Clinical trial results:
Effects of Varenicline and Cognitive Bias Modification on Neural Response to Smoking Cues

Summary

EudraCT number	2011-004169-34
Trial protocol	GB
Global end of trial date	01 July 2014

Results information

Result version number	v1 (current)
This version publication date	28 July 2018
First version publication date	28 July 2018

Trial information

Trial identification

Sponsor protocol code	UoB1407

Additional study identifiers

ISRCTN number	ISRCTN65690030
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Funder-Pfizer: WS676950

Notes:

Sponsors

Sponsor organisation name	University of Bristol
Sponsor organisation address	Senate House, Tyndall Avenue, Bristol, United Kingdom, BS8 1TH
Public contact	Dr Birgit Whitman, University of Bristol, Research Enterprise and Development, +44 01173317130, Birgit.Whitman@bristol.ac.uk
Scientific contact	Dr Birgit Whitman, University of Bristol, Research Enterprise and Development, +44 01173317130, Birgit.Whitman@bristol.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	11 January 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 July 2014
Global end of trial reached?	Yes
Global end of trial date	01 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1) Does cognitive bias modification alter neural response to smoking-related cues? H1a: We hypothesise that experimental procedures designed to induce attentional bias towards smoking-relates cues will lead to an increase in neural response to smoking-related cues, in brain regions previously implicated in cue reactivity in cigarette smokers. H1b: We hypothesise that experimental procedures designed to induce attentional bias away from smoking-relates cues will lead to a decrease in neural response to smoking-related cues, in brain regions previously implicated in cue reactivity in cigarette smokers.

Protection of trial subjects:

The study medication was a licensed medication to aid smoking cessation, and no serious adverse events were expected. The drug (varenicline) is associated with some side effects which were explained to the participant who was told they were able to stop the study medication at any time. The more common side effects may be unpleasant but are not considered serious or long lasting (e.g., fatigue, vivid dreams, nausea).

There is some weak scientific evidence to suggest a small increase in cardiovascular events for participants taking varenicline compared to placebo. The research has been criticised methodologically but to mitigate any risk we included an upper age limit of 40 years (the mean ages of participants in studies in the meta analysis in question was 39 - 57). There is also association of the drug with depressive symptoms. To mitigate risk participants were screened by a psychiatrist prior to enrolment.

Background therapy:

None

Evidence for comparator:

N/a

Actual start date of recruitment	01 November 2011
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: 89
Worldwide total number of subjects	89
EEA total number of subjects	89

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)	89
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from the Bristol area (south west United Kingdom). All participants were current smokers (i.e., at least 10 manufactured or 15 roll-up cigarettes per day).

The first participant was enrolled on 5th November 2011 and the last participant was enrolled on 24th June 2014.

Pre-assignment

Screening details:

Inclusion: aged 18-40
Exclusion: pregnancy/breastfeeding, drug misuse disorder, psychiatric illness, clinically significant abnormality (including CV risk), ongoing medication, uncorrected visual/auditory impairment, hypersensitivity to varenciline, cannot have MRI scan.

Exclusion breakdown information no longer available.

Pre-assignment period milestones

Number of subjects started	312[1]
Number of subjects completed	89

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Not eligible or lost contact: 223

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The pre-assignment phase is a screening phase in which potential participants were screened for eligibility. This occurred before enrollment and therefore the number is higher than those enrolled.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Baseline measurements taken on all participants prior to randomisation to drug and CBM experimental conditions

Arms

Arm title	Baseline

Arm description:

Baseline testing (pre-randomization)

Arm type	Baseline
Investigational medicinal product name	None
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Wound stick
Routes of administration	Other use

Dosage and administration details:

No product given in this stage. Above (pharmaceutical forms) added as was mandatory, but not relevant here.

Number of subjects in period 1	Baseline
Started	89
Completed	89

Period 2

Period 2 title	Drug regime (7 days)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Varenicline or matched placebo was prescribed for one week, to be taken as 0.5 mg once daily for days 1 - 3, and 0.5 mg twice daily for days 4 - 6, and 0.5 mg once daily for day 7. Drugs were were dispatched from Bristol Royal Infirmary Pharmacy, who randomised drug to participant numbers. Pharmacy provided drug bottles pre-labelled with blinded condition allocation, and a unblinding sheet for study file

Arms

Are arms mutually exclusive?	Yes
Arm title	Varenicline

Arm description:

Active drug condition

Arm type	Experimental
Investigational medicinal product name	Varenicline
Investigational medicinal product code	CP526-555
Other name	Champix, Chantix
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Varenicline was administered for one week, to be taken as 0.5 mg once daily for days 1 - 3, and 0.5 mg twice daily for days 4 - 6, and 0.5 mg once daily for day 7, consistent with early standard dosing regimen for smoking cessation. Smoking cessation usage usually extends beyond a single week however (depending on need of patient).

Arm title	Placebo

Arm description:

Control drug (matched placebo to varenicline)

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

Dosage and administration details:

Matched to active drug

Number of subjects in period 2	Varenicline	Placebo
Started	46	43
Completed	44	41
Not completed	2	2
Consent withdrawn by subject	1	1
Adverse event, non-fatal	1	1

Period 3

Period 3 title	Cognitive bias modification
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Participants were andomly assigned to CBM groups, but equal numbers of participants per group were maintained, and groups were balanced for sex and drug condition.

In advance of the study, an experimental collaborator prepared a numeric code using random number assignment software.

Arms

Are arms mutually exclusive?	Yes
Arm title	CBM Avoid

Arm description:

Cognitive bias modification that trained participants to avoid smoking related cues

Arm type	Experimental
Investigational medicinal product name	CBM Avoidance training (computer-based task)
Investigational medicinal product code	n/a
Other name	
Pharmaceutical forms	Wound stick
Routes of administration	Other use

Dosage and administration details:

Pharmaceutical form (wound stick) is wrong. Entry was mandatory but not relevant. This product is an active version of a computer based cognitive bias training programme. This version trains smokers to attend away (i.e., avoid) smoking-related cues.

Arm title	CBM Neutral

Arm description:

Control task with no active training

Arm type	Placebo
Investigational medicinal product name	CBM Neutral (computer based task)
Investigational medicinal product code	n/a
Other name	
Pharmaceutical forms	Wound stick
Routes of administration	Other use

Dosage and administration details:

Pharmaceutical form (wound stick) is wrong. Entry was mandatory but not relevant. This product is a the control version of a computer based cognitive bias training programme.

Arm title	CBM Attend

Arm description:

Cognitive bias training that trained participants to attend to smoking related cues

Arm type	Active comparator
Investigational medicinal product name	CBM Attend (computer-based task)
Investigational medicinal product code	n/a
Other name	
Pharmaceutical forms	Wound stick
Routes of administration	Other use

Dosage and administration details:

Pharmaceutical form (wound stick) is wrong. Entry was mandatory but not relevant. This product is an active version of a computer based cognitive bias training programme. This version trains smokers to attend towards (i.e., attend) smoking-related cues.

Number of subjects in period 3	CBM Avoid	CBM Neutral	CBM Attend
Started	38	23	24
Completed	22	22	24
Not completed	16	1	0
Computer task failed to record	-	1	-
Computer error	16	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Baseline
Reporting group description:	
Baseline characteristics for all subjects in final analysis (n = 68), excluding withdrawals (n = 4) and participants who had to be replaced due to computer error (n=17).	

Reporting group values	Baseline	Total	
Number of subjects	89	89	
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	23		
standard deviation	± 5	-	
Gender categorical			
Units: Subjects			
Female	41	41	
Male	48	48	
Smoking heaviness			
Units: Cigarettes per day			
arithmetic mean	15		
standard deviation	± 3	-	

End points

End points reporting groups

Reporting group title	Baseline
Reporting group description: Baseline testing (pre-randomization)	
Reporting group title	Varenicline
Reporting group description: Active drug condition	
Reporting group title	Placebo
Reporting group description: Control drug (matched placebo to varenicline)	
Reporting group title	CBM Avoid
Reporting group description: Cognitive bias modification that trained participants to avoid smoking related cues	
Reporting group title	CBM Neutral
Reporting group description: Control task with no active training	
Reporting group title	CBM Attend
Reporting group description: Cognitive bias training that trained participants to attend to smoking related cues	
Subject analysis set title	Varenicline / CBM Avoid
Subject analysis set type	Per protocol
Subject analysis set description: Participants who received varenciline and completed CBM training to avoid to smoking cues	
Subject analysis set title	Varenicline / CBM Attend
Subject analysis set type	Per protocol
Subject analysis set description: Participants who received varenciline and completed CBM training to attend to smoking cues	
Subject analysis set title	Varenicline / CBM control
Subject analysis set type	Per protocol
Subject analysis set description: Participants who received varenciline and completed CBM control task (no training)	
Subject analysis set title	Placebo / CBM attend
Subject analysis set type	Per protocol
Subject analysis set description: Participants who received placebo and completed CBM training to attend to smoking cues	
Subject analysis set title	Placebo / CBM avoid
Subject analysis set type	Per protocol
Subject analysis set description: Participants who received placebo and completed CBM training to avoid to smoking cues	
Subject analysis set title	Placebo / CBM control
Subject analysis set type	Per protocol
Subject analysis set description: Participants who received placebo and completed CBM control task (i.e., no training)	

Primary: Neural response to smoking cues

End point title	Neural response to smoking cues

End point description:

End point type	Primary

End point timeframe:

One measure after 7-day drug regime and immediately after CBM

End point values	Varenicline / CBM Avoid	Varenicline / CBM Attend	Varenicline / CBM control	Placebo / CBM attend
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	10[1]	10	12
Units: % BOLD signal				
number (not applicable)	-0.003	0.092	0.057	0.139

Notes:

[1] - Two participants were removed from the analysis due to poor quality images

End point values	Placebo / CBM avoid	Placebo / CBM control		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	11[2]		
Units: % BOLD signal				
number (not applicable)	0.038	0.222		

Notes:

[2] - One participant were removed from the analysis due to poor quality images

Statistical analyses

Statistical analysis title	ANOVA

Statistical analysis description:

A 2 (varenicline, placebo) × 3 (attend, avoid, control) mixed-model whole-brain ANOVA was used to examine smoking cue reactivity (smoking greater than control) between each group

Comparison groups	Varenicline / CBM Avoid v Varenicline / CBM Attend v Varenicline / CBM control v Placebo / CBM attend v Placebo / CBM avoid v Placebo / CBM control
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANOVA

Primary: Stroop Time 2 (Generalised Attentional Bias post drug, pre CBM)

End point title	Stroop Time 2 (Generalised Attentional Bias post drug, pre CBM)

End point description:

A pictorial version of the modified Stroop task was used to investigate the effect of dot-probe CBM on a different measure of cognitive bias. The task began with 16 practice trials followed by two experimental

blocks, each comprising 8 buffer and 96 experimental trials (i.e., 208 trials in total). For each trial a picture was presented (smoking-related or neutral) centrally on screen. The picture was surrounded by a coloured border and the participant was required to identify the colour of the border (red, blue, yellow or green) using colour-marked keys on the keyboard. Error scores are bias scores calculated by subtracting the number of errors made to neutral images from the number of errors made to smoking images) - thus positive scores are indicative of smoking attentional bias.

Note on outliers: For error data, three participants were identified as outliers in the pre-CBM condition and one in the post-CBM condition. These data were removed from analyses.

End point type	Primary

End point timeframe:

This measure of attentional bias was taken on day 7 (i.e., after varenicline treatment), but before CBM training.

End point values	Varenicline	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33[3]	31[4]		
Units: Errors (bias)				
arithmetic mean (standard deviation)	0.13 (± 1.91)	-0.45 (± 1.87)		

Notes:

[3] - One outlier removed

[4] - Three outliers removed

Statistical analyses

Statistical analysis title	Stroop by drug group

Statistical analysis description:

Test of attentional bias following 7 day drug regime. This Univariate ANOVA comprised one between-subjects factor of drug: varenicline/placebo.

Comparison groups	Varenicline v Placebo
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.22
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.55
upper limit	0.81
Variability estimate	Standard error of the mean
Dispersion value	0.34

Secondary: Stroop Time 3 (Generalised attentional bias post drug and training)

End point title	Stroop Time 3 (Generalised attentional bias post drug and training)

End point description:

A pictorial version of the modified Stroop task was used to investigate the effect of dot-probe CBM on a different measure of cognitive bias. The task began with 16 practice trials followed by two experimental blocks, each comprising 8 buffer and 96 experimental trials (i.e., 208 trials in total). For each trial a picture was presented (smoking-related or neutral) centrally on screen. The picture was surrounded by a coloured border and the participant was required to identify the colour of the border (red, blue, yellow or green) using colour-marked keys on the keyboard. Error scores are bias scores calculated by subtracting the number of errors made to neutral images from the number of errors made to smoking images) - thus positive scores are indicative of smoking attentional bias.

Note on outliers: For error data, three participants were identified as outliers in the pre-CBM condition and one in the post-CBM condition. These data were removed from analyses.

End point type	Secondary

End point timeframe:

This measure of attentional bias was taken on day 7 (i.e., after varenicline treatment and CBM training)

End point values	CBM Avoid	CBM Neutral	CBM Attend	Varenicline / CBM Avoid
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	19[5]	22[6]	22[7]	10
Units: Errors (Bias)				
arithmetic mean (standard deviation)	-1.16 (± 2.29)	-0.95 (± 1.91)	-0.09 (± 1.82)	-1.2 (± 2.97)

Notes:

[5] - Outliers removed

[6] - Outliers removed

[7] - Outliers removed

End point values	Varenicline / CBM Attend	Varenicline / CBM control	Placebo / CBM attend	Placebo / CBM avoid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	10	11	9
Units: Errors (Bias)				
arithmetic mean (standard deviation)	-1.18 (± 1.47)	-1.0 (± 2.30)	1.0 (± 1.48)	-1.11 (± 1.36)

End point values	Placebo / CBM control			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: Errors (Bias)				
arithmetic mean (standard deviation)	-0.92 (± 1.62)			

Statistical analyses

Statistical analysis title	Stroop by CBM group (post training)
Comparison groups	CBM Avoid v CBM Neutral v CBM Attend

Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.194
Method	ANOVA
Parameter estimate	Slope
Point estimate	-0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.18
upper limit	-0.099
Variability estimate	Standard error of the mean
Dispersion value	0.428

Statistical analysis title	Stroop: Drug by CBM
Comparison groups	Varenicline / CBM Avoid v Varenicline / CBM Attend v Varenicline / CBM control v Placebo / CBM attend v Placebo / CBM avoid v Placebo / CBM control
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.134
Method	ANOVA
Parameter estimate	Slope
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.23
upper limit	0.23
Variability estimate	Standard error of the mean
Dispersion value	0.614

Secondary: Visual dot probe 2 (Attentional bias)

End point title	Visual dot probe 2 (Attentional bias)

End point description:

Each trial began with a fixation cross (500 ms), before a picture pair (smoking image, neutral image) was presented on a computer screen. The picture pair stayed on screen for 500 ms and then was replaced by a probe (small square or circle) in a location previously occupied by one of the pictures. Participants were required to identity whether the probe was a square or circle by pressing designated keyboard keys. There were 128 test with the probe appearing with equal frequency in the location of the smoking-related or neutral picture. The inter-trial interval jittered between 750 ms and 1,250 ms.

To create a reaction time bias score, RTs to smoking images were subtracted from RT to neutral images. Thus positive RT scores are indicative of a smoking attentional bias.

End point type	Secondary

End point timeframe:

This measure of attentional bias was taken on day 7 (i.e., after varenicline treatment), but before CBM

training.

End point values	Varenicline	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	34		
Units: Reaction Time Bias (ms)				
arithmetic mean (standard deviation)	11.97 (± 37.76)	-1.76 (± 29.38)		

Statistical analyses

Statistical analysis title	VDP after varenicline treatment
Comparison groups	Varenicline v Placebo
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.099
Method	ANOVA
Parameter estimate	Slope
Point estimate	11.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.387
upper limit	23.552
Variability estimate	Standard error of the mean
Dispersion value	5.801

Secondary: Visual Dot Probe 3 - Attentional bias

End point title	Visual Dot Probe 3 - Attentional bias

End point description:

Each trial began with a fixation cross (500 ms), before a picture pair (smoking image, neutral image) was presented on a computer screen. The picture pair stayed on screen for 500 ms and then was replaced by a probe (small square or circle) in a location previously occupied by one of the pictures. Participants were required to identity whether the probe was a square or circle by pressing designated keyboard keys. There were 128 test with the probe appearing with equal frequency in the location of the smoking-related or neutral picture. The inter-trial interval jittered between 750 ms and 1,250 ms.

To calculate a reaction time bias score, reaction time to smoking images was subtracted from reaction time to neutral images. Thus positive reaction time scores are indicative of smoking attentional bias. Due to computer malfunction, post-training CBM data were not recorded for one participant, therefore post-training sample comprises 67 participants.

End point type	Secondary

End point timeframe:

This measure of attentional bias was taken on day 7 (i.e., after varenicline treatment and CBM training).

End point values	CBM Avoid	CBM Neutral	CBM Attend	Varenicline / CBM Avoid
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	22	22	23	12
Units: Reaction time bias (ms)				
arithmetic mean (standard deviation)	-1.63 (± 18.34)	-9.32 (± 29.14)	11.75 (± 45.07)	-1.79 (± 15.16)

End point values	Varenicline / CBM Attend	Varenicline / CBM control	Placebo / CBM attend	Placebo / CBM avoid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	10	12	10
Units: Reaction time bias (ms)				
arithmetic mean (standard deviation)	15.42 (± 48.29)	-8.36 (± 40.22)	8.39 (± 43.78)	-1.45 (± 22.45)

End point values	Placebo / CBM control			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: Reaction time bias (ms)				
arithmetic mean (standard deviation)	-10.12 (± 17.22)			

Statistical analyses

Statistical analysis title	VDP after CBM treatment
Comparison groups	CBM Avoid v CBM Neutral v CBM Attend
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.103
Method	ANOVA
Parameter estimate	Slope
Point estimate	-9.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.36
upper limit	4.73
Variability estimate	Standard error of the mean
Dispersion value	7.03

Statistical analysis title	VDP by CBM and varenicline treatment
Comparison groups	Varenicline / CBM Avoid v Varenicline / CBM Attend v Varenicline / CBM control v Placebo / CBM attend v Placebo / CBM avoid v Placebo / CBM control
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.931
Method	ANOVA
Parameter estimate	Slope
Point estimate	-8.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.67
upper limit	12.95
Variability estimate	Standard error of the mean
Dispersion value	10.66

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Data collection period from November 2011 to July 2014

Adverse event reporting additional description:

Participants were given reporting cards to log any AEs. These were collected by the researcher on day 7 (final day) of drug regime. Participants were advised to contact the researcher during the drug regime if they were concerned about side effects, or were experiencing unexpected or severe side effects.

Assessment type	Systematic

Dictionary used

Dictionary name	Champix CDS
Dictionary version	10

Reporting groups

Reporting group title	Varenicline group

Reporting group description:

Participants allocated to varenicline medication for 7 days.

Reporting group title	Placebo group

Reporting group description:

Individuals in control arm who were administered 7 days placebo treatment

Serious adverse events	Varenicline group	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 46 (0.00%)	0 / 43 (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	Varenicline group	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 46 (43.48%)	18 / 43 (41.86%)	
General disorders and administration site conditions			
Headache			
subjects affected / exposed	3 / 46 (6.52%)	4 / 43 (9.30%)	
occurrences (all)	3	4	
Tiredness/drowsiness			
subjects affected / exposed	2 / 46 (4.35%)	7 / 43 (16.28%)	
occurrences (all)	2	7	

Vivid dreams / disrupted sleep			
subjects affected / exposed	7 / 46 (15.22%)	1 / 43 (2.33%)	
occurrences (all)	7	1	
Thirst/dry mouth			
subjects affected / exposed	1 / 46 (2.17%)	1 / 43 (2.33%)	
occurrences (all)	1	1	
Cigarettes tasted bad			
subjects affected / exposed	1 / 46 (2.17%)	0 / 43 (0.00%)	
occurrences (all)	1	0	
Fainting			
subjects affected / exposed	0 / 46 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Eye disorders			
Eye twitch			
subjects affected / exposed	0 / 46 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Nausea, vomiting, stomach cramps			
subjects affected / exposed	8 / 46 (17.39%)	4 / 43 (9.30%)	
occurrences (all)	8	4	
General	Additional description: Includes diarrhea, constipation, heartburn		
subjects affected / exposed	2 / 46 (4.35%)	1 / 43 (2.33%)	
occurrences (all)	2	1	
Appetite loss			
subjects affected / exposed	0 / 46 (0.00%)	1 / 43 (2.33%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety/agitation			
subjects affected / exposed	1 / 46 (2.17%)	1 / 43 (2.33%)	
occurrences (all)	1	1	
Mood changes	Additional description: Low mood / mood swings		
subjects affected / exposed	1 / 46 (2.17%)	1 / 43 (2.33%)	
occurrences (all)	1	1	
Infections and infestations			
Cold symptoms	Additional description: Includes runny nose, sore throat, cough		
subjects affected / exposed	2 / 46 (4.35%)	3 / 43 (6.98%)	
occurrences (all)	2	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 July 2012	Correction of description of drug vehicle in study documentation from capsule to tablet. Inclusion criteria regarding cannabis use was relaxed to aid recruitment.
24 June 2013	A structural scan was originally scheduled for baseline session (week one). This was moved to the test session (week two) when there was a function scan. This negated the need to book the scanner twice.
05 February 2014	17 participants had to be replaced (new participants recruited) due to computer error

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
12 December 2011	After original target was met and data were extracted, we found that computer data had failed to record for one condition. We therefore had to replace 17 participants who did not complete their allocated training appropriately. There was an interruption to testing in order for us to obtain ethics approval (amendment) to continue and to receive more drug.	18 March 2014

Notes:

Limitations and caveats

None reported