Clinical trial results:
Cannabidiol enhancement of exposure therapy in treatment refractory patients with phobias.

Summary

EudraCT number	2014-004094-17
Trial protocol	NL
Global end of trial date	20 May 2020

Results information

Result version number	v1 (current)
This version publication date	17 December 2023
First version publication date	17 December 2023

Trial information

Trial identification

Sponsor protocol code	40-41200-98-9269

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	NTR: 21801

Notes:

Sponsors

Sponsor organisation name	Utrecht University
Sponsor organisation address	Heidelberglaan 1, Utrecht, Netherlands, 3584 CS
Public contact	Dr. J.M.P. Baas, Utrecht University, +31 302533018, j.m.p.baas@uu.nl
Scientific contact	Dr. J.M.P. Baas, Utrecht University, +31 302533018, j.m.p.baas@uu.nl

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	21 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 May 2020
Global end of trial reached?	Yes
Global end of trial date	20 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To test the hypothesis that administration of cannabidiol as an augmentation step in combination with exposure therapy can strengthen treatment outcome in patients with phobic disorders (generalized social anxiety and panic disorder with agoraphobia) who do not respond satisfactorily to treatment as usual.

Protection of trial subjects:

Trial subjects were under care of the treating facility during participation in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 80
Worldwide total number of subjects	80
EEA total number of subjects	80

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)	80
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	80
Number of subjects completed	80

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, Carer

Blinding implementation details:

Randomization code was broken and participation discontinued because of an unplanned pregnancy. Data for the remaining patients were unblinded after the last post-treatment measurement (December 3, 2019) to allow timely reporting to the trial funder. Research assistants who remained blinded collected remaining follow-up measurements. Patients were unblinded after the last follow up measurement.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cannabidiol (CBD)

Arm description: -

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

Dosage and administration details:

300 mg 2h prior to 8 weekly exposure therapy sessions

Arm title	Placebo

Arm description: -

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:

300 mg 2h prior to 8 weekly exposure therapy sessions

Number of subjects in period 1	Cannabidiol (CBD)	Placebo
Started	39	41
Completed	27	34
Not completed	12	7
no information	3	-
non-matching work/therapy schedule	3	2
Adverse event, non-fatal	1	-
unwillingness to be randomized	1	-
unsuitable for exposure therapy	3	4
Pregnancy	-	1
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Cannabidiol (CBD)
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Cannabidiol (CBD)	Placebo	Total
Number of subjects	39	41	80
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)	39	41	80
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	17	15	32
Male	22	26	48

End points

End points reporting groups	
Reporting group title	Cannabidiol (CBD)
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Clinical change until FU 6 months on Fear Questionnaire	
End point title	Clinical change until FU 6 months on Fear Questionnaire
End point description:	
End point type	Primary
End point timeframe:	
Baseline to follow-up after 6 months	

End point values	Cannabidiol (CBD)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: 1.11				
number (confidence interval 95%)	0.32 (-0.60 to 1.25)	0.32 (-0.60 to 1.25)		

Statistical analyses

Statistical analysis title	FQ across diagnostic groups
Comparison groups	Placebo v Cannabidiol (CBD)
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Slope
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	1.25

Statistical analysis title	FQ within diagnostic groups
Comparison groups	Placebo v Cannabidiol (CBD)
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Slope
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.62
upper limit	1.4
Variability estimate	Standard error of the mean

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 16-04-2016 until 20-05-2020	
Adverse event reporting additional description: Patients were seen by a carer after each administration of study medication and asked about adverse events.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	self-defined
Dictionary version	1

Reporting groups	
Reporting group title	Cannabidiol (CBD)
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Cannabidiol (CBD)	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 38 (0.00%)	0 / 39 (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: 0 %

Non-serious adverse events	Cannabidiol (CBD)	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 38 (10.53%)	6 / 39 (15.38%)	
General disorders and administration site conditions			
tiredness			
subjects affected / exposed	1 / 38 (2.63%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
drowsiness			
subjects affected / exposed	1 / 38 (2.63%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
Dizziness			

subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	1 / 38 (2.63%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
feeling strong blood flow			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Gout			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
hot flushes			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Infections and infestations			
flu			
subjects affected / exposed	0 / 38 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 October 2015	Change in the participant insurance of Utrecht University to CNA instead of Marketform.
27 May 2016	- Because of the relatively high incidence of autism in patients with social phobia an exclusion criterion based on an autism questionnaire was added; - A more realistic time investment of patients was made and changed in the information letter and ABR form; - In order to enhance inclusion of participants we will recruit patients via media.
23 May 2017	An additional treatment center will recruit patients for the study.
14 July 2017	The medication manufacturer changed. The IB has been updated and funders ZonMw and Dutch Brain Foundation are now mentioned in the information letter and flyer. Plasma samples of 10 ml instead of 9 ml will be taken and all serotonergic antidepressants will be allowed instead of only serotonin reuptake inhibitors.
28 November 2017	The number of patients to be included has decreased due to an updated power analysis. The previous power analysis contained an error.

Notes:

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/35561538