Clinical trial results:
A trial to study effects of a single dose Citalopram on emotion processing in female patients with Borderline Personality Disorder and the associated modulation of fMRI BOLD signals

Summary

EudraCT number	2018-001212-30
Trial protocol	DE
Global end of trial date	22 October 2019

Results information

Result version number	v1 (current)
This version publication date	27 October 2021
First version publication date	27 October 2021
Summary attachment (see zip file)	Original publication (Paret_2021_Single dose effect Citalopram Borderline.pdf) Online supplement (ECEP-supplement_20210105.docx)

Trial information

Trial identification

Sponsor protocol code	ECEP-BPD

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Central Institute of Mental Health
Sponsor organisation address	J5, Mannheim, Germany, D-68159
Public contact	Department PSM, Central Institute of Mental Health, +49 62117034002, Christian.schmahl@zi-mannheim.de
Scientific contact	Department PSM, Central Institute of Mental Health, +49 62117034002, Christian.schmahl@zi-mannheim.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	29 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 October 2019
Global end of trial reached?	Yes
Global end of trial date	22 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effects of a single dose of Citalopram (20 mg) compared to placebo on BOLD responses on the amygdala and related brain structures induced by emotional stimuli using functional Magnetic Resonance Imaging (fMRI) in un-medicated female participants with Borderline Personality Disorder.

Protection of trial subjects:

Vital signs: Vital signs (pulse rate, systolic and diastolic blood pressure and body temperature) determined on predefined study days were documented as numerical values on appropriate CRF-pages. Furthermore, vital signs were recorded at any time, if medically imperative for clarification of clinical signs and symptoms.

12-lead ECG: Only pathological and clinically relevant findings in 12-lead ECG determined on predefined study days were documented on appropriate CRF-pages.
12-lead ECG could be recorded at any time at discretion of the responsible investigator, if medically imperative for clarification of clinical signs and symptoms.

Clinical chemistry, hematology and clotting: Following parameters were determined on the predefined study days:
Clinical chemistry: sodium, potassium, calcium, magnesium, total protein, albumin, glucose, creatinine, urea, bilirubin, ASAT, ALAT, GGT, LDH, AP, CRP.
Hematology: leukocytes, granulocytes, neutrophils, eosinophils, basophiles, lymphocytes, monocytes, erythrocytes, thrombocytes, haematocrit, haemoglobin.
Clotting: aPTT, INR.
After collection, the samples were immediately be delivered to the laboratory for respective determinations. All parameters were documented on appropriate CRF-pages.
Further laboratory parameters could be determined at any time during the study at discretion of the responsible investigator.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 October 2018
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: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	30
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from the in- and out-patient units of the Department of Psychosomatic Medicine and Psychotherapy.

Pre-assignment

Screening details:

Assessed for eligibility: n=209
Excluded: n=179
not meeting inclusion criteria: n=111
not interested to participate: n=32
expressed interest at first call, but were not anymore reached: n=29
other reasons: n=7

Period 1

Period 1 title	Allocation to sequence (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Assessor

Blinding implementation details:

In addition to the trial medication the investigator received a set of sealed envelopes, one for each randomisation number. An identical set of sealed envelopes was held at pharmacovigilance. These envelopes contained information on the subject's trial medication and were to be opened only under circumstances in which it is medically imperative to know what the subject is receiving. The randomisation envelopes were not to be opened.

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence Citalopram-Placebo

Arm description:

Patients received Citalopram in the first visit and Placebo in the second visit, after 1 week washout. After substance intake and a waiting period of 3h, participants were asked to report current mood with the Positive and Negative Affect Schedule (PANAS). Afterwards, they participated in the fMRI experiment.

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

Dosage and administration details:

The subject was administered the study medication orally (20 mg of Citalopram).

Investigational medicinal product name	DAC filler (99.5 % mannitol und 0.5 % highly dispersed silicon dioxide)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The subject was administered the study medication orally

Arm title	Sequence Placebo-Citalopram

Arm description:

Patients in this arm received placebo first and after the 1-week washout, received Citalopram. After substance intake and a waiting period of 3h, participants were asked to report current mood with the

Positive and Negative Affect Schedule (PANAS). Afterwards, they participated in the fMRI experiment.

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

Dosage and administration details:
20 mg administered orally

Investigational medicinal product name	DAC filler (99.5 % mannitol und 0.5 % highly dispersed silicon dioxide)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
administered orally

Number of subjects in period 1	Sequence Citalopram-Placebo	Sequence Placebo-Citalopram
Started	15	15
Received treatment	14	14
Completed	14	14
Not completed	1	1
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Sequence Citalopram-Placebo
Reporting group description:	
Patients received Citalopram in the first visit and Placebo in the second visit, after 1 week washout. After substance intake and a waiting period of 3h, participants were asked to report current mood with the Positive and Negative Affect Schedule (PANAS). Afterwards, they participated in the fMRI experiment.	
Reporting group title	Sequence Placebo-Citalopram
Reporting group description:	
Patients in this arm received placebo first and after the 1-week washout, received Citalopram. After substance intake and a waiting period of 3h, participants were asked to report current mood with the Positive and Negative Affect Schedule (PANAS). Afterwards, they participated in the fMRI experiment.	

Reporting group values	Sequence Citalopram-Placebo	Sequence Placebo-Citalopram	Total
Number of subjects	15	15	30
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	28.53	33.40	
standard deviation	± 7.74	± 7.28	-
Gender categorical			
Only female participants were included.			
Units: Subjects			
Female	15	15	30
Male	0	0	0
Comorbid DSM-5 Disorders Units: Subjects			
Major Depression	0	0	0
Dysthymia	0	0	0
Double Depression	0	0	0
Panic disorder	0	0	0
Social phobia	0	0	0
Specific phobia	0	0	0
Posttraumatic Stress Disorder	0	0	0
Anorexia nervosa	0	0	0
Bulimia nervosa	0	0	0
Binge-eating disorder	0	0	0

other	15	15	30

BPD DSM-5 criteria			
Number of DSM-5 BPD criteria			
Units: points			
arithmetic mean	5.53	5.87	
standard deviation	± 0.83	± 0.92	-
MADRS			
Units: points			
arithmetic mean	15.47	14.53	
standard deviation	± 7.99	± 6.70	-
ZAN-BPD			
Interview version of Zanarini rating scale			
Units: points			
arithmetic mean	10.40	12.47	
standard deviation	± 4.52	± 3.50	-
BDI			
Beck Depression Inventory			
Units: points			
arithmetic mean	21.20	24.33	
standard deviation	± 8.65	± 11.65	-
BAI			
Beck Anxiety Inventory			
Units: points			
arithmetic mean	20.53	15.47	
standard deviation	± 8.88	± 8.84	-
BSL-23			
Borderline Symptom List short version			
Units: points			
arithmetic mean	33.53	34.33	
standard deviation	± 15.45	± 18.96	-

Subject analysis sets

Subject analysis set title	Citalopram treatment
Subject analysis set type	Full analysis

Subject analysis set description:

This is a within-subject trial; all subjects received Citalopram and Placebo treatment in a crossover design.

Subject analysis set title	Placebo treatment
Subject analysis set type	Full analysis

Subject analysis set description:

This is a withinsubject crossover design: all subjects received Citalopram and Placebo treatment

Reporting group values	Citalopram treatment	Placebo treatment	
Number of subjects	15	15	
Age categorical			
Units: Subjects			
In utero			

Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	±	±	
Gender categorical			
Only female participants were included.			
Units: Subjects			
Female Male			
Comorbid DSM-5 Disorders Units: Subjects			
Major Depression Dysthymia Double Depression Panic disorder Social phobia Specific phobia Posttraumatic Stress Disorder Anorexia nervosa Bulimia nervosa Binge-eating disorder other	15	15	
BPD DSM-5 criteria			
Number of DSM-5 BPD criteria			
Units: points arithmetic mean standard deviation	±	±	
MADRS Units: points arithmetic mean standard deviation	±	±	
ZAN-BPD			
Interview version of Zanarini rating scale			
Units: points arithmetic mean standard deviation	±	±	
BDI			
Beck Depression Inventory			
Units: points arithmetic mean standard deviation	±	±	
BAI			

Beck Anxiety Inventory			
Units: points arithmetic mean standard deviation	± 	± 	
BSL-23			
Borderline Symptom List short version			
Units: points arithmetic mean standard deviation	± 	± 	

End points

End points reporting groups

Reporting group title	Sequence Citalopram-Placebo
Reporting group description:	
Patients received Citalopram in the first visit and Placebo in the second visit, after 1 week washout. After substance intake and a waiting period of 3h, participants were asked to report current mood with the Positive and Negative Affect Schedule (PANAS). Afterwards, they participated in the fMRI experiment.	
Reporting group title	Sequence Placebo-Citalopram
Reporting group description:	
Patients in this arm received placebo first and after the 1-week washout, received Citalopram. After substance intake and a waiting period of 3h, participants were asked to report current mood with the Positive and Negative Affect Schedule (PANAS). Afterwards, they participated in the fMRI experiment.	
Subject analysis set title	Citalopram treatment
Subject analysis set type	Full analysis
Subject analysis set description:	
This is a within-subject trial; all subjects received Citalopram and Placebo treatment in a crossover design.	
Subject analysis set title	Placebo treatment
Subject analysis set type	Full analysis
Subject analysis set description:	
This is a withinsubject crossover design: all subjects received Citalopram and Placebo treatment	

Primary: Left amygdala BOLD response to negative scenes

End point title	Left amygdala BOLD response to negative scenes
End point description:	
We presented 42 pictures from the OASIS picture set (39) to induce negative affect. We used pictures with negative affective valence and high arousal (AC) in a block-design. During each of 14 blocks, lasting 18 seconds, three picture stimuli were presented for 6 seconds each, resulting in a set of 42 negative pictures in total. Due to the within-subject design, we used two picture sets with similar characteristics concerning affective valence and arousal to avoid habituation to picture content. These two sets were randomized between treatment visits to avoid undesired effects of systematic presentation order. Scrambled pictures were used in a non-affective control condition (NC) with the same number of trials and presentation time. During the intertrial interval (jittered to nine, 10, or 11 seconds), participants viewed a white fixation cross on a black background.	
End point type	Primary
End point timeframe:	
3 hrs after substance intake	

End point values	Citalopram treatment	Placebo treatment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	23		
Units: %BOLD signal change				
arithmetic mean (standard deviation)	0.166 (± 0.1002)	0.1604 (± 0.1423)		

Statistical analyses

Statistical analysis title	Region-of-interest anlysis

Statistical analysis description:

Regions-of-interest (ROIs) were localized by intersecting the AC>NC (faces-task and scenes-task) activation maps derived from a 15-participant prestudy (unpublished data) with substructures of the Harvard-Oxford atlas (HOA) implemented in FSL (41). The statistical maps were thresholded at z > 2.3, while the atlas regions were thresholded at 50% probability.

Comparison groups	Placebo treatment v Citalopram treatment
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05 [2]
Method	Permutation test
Parameter estimate	Mean difference (final values)

Notes:

[1] - For the hypothesis-test, we used the mean percent signal change of all voxels within each ROI. We did not correct for multiple comparisons where we had a-priori hypotheses about treatment effects. First-level GLM results were converted into %BOLD signal change values and initially characterised at the group level as the 90th percentile value per participant within pre-specified ROIs.

[2] - To test for the effect of Citalopram versus Placebo we derived p-values based on permutation analyses.

Primary: Right amygdala BOLD response to negative scenes

End point title	Right amygdala BOLD response to negative scenes

End point description:

End point type	Primary

End point timeframe:

3 hrs after substance intake

End point values	Citalopram treatment	Placebo treatment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	23		
Units: %BOLD signal change				
arithmetic mean (standard deviation)	0.1673 (± 0.1019)	0.1797 (± 0.1356)		

Statistical analyses

Statistical analysis title	Region-of-interest analysis
Comparison groups	Placebo treatment v Citalopram treatment
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided

Secondary: Left amygdala BOLD response to faces

End point title	Left amygdala BOLD response to faces

End point description:

Participants viewed faces with emotional expression (disgust, sadness, and fear were chosen based on meta-analyses) from the Warsaw Set of Emotional Facial Expression Pictures (WSEFEP, http://www.emotional-face.org/). A block design of 12 blocks with 6 faces each (aversive condition, AC; negative emotional expressions were randomly mixed within blocks) and 12 blocks with scrambled faces (neutral condition, NC) was used. Scrambled faces were chosen as control because of two reasons: First, we wanted to match the faces task with the scenes task in terms of the analyzed contrast. Second, previous work suggested altered responding in BPD not only to emotional expressions but also to faces with neutral expression (37), which would compromise the sensitivity of our design to detect drug-induced changes. In sum, 72 negative faces of 24 actors (12 female, 12 male) were shown for 3

End point type	Secondary

End point timeframe:

3 hrs after substance intake

End point values	Citalopram treatment	Placebo treatment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	25		
Units: %BOLD signal change				
arithmetic mean (standard deviation)	0.1601 (± 0.1148)	0.2342 (± 0.1543)		

Statistical analyses

Statistical analysis title	Region-of-interest analysis

Statistical analysis description:

see primary outcome

Comparison groups	Placebo treatment v Citalopram treatment
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided

Secondary: Right amygdala BOLD response to faces

End point title	Right amygdala BOLD response to faces

End point description:

see primary outcome

End point type	Secondary

End point timeframe:

3 hrs after substance intake

End point values	Citalopram treatment	Placebo treatment		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	25		
Units: %BOLD signal change				
arithmetic mean (standard deviation)	0.1881 (± 0.1171)	0.2564 (± 0.1369)		

Statistical analyses

Statistical analysis title	Region-of-interest analysis
Statistical analysis description: see primary outcomes	
Comparison groups	Placebo treatment v Citalopram treatment
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first to last visit

Adverse event reporting additional description:

A detailed description of AEs is given in the open access online-supplement to the original publication of this trial and can be downloaded via this link: https://doi.org/10.1016/j.bpsc.2021.02.002.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	N/A

Reporting groups

Reporting group title	Full sample, Citalopram treatment

Reporting group description: -

Reporting group title	Full sample, Placebo treatment

Reporting group description: -

Serious adverse events	Full sample, Citalopram treatment	Full sample, Placebo treatment	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (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: 5 %

Non-serious adverse events	Full sample, Citalopram treatment	Full sample, Placebo treatment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 29 (48.28%)	8 / 29 (27.59%)	
General disorders and administration site conditions			
Headache			
subjects affected / exposed	5 / 29 (17.24%)	6 / 29 (20.69%)	
occurrences (all)	5	6	
Sleep disorder			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Nausea			

subjects affected / exposed	2 / 29 (6.90%)	1 / 29 (3.45%)		
occurrences (all)	2	1		
Thirst				
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)		
occurrences (all)	1	0		
Cough				
subjects affected / exposed	2 / 29 (6.90%)	0 / 29 (0.00%)		
occurrences (all)	2	0		
Stress symptoms				
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)		
occurrences (all)	1	0		
Tinnitus				
subjects affected / exposed	1 / 29 (3.45%)	1 / 29 (3.45%)		
occurrences (all)	0	0		
Attention impaired				
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)		
occurrences (all)	0	1		
Depressed mood				
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)		
occurrences (all)	0	1		
Vertigo				
subjects affected / exposed	2 / 29 (6.90%)	0 / 29 (0.00%)		
occurrences (all)	2	0		
Tiredness				
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)		
occurrences (all)	0	0		
Restlessness				
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)		
occurrences (all)	0	0		
Dizziness				
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)		
occurrences (all)	1	0		
Mucus nasal increased				
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)		
occurrences (all)	1	0		
Pain behind eyes				

subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	2 / 29 (6.90%)	0 / 29 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Delusional disorder, paranoid type			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences (all)	0	0	
Dissociative disorder			
subjects affected / exposed	1 / 29 (3.45%)	1 / 29 (3.45%)	
occurrences (all)	1	1	
Endocrine disorders			
Sweating increased			
subjects affected / exposed	2 / 29 (6.90%)	1 / 29 (3.45%)	
occurrences (all)	2	1	
Musculoskeletal and connective tissue disorders			
Tightness of jaw muscles			
subjects affected / exposed	2 / 29 (6.90%)	0 / 29 (0.00%)	
occurrences (all)	2	0	
Muskoloskeletal chest pain			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Muscle pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Neck stiffness			
subjects affected / exposed	1 / 29 (3.45%)	1 / 29 (3.45%)	
occurrences (all)	0	0	
Tremor			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	
occurrences (all)	0	0	

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Interested readers are referred to the original publication of this trial: https://doi.org/10.1016/j.bpsc.2021.02.002 (see also summary text files) provided with CC BY license (http://creativecommons.org/licenses/by/4.0/).

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33607327