Clinical trial results:
A phase IIa/b, randomised, double-blind, placebo-controlled, single-site, parallel group clinical trial to examine cannabidiol (CBD) as a pharmacological treatment for cannabis dependence in a young cannabis dependent population.

Summary

EudraCT number	2013-000361-36
Trial protocol	GB
Global end of trial date	05 June 2017

Results information

Result version number	v1 (current)
This version publication date	
First version publication date	

Trial information

Trial identification

Sponsor protocol code	12/0278

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Joint Research Office
Sponsor organisation address	1st Floor Maple House (Suite A) 149 Tottenham Court Road, London, United Kingdom, W1T 7DN
Public contact	Samim Patel, Joint Research Office, UCL, +44 0207 679 9320 , samim.patel@ucl.ac.uk
Scientific contact	Samim Patel, Joint Research Office, UCL, +44 0207 679 9320 , samim.patel@ucl.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	09 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 February 2017
Global end of trial reached?	Yes
Global end of trial date	05 June 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

What is the most effective dose of cannabidiol for reducing cannabis use, and is this dose effective as a treatment for cannabis dependence?

Protection of trial subjects:

The risk of the IMP is minimal and it has been used in humans previously for up to 18 weeks, and with doses of up to 1500mg with no serious side effects. The maximum daily dose and the duration of the trial (800mg for 4 weeks) is the same as a study carried out in a schizophrenic population. All adverse events will be recorded. If the investigator suspects that the subjects' disease has progressed faster due to the administration of the IMP, then she/he will record and report this as an unexpected adverse event.

Background therapy:

All subjects (across each of the treatment conditions) are given motivational interviewing to help them stop using cannabis, which can be harmful to their health.

Evidence for comparator:

CBD has been found to (a) reduce the effects of drug cues - which play a key role in addiction relapse - in cannabis, tobacco and opiate users; (b) offset the harmful effects of THC and brain and behaviour; (c) reduce cigarette smoking.

Actual start date of recruitment	31 March 2014
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: 82
Worldwide total number of subjects	82
EEA total number of subjects	82

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)	82
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Community based recruitment within the UK

Pre-assignment

Screening details:

Screening at telephone interview and screening visit for eligibility

Period 1

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

Arms

Are arms mutually exclusive?	Yes
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: Twice daily oral dose	
Investigational medicinal product name	Cannabidiol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: Twice daily oral dose	
Arm title	200mg 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: Oral twice daily	
Arm title	400mg 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:
Oral twice daily

Arm title	800mg 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:
Oral twice daily

Number of subjects in period 1	Placebo	200mg CBD	400mg CBD
Started	23	12	24
Completed	21	10	23
Not completed	2	2	1
Lost to follow-up	2	2	1

Number of subjects in period 1	800mg CBD		
Started	23		
Completed	23		
Not completed	0		
Lost to follow-up	-		

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	200mg CBD
Reporting group description: -	
Reporting group title	400mg CBD
Reporting group description: -	
Reporting group title	800mg CBD
Reporting group description: -	

Reporting group values	Placebo	200mg CBD	400mg CBD
Number of subjects	23	12	24
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)	23	12	24
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	24.869565	27.333333	26.583333
standard deviation	± 7.436424	± 7.426407	± 6.794606
Gender categorical Units: Subjects			
Female	6	3	7
Male	17	9	17

Reporting group values	800mg CBD	Total	
Number of subjects	23	82	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	23	82	
From 65-84 years	0	0	

85 years and over	0	0	

Age continuous Units: years			
arithmetic mean	27.434783		
standard deviation	± 5.829596	-	
Gender categorical Units: Subjects			
Female	7	23	
Male	16	59	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	200mg CBD
Reporting group description: -	
Reporting group title	400mg CBD
Reporting group description: -	
Reporting group title	800mg CBD
Reporting group description: -	

Primary: Lower urinary THC-COOH:creatinine compared to placebo (stage 1)

End point title	Lower urinary THC-COOH:creatinine compared to placebo (stage 1)

End point description:

Aim: to identify the Most Effective Dose of CBD for reducing cannabis use compared to placebo (MED). A Bayesian model computed the predictive distribution of the outcome, given the evidence available up to that point (weeks 1, 2, 3 and 4). Based on these distributions, for each dose the probability that it is the MED is evidenced by a probability exceeding the pre-specified threshold (Pu) of 0.9; the pre-specified threshold for an ineffective dose (Pl) was 0.1.

In this adaptive Bayesian trial, randomisation occurred in two stages. Stage 1 included 200mg CBD, 400mg CBD, 800mg CBD as well as placebo.

End point type	Primary

End point timeframe:

During treatment weeks (1-4)

End point values	Placebo	200mg CBD	400mg CBD	800mg CBD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	12	12
Units: ng/ml				
number (not applicable)	0	0	0	0

Statistical analyses

Statistical analysis title	Co-primary endpoint 1 (stage 1)

Statistical analysis description:

In this adaptive Bayesian trial, randomisation occurred in two stages. Stage 1 included 200mg CBD, 400mg CBD, 800mg CBD as well as placebo
Co-primary endpoint 1 (stage 1): lower urinary THC-COOH:creatinine compared to placebo: 200mg CBD P=0.4191; 400mg CBD P=0.9827; 800mg CBD P=0.9488

Comparison groups	Placebo v 200mg CBD v 400mg CBD v 800mg CBD
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority[1]

P-value	> 0.9 [2]
Method	Bayesian model

Notes:

[1] - Aim: to identify the Most Effective Dose of CBD for reducing cannabis use compared to placebo (MED). A Bayesian model computed the predictive distribution of the outcome, given the evidence available up to that point (weeks 1, 2, 3 and 4). Based on these distributions, for each dose the probability that it is the MED is evidenced by a probability exceeding the pre-specified threshold (Pu) of 0.9; the pre-specified threshold for an ineffective dose (Pl) was 0.1.
[2] - Co-primary endpoint 1 (stage 1): lower urinary THC-COOH:creatinine compared to placebo: 200mg CBD P=0.4191; 400mg CBD P=0.9827; 800mg CBD P=0.9488

Primary: More self-reported days abstinent compared to placebo (stage 1)

End point title	More self-reported days abstinent compared to placebo (stage 1)

End point description:

Aim: to identify the Most Effective Dose of CBD for reducing cannabis use compared to placebo (MED). A Bayesian model computed the predictive distribution of the outcome, given the evidence available up to that point (weeks 1, 2, 3 and 4). Based on these distributions, for each dose the probability that it is the MED is evidenced by a probability exceeding the pre-specified threshold (Pu) of 0.9; the pre-specified threshold for an ineffective dose (Pl) was 0.1.

In this adaptive Bayesian trial, randomisation occurred in two stages. Stage 1 included 200mg CBD, 400mg CBD, 800mg CBD as well as placebo.

End point type	Primary

End point timeframe:

During treatment weeks (1-4)

End point values	Placebo	200mg CBD	400mg CBD	800mg CBD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	12	12	12
Units: Days				
number (not applicable)	0	0	0	0

Statistical analyses

Statistical analysis title	Co-primary endpoint 2 (stage 1)

Statistical analysis description:

In this adaptive Bayesian trial, randomisation occurred in two stages. Stage 1 included 200mg CBD, 400mg CBD, 800mg CBD as well as placebo

Co-primary endpoint 2 (stage 1): more self-reported days abstinent compared to placebo: 200mg CBD P=0.0082; 400mg CBD P=0.9354; 800mg CBD P=0.8660

Comparison groups	Placebo v 200mg CBD v 400mg CBD v 800mg CBD
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	> 0.9 [4]
Method	Bayesian model

Notes:

[3] - Aim: to identify the Most Effective Dose of CBD for reducing cannabis use compared to placebo (MED). A Bayesian model computed the predictive distribution of the outcome, given the evidence available up to that point (weeks 1, 2, 3 and 4). Based on these distributions, for each dose the

probability that it is the MED is evidenced by a probability exceeding the pre-specified threshold (Pu) of 0.9; the pre-specified threshold for an ineffective dose (Pl) was 0.1.
[4] - Co-primary endpoint 2 (stage 1): more self-reported days abstinent compared to placebo: 200mg CBD P=0.0082; 400mg CBD P=0.9354; 800mg CBD P=0.8660

Primary: Lower urinary THC-COOH:creatinine compared to placebo (stage 2)

End point title	Lower urinary THC-COOH:creatinine compared to placebo (stage 2)

End point description:

Aim: to identify the Most Effective Dose of CBD for reducing cannabis use compared to placebo (MED). A Bayesian model computed the predictive distribution of the outcome, given the evidence available up to that point (weeks 1, 2, 3 and 4). Based on these distributions, for each dose the probability that it is the MED is evidenced by a probability exceeding the pre-specified threshold (Pu) of 0.9; the pre-specified threshold for an ineffective dose (Pl) was 0.1.

In this adaptive Bayesian trial, randomisation occurred in two stages. Stage 1 found evidence for ineffectiveness of 200mg CBD, therefore this dose was eliminated and no further randomisation occurred to this dose in stage 2. There was evidence for effectiveness of both 200mg CBD and 400mg CBD compared to placebo. Therefore in stage 2, randomisation continued to the existing groups of placebo, 400mg CBD and 800mg CBD.

End point type	Primary

End point timeframe:

Treatment weeks (1-4)

End point values	Placebo	400mg CBD	800mg CBD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	24	23	
Units: ng/ml				
number (not applicable)	0	0	0	

Statistical analyses

Statistical analysis title	Co-primary endpoint 1 (stage 2)

Statistical analysis description:

Stage 1 found evidence for ineffectiveness of 200mg CBD, therefore this dose was eliminated and no further randomisation occurred to this dose in stage 2. There was evidence for effectiveness of both 200mg CBD and 400mg CBD compared to placebo. Therefore in stage 2, randomisation continued to the existing groups of placebo, 400mg CBD and 800mg CBD

Co-primary endpoint 1 (stage 2): lower urinary THC-COOH:creatinine compared to placebo: 400mg CBD P=0.9995; 800mg CBD P=0.9965

Comparison groups	400mg CBD v 800mg CBD v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	> 0.9 [6]
Method	Bayesian model

Notes:

[5] - Aim: to identify the Most Effective Dose of CBD for reducing cannabis use compared to placebo (MED). A Bayesian model computed the predictive distribution of the outcome, given the evidence available up to that point (weeks 1, 2, 3 and 4). Based on these distributions, for each dose the probability that it is the MED is evidenced by a probability exceeding the pre-specified threshold (Pu) of 0.9; the pre-specified threshold for an ineffective dose (Pl) was 0.1.

[6] - Co-primary endpoint 1 (stage 2): lower urinary THC-COOH:creatinine compared to placebo: 400mg CBD P=0.9995; 800mg CBD P=0.9965

Primary: More self-reported days abstinent compared to placebo (stage 2)

End point title	More self-reported days abstinent compared to placebo (stage 2)

End point description:

Aim: to identify the Most Effective Dose of CBD for reducing cannabis use compared to placebo (MED). A Bayesian model computed the predictive distribution of the outcome, given the evidence available up to that point (weeks 1, 2, 3 and 4). Based on these distributions, for each dose the probability that it is the MED is evidenced by a probability exceeding the pre-specified threshold (Pu) of 0.9; the pre-specified threshold for an ineffective dose (Pl) was 0.1.

In this adaptive Bayesian trial, randomisation occurred in two stages. Stage 1 found evidence for ineffectiveness of 200mg CBD, therefore this dose was eliminated and no further randomisation occurred to this dose in stage 2. There was evidence for effectiveness of both 200mg CBD and 400mg CBD compared to placebo. Therefore in stage 2, randomisation continued to the existing groups of placebo, 400mg CBD and 800mg CBD.

End point type	Primary

End point timeframe:

Treatment weeks (1-4)

End point values	Placebo	400mg CBD	800mg CBD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	24	23	
Units: Days				
number (not applicable)	0	0	0	

Statistical analyses

Statistical analysis title	Co-primary endpoint 2 (stage 2)

Statistical analysis description:

Stage 1 found evidence for ineffectiveness of 200mg CBD, therefore this dose was eliminated and no further randomisation occurred to this dose in stage 2. There was evidence for effectiveness of both 200mg CBD and 400mg CBD compared to placebo. Therefore in stage 2, randomisation continued to the existing groups of placebo, 400mg CBD and 800mg CBD

Co-primary endpoint 2 (stage 2): more self-reported days abstinent compared to placebo: 400mg CBD P=0.9966; 800mg CBD P=0.9247

Comparison groups	Placebo v 400mg CBD v 800mg CBD
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	> 0.9 [8]
Method	Bayesian model

Notes:

[7] - Aim: to identify the Most Effective Dose of CBD for reducing cannabis use compared to placebo (MED). A Bayesian model computed the predictive distribution of the outcome, given the evidence available up to that point (weeks 1, 2, 3 and 4). Based on these distributions, for each dose the probability that it is the MED is evidenced by a probability exceeding the pre-specified threshold (Pu) of 0.9; the pre-specified threshold for an ineffective dose (Pl) was 0.1.

[8] - Co-primary endpoint 2 (stage 2): more self-reported days abstinent compared to placebo: 400mg CBD P=0.9966; 800mg CBD P=0.9247

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomisation to the final follow up (week 24)

Adverse event reporting additional description:

Total number of adverse events (AEs) reported in each group
Placebo (n=23): mild (62), moderate (10), severe (0)
200mg CBD (n=12): mild (40), moderate (4), severe (0)
400mg CBD (n=24): mild (94), moderate (8), severe (0)
800mg CBD (n=23): mild (77), moderate (8), severe (0)

Assessment type	Systematic

Dictionary used

Dictionary name	
Dictionary version	

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