkosch@charite.de
Scientific contact	Prof. Dr. Andreas Ströhle, Charité - Universitätsmedizin Berlin Klinik für Psychiatrie und Psychotherapie, +49 30 450517034 , andreas.stroehle@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	25 April 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 April 2014
Global end of trial reached?	Yes
Global end of trial date	25 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Aim of the trial is to investigate if d-cycloserine augmented exposure therapy reduces agoraphobic symptomatology to a greater extend than placebo augmented exposure therapy.

Protection of trial subjects:

Safty/Data- Committees and Evaluation- Comitte: 2 external Monitoring appointments (12.12.2012, 07.03.2014)
fallowed by a continuous monitoring by a project-external employee .

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 November 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 73
Worldwide total number of subjects	73
EEA total number of subjects	73

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)	71
From 65 to 84 years	2

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Clinical and diagnosic sessions were held -56 to -1 days before the first therapy session.

Pre-assignment

Screening details:

Screening: 145
Informed Consent: 94
Study inclusion: 78
Randomization: 73
Dropouts: 4

For participating in the study inclusion and exclusion criteria according to AMG §40 had to be confirmed.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	DCS Arm

Arm description:

Patients underwent 3 exposure sessions with two rounds respectively. Within 30 min after the second round of exposure patients were given double blind and randomized 50 mg of DCS by oral administration.

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

Dosage and administration details:

Each capsule contains 50mg Cycloserin. Subjects received one caspule after therapy session: 3, 4 and 5.

Arm title	PBO Arm

Arm description:

Patients underwent 3 exposure sessions with two rounds respectively. Within 30 min after the second round of exposure patients were given double blind and randomized the PBO.

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

Dosage and administration details:

each capsule contains 50mg of placebo (DAC NRF :99,5% Mannitol, 0,5% highly dispersed Siliciumdioxid). Subjects received a capsule after the session 3,4 and 5.

Number of subjects in period 1	DCS Arm	PBO Arm
Started	36	37
Completed	36	33
Not completed	0	4
Protocol deviation	-	4

Baseline characteristics

Reporting groups	
Reporting group title	DCS Arm
Reporting group description:	
Patients underwent 3 exposure sessions with two rounds respectively. Within 30 min after the second round of exposure patients were given double blind and randomized 50 mg of DCS by oral administration.	
Reporting group title	PBO Arm
Reporting group description:	
Patients underwent 3 exposure sessions with two rounds respectively. Within 30 min after the second round of exposure patients were given double blind and randomized the PBO.	

Reporting group values	DCS Arm	PBO Arm	Total
Number of subjects	36	37	73
Age categorical Units: Subjects			
Adults (18-75 years)	36	37	73
Age continuous Units: years			
arithmetic mean	34.10	40.86	
standard deviation	± 10.37	± 12.94	-
Gender categorical Units: Subjects			
Female	14	11	25
Male	22	26	48
Diagnosis			
F40.00: No indication of panic disorder F40.01: With panic disorder			
Units: Subjects			
F40.00	10	10	20
F40.01	26	27	53
Axis I comorbidities Units: Subjects			
none	24	25	49
>= one	12	12	24
Axis II personality disorders Units: Subjects			
none	24	25	49
>= one	12	12	24
Ongoing psychopharmacotherapy Units: Subjects			
No	24	18	42
Yes	12	19	31
Family status Units: Subjects			
Single	16	16	32
Stable relationship	20	21	41
Living situation Units: Subjects			

Alone	14	8	22
With family/ friends	22	29	51
Education Units: Subjects			
No high school diploma	13	11	24
High school diploma or higher	23	26	49
Occupational status Units: Subjects			
None	8	7	15
Part time or other	15	7	22
Full time	13	22	35
N/A	0	1	1
PAS observer-rated sum score			
The Panic and Agoraphobia Scale (PAS): The PAS is a reliable, valid and internationally used scale for the determination of severity of disease in patients with agoraphobia and/ or panic disorder (Bandelow, 1995). In many therapy studies also its sensitivity for measuring change or improvement of symptomatology was demonstrated (Bandelow, 1995). For the present trial, the PAS was used in the self-rated and observer-rated (by therapist) version.			
Units: Scale			
arithmetic mean	24.74	22.03	
standard deviation	± 8.96	± 7.77	-
PAS self-rated sum score			
The Panic and Agoraphobia Scale (PAS): The PAS is a reliable, valid and internationally used scale for the determination of severity of disease in patients with agoraphobia and/ or panic disorder (Bandelow, 1995). In many therapy studies also its sensitivity for measuring change or improvement of symptomatology was demonstrated (Bandelow, 1995). For the present trial, the PAS was used in the self-rated and observer-rated (by therapist) version.			
Units: Scale			
arithmetic mean	20.68	19.20	
standard deviation	± 10.31	± 9.69	-
ACQ mean			
Agoraphobic Cognitions Questionnaire (ACQ): The ACQ consists of 14 items measuring the patients central phobic cognitions, e. g. "I am going to pass out". It may be scored as a total scale or according to its two subscales (loss of control and physical concerns).			
Units: Scale			
arithmetic mean	2.11	2.01	
standard deviation	± 0.44	± 0.55	-
BSQ mean			
Body Sensations Questionnaire (BSQ): The BSQ, consisting of 17 items, is a valid an reliable instrument to assess the patients phobic fear of bodily symptoms such as "heart beat" or "dizziness".			
Units: Scale			
arithmetic mean	2.67	2.68	
standard deviation	± 0.74	± 0.83	-
MI alone mean			
Mobility Inventory (MI): In the MI 26 situations are rated for avoidance by the patients both when they are alone (subscale MI alone) or when they are accompanied (subscale MI accompanied).			
Units: Scale			
arithmetic mean	2.69	2.56	
standard deviation	± 0.99	± 0.84	-
MI accompanied mean			

Mobility Inventory (MI): In the MI 26 situations are rated for avoidance by the patients both when they are alone (subscale MI alone) or when they are accompanied (subscale MI accompanied).			
Units: Scale			
arithmetic mean	2.10	1.88	
standard deviation	± 0.79	± 0.61	-
ASI sum score			
Anxiety Sensitivity Index (ASI): The 16-item ASI measures the patients' fear of anxiety-related sensations and the evaluation about their harmful consequences. The ASI was shown to also display good sensitivity to change over the course of treatment.			
Units: Score			
arithmetic mean	27.55	28.13	
standard deviation	± 10.32	± 9.17	-
BAI sum score			
Beck Anxiety Inventory (BAI): The BAI, containing 21 items, is a valid and reliable inventory for measuring common symptoms of clinical anxiety, e. g. numbness or sweating.			
Units: Score			
arithmetic mean	21.44	21.25	
standard deviation	± 12.24	± 12.21	-
BDI II sum score			
Beck Depression Inventory (BDI): As for the high overlap between anxiety and depression we considered it important to also assess depressive symptoms in our patient sample with the help of the most commonly used inventory BDI II.			
Units: Score			
arithmetic mean	12.03	10.94	
standard deviation	± 8.62	± 8.76	-
BSI sum score			
Brief Symptom Inventory (BSI): We decided to apply the BSI in order to also have a measure for general psychopathological symptoms pertaining to different disorder-specific domains.			
Units: Score			
arithmetic mean	39.71	35.58	
standard deviation	± 26.00	± 26.58	-
CGI			
Clinical Global Impression (CGI): The CGI is a very easy to apply clinician rated scale measuring global severity of illness. Although short it is one of the most widely used brief assessment tools in psychiatry.			
Units: Scale			
arithmetic mean	5.31	4.89	
standard deviation	± 0.62	± 0.61	-
Duration of disease Units: Months			
arithmetic mean	49.91	122.25	
standard deviation	± 53.97	± 111.59	-

End points

End points reporting groups

Reporting group title	DCS Arm
Reporting group description:	
Patients underwent 3 exposure sessions with two rounds respectively. Within 30 min after the second round of exposure patients were given double blind and randomized 50 mg of DCS by oral administration.	
Reporting group title	PBO Arm
Reporting group description:	
Patients underwent 3 exposure sessions with two rounds respectively. Within 30 min after the second round of exposure patients were given double blind and randomized the PBO.	

Primary: PAS observer-rated sum score

End point title	PAS observer-rated sum score
End point description:	
The Panic and Agoraphobia Scale (PAS): The PAS is a reliable, valid and internationally used scale for the determination of severity of disease in patients with agoraphobia and/ or panic disorder (Bandelow, 1995). In many therapy studies also its sensitivity for measuring change or improvement of symptomatology was demonstrated (Bandelow, 1995). For the present trial, the PAS was used in the self-rated and observer-rated (by therapist) version.	
End point type	Primary
End point timeframe:	
t1 up to t11	

End point values	DCS Arm	PBO Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	37		
Units: Scale				
arithmetic mean (standard deviation)	7.69 (± 6.30)	6.61 (± 7.96)		

Attachments (see zip file)	ANOVA Rep Meas_primary endpoints.pdf

Statistical analyses

Statistical analysis title	ANOVA Repeated Measures
Statistical analysis description:	
We employed for all outcome criteria repeated measures ANOVAS with one between-subject factor (group: DCS, PBO) and one within-subject factor (time: t1, t4, t10 and t11). Sphericity was analyzed by Mauchley testing and degrees of freedom were adjusted by Greenhouse-Geisser correction if $p < 0.05$. Effect sizes were reported as partial eta-squared ($\eta 2p$). Tests were employed two-tailed and statistical significance was accepted if $p < 0.05$.	
Comparison groups	DCS Arm v PBO Arm

Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANOVA
Parameter estimate	F-test
Variability estimate	Standard error of the mean

Primary: PAS self-rated sum score

End point title	PAS self-rated sum score

End point description:

The Panic and Agoraphobia Scale (PAS):
The PAS is a reliable, valid and internationally used scale for the determination of severity of disease in patients with agoraphobia and/ or panic disorder (Bandelow, 1995). In many therapy studies also its sensitivity for measuring change or improvement of symptomatology was demonstrated (Bandelow, 1995). For the present trial, the PAS was used in the self-rated and observer-rated (by therapist) version.

End point type	Primary

End point timeframe:

t1 up to t11

End point values	DCS Arm	PBO Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	37		
Units: Scale				
arithmetic mean (standard deviation)	8.22 (± 6.28)	7.71 (± 8.26)		

Attachments (see zip file)	ANOVA Rep Meas_primary endpoints.pdf

Statistical analyses

Statistical analysis title	ANOVA Repeated Measures

Statistical analysis description:

We employed for all outcome criteria repeated measures ANOVAS with one between-subject factor (group: DCS, PBO) and one within-subject factor (time: t1, t4, t10 and t11). Sphericity was analyzed by Mauchley testing and degrees of freedom were adjusted by Greenhouse-Geisser correction if $p < 0.05$. Effect sizes were reported as partial eta-squared ($\eta 2p$). Tests were employed two-tailed and statistical significance was accepted if $p < 0.05$.

Comparison groups	DCS Arm v PBO Arm
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANOVA
Parameter estimate	F-test

Variability estimate	Standard error of the mean

Secondary: ACQ mean

End point title	ACQ mean

End point description:

Agoraphobic Cognitions Questionnaire (ACQ):
The ACQ consists of 14 items measuring the patients central phobic cognitions, e. g. "I am going to pass out".
It may be scored as a total scale or according to its two subscales (loss of control and physical concerns).

End point type	Secondary

End point timeframe:

t1 up to t11

End point values	DCS Arm	PBO Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	37		
Units: Scale				
arithmetic mean (standard deviation)	1.46 (± 0.45)	1.43 (± 0.42)		

Attachments (see zip file)	ANOVA Rep Meas_secondary endpoints.pdf

Statistical analyses

Statistical analysis title	ANOVA Repeated Measures

Statistical analysis description:

We employed for all outcome criteria repeated measures ANOVAS with one between-subject factor (group: DCS, PBO) and one within-subject factor (time: t1, t4, t10 and t11). Sphericity was analyzed by Mauchley testing and degrees of freedom were adjusted by Greenhouse-Geisser correction if $p < 0.05$. Effect sizes were reported as partial eta-squared ($\eta 2p$). Tests were employed two-tailed and statistical significance was accepted if $p < 0.05$.

Comparison groups	DCS Arm v PBO Arm
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANOVA
Parameter estimate	F-test
Variability estimate	Standard error of the mean

Secondary: BSQ mean

End point title	BSQ mean

End point description:

Body Sensations Questionnaire (BSQ):
The BSQ, consisting of 17 items, is a valid an reliable instrument to assess the patients phobic fear of bodily
symptoms such as “heart beat” or “dizziness”.

End point type	Secondary

End point timeframe:

t1 up to t11

End point values	DCS Arm	PBO Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	37		
Units: Scale				
arithmetic mean (standard deviation)	1.83 (± 0.62)	1.83 (± 0.61)		

Attachments (see zip file)	ANOVA Rep Meas_secondary endpoints.pdf

Statistical analyses

Statistical analysis title	ANOVA Repeated Measures

Statistical analysis description:

We employed for all outcome criteria repeated measures ANOVAS with one between-subject factor (group: DCS, PBO) and one within-subject factor (time: t1, t4, t10 and t11). Sphericity was analyzed by Mauchley testing and degrees of freedom were adjusted by Greenhouse-Geisser correction if $p < 0.05$. Effect sizes were reported as partial eta-squared ($\eta 2p$). Tests were employed two-tailed and statistical significance was accepted if $p < 0.05$.

Comparison groups	DCS Arm v PBO Arm
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANOVA
Parameter estimate	F-test
Variability estimate	Standard error of the mean

Secondary: MI alone mean

End point title	MI alone mean

End point description:

Mobility Inventory (MI):
In the MI 26 situations are rated for avoidance by the patients both when they are alone (subscale MI alone) or when they are accompanied (subscale MI accompanied).

End point type	Secondary

End point timeframe:

t1 up to t11

End point values	DCS Arm	PBO Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	37		
Units: Scale				
arithmetic mean (standard deviation)	1.58 (± 0.60)	1.59 (± 0.69)		

Attachments (see zip file)	ANOVA Rep Meas_secondary endpoints.pdf

Statistical analyses

Statistical analysis title	ANOVA Repeated Measures

Statistical analysis description:

We employed for all outcome criteria repeated measures ANOVAS with one between-subject factor (group: DCS, PBO) and one within-subject factor (time: t1, t4, t10 and t11). Sphericity was analyzed by Mauchley testing and degrees of freedom were adjusted by Greenhouse-Geisser correction if $p < 0.05$. Effect sizes were reported as partial eta-squared ($\eta 2p$). Tests were employed two-tailed and statistical significance was accepted if $p < 0.05$.

Comparison groups	DCS Arm v PBO Arm
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANOVA
Parameter estimate	F-test
Variability estimate	Standard error of the mean

Secondary: Mi accompanied mean

End point title	Mi accompanied mean

End point description:

Mobility Inventory (MI):
In the MI 26 situations are rated for avoidance by the patients both when they are alone (subscale MI alone) or when they are accompanied (subscale MI accompanied).

End point type	Secondary

End point timeframe:

t1 up to t11

End point values	DCS Arm	PBO Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	37		
Units: Scale				
arithmetic mean (standard deviation)	1.35 (± 0.40)	1.25 (± 0.32)		

Attachments (see zip file)	ANOVA Rep Meas_secondary endpoints.pdf

Statistical analyses

Statistical analysis title	ANOVA Repeated Measures

Statistical analysis description:

We employed for all outcome criteria repeated measures ANOVAS with one between-subject factor (group: DCS, PBO) and one within-subject factor (time: t1, t4, t10 and t11). Sphericity was analyzed by Mauchley testing and degrees of freedom were adjusted by Greenhouse-Geisser correction if $p < 0.05$. Effect sizes were reported as partial eta-squared ($\eta 2p$). Tests were employed two-tailed and statistical significance was accepted if $p < 0.05$.

Comparison groups	DCS Arm v PBO Arm
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANOVA
Parameter estimate	F-test
Variability estimate	Standard error of the mean

Secondary: ASI sum score

End point title	ASI sum score

End point description:

Anxiety Sensitivity Index (ASI):
The 16-item ASI measures the patients' fear of anxiety-related sensations and the evaluation about their harmful consequences. The ASI was shown to also display good sensitivity to change over the course of treatment.

End point type	Secondary

End point timeframe:

t1 up to t11

End point values	DCS Arm	PBO Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	37		
Units: Scale				
arithmetic mean (standard deviation)	12.67 (± 9.18)	12.01 (± 8.36)		

Attachments (see zip file)	ANOVA Rep Meas_secondary endpoints.pdf

Statistical analyses

Statistical analysis title	ANOVA Repeated Measures

Statistical analysis description:

We employed for all outcome criteria repeated measures ANOVAS with one between-subject factor (group: DCS, PBO) and one within-subject factor (time: t1, t4, t10 and t11). Sphericity was analyzed by Mauchley testing and degrees of freedom were adjusted by Greenhouse-Geisser correction if $p < 0.05$. Effect sizes were reported as partial eta-squared ($\eta 2p$). Tests were employed two-tailed and statistical significance was accepted if $p < 0.05$.

Comparison groups	DCS Arm v PBO Arm
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANOVA
Parameter estimate	F-test
Variability estimate	Standard error of the mean

Secondary: BAI sum score

End point title	BAI sum score

End point description:

Beck Anxiety Inventory (BAI):
The BAI, containing 21 items, is a valid and reliable inventory for measuring common symptoms of clinical anxiety, e. g. numbness or sweating.

End point type	Secondary

End point timeframe:

t1 up to t11

End point values	DCS Arm	PBO Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	37		
Units: Scale				
arithmetic mean (standard deviation)	8.57 (± 8.04)	8.98 (± 7.43)		

Attachments (see zip file)	ANOVA Rep Meas_secondary endpoints.pdf

Statistical analyses

Statistical analysis title	ANOVA Repeated Measures

Statistical analysis description:

We employed for all outcome criteria repeated measures ANOVAS with one between-subject factor (group: DCS, PBO) and one within-subject factor (time: t1, t4, t10 and t11). Sphericity was analyzed by Mauchley testing and degrees of freedom were adjusted by Greenhouse-Geisser correction if $p < 0.05$. Effect sizes were reported as partial eta-squared ($\eta 2p$). Tests were employed two-tailed and statistical significance was accepted if $p < 0.05$.

Comparison groups	DCS Arm v PBO Arm
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANOVA
Parameter estimate	F-test
Variability estimate	Standard error of the mean

Secondary: BDI II sum score

End point title	BDI II sum score

End point description:

Beck Depression Inventory (BDI):
As for the high overlap between anxiety and depression we considered it important to also assess depressive symptoms in our patient sample with the help of the most commonly used inventory BDI II.

End point type	Secondary

End point timeframe:

t1 up to t11

End point values	DCS Arm	PBO Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	37		
Units: Scale				
arithmetic mean (standard deviation)	4.69 (± 4.53)	4.00 (± 4.45)		

Attachments (see zip file)	ANOVA Rep Meas_secondary endpoints.pdf

Statistical analyses

Statistical analysis title	ANOVA Repeated Measures

Statistical analysis description:

We employed for all outcome criteria repeated measures ANOVAS with one between-subject factor (group: DCS, PBO) and one within-subject factor (time: t1, t4, t10 and t11). Sphericity was analyzed by Mauchley testing and degrees of freedom were adjusted by Greenhouse-Geisser correction if $p < 0.05$. Effect sizes were reported as partial eta-squared ($\eta 2p$). Tests were employed two-tailed and statistical significance was accepted if $p < 0.05$.

Comparison groups	DCS Arm v PBO Arm

Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANOVA
Parameter estimate	F-test
Variability estimate	Standard error of the mean

Secondary: BSI sum score

End point title	BSI sum score

End point description:

Brief Symptom Inventory (BSI):
We decided to apply the BSI in order to also have a measure for general psychopathological symptoms pertaining to different disorder-specific domains.

End point type	Secondary

End point timeframe:

t1 up to t11

End point values	DCS Arm	PBO Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	37		
Units: Scale				
arithmetic mean (standard deviation)	12.54 (± 9.33)	13.46 (± 11.45)		

Attachments (see zip file)	ANOVA Rep Meas_secondary endpoints.pdf

Statistical analyses

Statistical analysis title	ANOVA Repeated Measures

Statistical analysis description:

We employed for all outcome criteria repeated measures ANOVAS with one between-subject factor (group: DCS, PBO) and one within-subject factor (time: t1, t4, t10 and t11). Sphericity was analyzed by Mauchley testing and degrees of freedom were adjusted by Greenhouse-Geisser correction if $p < 0.05$. Effect sizes were reported as partial eta-squared ($\eta 2p$). Tests were employed two-tailed and statistical significance was accepted if $p < 0.05$.

Comparison groups	DCS Arm v PBO Arm
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANOVA
Parameter estimate	F-test
Variability estimate	Standard error of the mean

Secondary: CGI

End point title	CGI

End point description:

Clinical Global Impression (CGI):
The CGI is a very easy to apply clinician rated scale measuring global severity of illness. Although short it is one of the most widely used brief assessment tools in psychiatry.

End point type	Secondary

End point timeframe:

t1 up to t11

End point values	DCS Arm	PBO Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	37		
Units: Scale				
arithmetic mean (standard deviation)	2.98 (± 0.94)	2.46 (± 1.11)		

Attachments (see zip file)	ANOVA Rep Meas_secondary endpoints.pdf

Statistical analyses

Statistical analysis title	ANOVA Repeated Measures

Statistical analysis description:

We employed for all outcome criteria repeated measures ANOVAS with one between-subject factor (group: DCS, PBO) and one within-subject factor (time: t1, t4, t10 and t11). Sphericity was analyzed by Mauchley testing and degrees of freedom were adjusted by Greenhouse-Geisser correction if $p < 0.05$. Effect sizes were reported as partial eta-squared ($\eta 2p$). Tests were employed two-tailed and statistical significance was accepted if $p < 0.05$.

Comparison groups	DCS Arm v PBO Arm
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANOVA
Parameter estimate	F-test
Variability estimate	Standard error of the mean

Adverse events

Adverse events information

Timeframe for reporting adverse events:

57 days

Adverse event reporting additional description:

Potential side effects of the study drug were elicited by protocol-guided questioning and monitored from therapy session t7 on.

Assessment type	Systematic

Dictionary used

Dictionary name	own
Dictionary version	1

Reporting groups

Reporting group title	DCS Arm

Reporting group description:

Patients underwent 3 exposure sessions with two rounds respectively. Within 30 minutes after the second round of exposure patients were given double blind and randomized either PBO or 50mg of DCS by oral administration. 50mg of DCS is a commonly used dosage in DCS studies with anxiety patients as clinical trials (e. g. Ressler et al., 2004) and meta-analyses (e. g. Mataix-Cols et al., 2017) could not show better efficacy with higher dosages. Study medication and the randomization list were generated by the Charité Pharmacy, Campus Virchow, with the aid of the software Randomization (version 01/08/2008) and using the method of randomly permuted blocks of pairs. The randomization list remained in the Charité Pharmacy until completion of data collection, thus assuring for blindness of patients, therapists and all study personal regarding the patients' study condition.

Reporting group title	PBO Arm

Reporting group description:

Patients underwent 3 exposure sessions with two rounds respectively. Within 30 minutes after the second round of exposure patients were given double blind and randomized either PBO or 50mg of DCS by oral administration. Study medication and the randomization list were generated by the Charité Pharmacy, Campus Virchow, with the aid of the software Randomization (version 01/08/2008) and using the method of randomly permuted blocks of pairs. The randomization list remained in the Charité Pharmacy until completion of data collection, thus assuring for blindness of patients, therapists and all study personal regarding the patients' study condition.

Serious adverse events	DCS Arm	PBO Arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 36 (0.00%)	0 / 37 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	DCS Arm	PBO Arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 36 (11.11%)	1 / 37 (2.70%)	

Investigations Overall subjects affected / exposed occurrences (all)	 4 / 36 (11.11%) 1	 1 / 37 (2.70%) 1	

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/30237105