Clinical Study Protocol

Randomized placebo controlled cross-over study investigating the influence of CBD on episodic memory in healthy subjects

SHORT TITLE : CoIL-Basel

Study Type:	Other clinical trial
Study Categorisation:	Risk category A
Study Registration:	Clinicaltrials.gov and www.kofam.ch
Study Identifier:	CoIL-Basel
Sponsor, Sponsor-Investigator or Principal Investigator:	**Prof. Dominique de Quervain, MD** Division of Cognitive Neuroscience University of Basel Birmannsgasse 8 4055 Basel Tel: +41 61 207 0237 Fax: +41 61 207 0241 Email: dominique.dequervain@unibas.ch
Investigational Product:	E-liquid 5% CBD (Cannabis sariva L.), CBD E LIQUID, Pharma Hemp
Protocol Version and Date:	Version 2 July 11 2018

Signature Pages

Study number	Clinicaltrial.gov and www.kofam.ch registry intended
Study Title	Randomized placebo controlled cross-over study on the influence of CBD on episodic memory in healthy subjects

The Sponsor-Investigator and trial statistician have approved the protocol version [2 (dated 11.07.2018)], and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm if applicable and the local legally applicable requirements.

Site	Division of Cognitive Neuroscience, University of Basel
Sponsor-Investigator	Prof. Dominique de Quervain, MD

Basel, 12. Juli 2018

Place/Date

Signature

Local Principal Investigator at study site:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

Site	Division of Cognitive Neuroscience, University of Basel
Subinvestigator	Janine Hotz

Basel, 12. Juli 2018 — Signature

Place/Date

Site	Division of Cognitive Neuroscience, University of Basel
Trial statistician	Nathalie Schicktanz, PhD

Basel, 12. Juli 2018 — i.V. — Signature

Place/Date

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STUDY SYNOPSIS

Sponsor-Investigator	Prof. Dominique de Quervain, MD
Study Title:	Randomized placebo controlled cross-over study investigating the influence of CBD on episodic memory in healthy subjects
Short Title / Study ID:	CoIL-Basel
Protocol Version and Date:	Version 2 11/07/2018
Trial registration:	Trial will be registered on clinicaltrials.gov and www.kofam.ch
Study category and Rationale	Other clinical trial with persons category A We will use Cannabidiol (CBD) e-liquid compliant to foodstuff and commodities regulation in usual amounts available on Swiss market. Low dose of CBD e-liquid and experimental setting bear only minimal risks for participants.
Clinical Phase:	Basic research
Background and Rationale:	The primary "non-psychoactive" phytochemical in cannabis CBD, is thought to have a broad range of therapeutic properties, including amelioration of the adverse psychological effects of THC, like impaired cognition (Osborne, Solowij, & Weston-Green, 2017; Zuardi, 2008). Here, we aim at investigating the effect of CBD on episodic memory.
Objective(s):	Primary objective of the study: Influence of CBD on episodic memory functions in healthy subjects Secondary objectives: Influence on working memory
Outcome(s):	The primary endpoints will be performance in a verbal memory task (de Quervain, Henke et al. 2003). The secondary endpoints will be performance in a working memory test.
Study design:	Placebo controlled, randomized, double blind, cross-over design.
Inclusion / Exclusion criteria:	**Inclusion criteria** • Normotensive (BP between 90/60mmHg and 140/90mmHg) • BMI between 18 and 30 kg/m2 • Male or female • Aged between 18 and 30 years • Native or fluent German-speaking **Exclusion criteria** • Acute or chronic psychiatric disorder including drug or alcohol abuse • Known hypersensitivity or allergy to propylene glycol • Women who are pregnant or breast feeding • Smoking (> 5 cigarettes per day) • Participation in one of our previous studies using the same verbal test in the past 2 years • Participation in a study with investigational drug within the 30 days preceding and during the present study • Intake of CBD / THC within the 7 days preceding and during the present study in any application form • Long-term systemic medication or topical steroids to treat an underlying disease within last 3 months

Measurements and procedures:	• Screening visit with questionnaires. • Visit 1, 2 (Visit 2 2 week + 8 week after visit 1): A urine sample will be taken to control for pre-visit cannabis consumption. Subject will learn a list of 15 words followed by an immediate recall. Then they will be randomized to vape (verum or placebo) for 15min. They will perform a working memory test (n-back) and rate different VAS (mood, arousal, motivation, tiredness, headache, tolerance). And then the episodic memory test words short delay will be performed. Assessment of safety: AE recording
Study Product / Intervention:	Single vape of 0.25ml 5% CBD e-liquid Citrus Fruits, Pharma Hemp (12.5mg CBD). We estimate 15min vape time.
Control Intervention (if applicable):	Single vape of 0.25ml e-liquid La Baronne Jaune, BORDO2 tastes like lemon and madeleine. 15min vape time.
Number of Participants with Rationale:	We are interested to detect cannabidiol effects with at least medium effect sizes. The estimation of N=34 is based on a power analysis using dependent t-tests assuming to detect a medium effect size (dz = 0.5) with a power of 80% at α =0.05 (software: G-power 3).
Study Duration:	Study duration is estimated 6 months
Study Schedule:	First participant in 10/2018 (planned) Last participant out 03/2019 (planned)
Investigator(s):	**Sponsor-Investigator** Prof. Dominique de Quervain, MD Division of Cognitive Neuroscience University of Basel Birmannsgasse 8 4055 Basel Tel: +41 61 207 0237 Fax: +41 61 207 0241 Email: dominique.dequervain@unibas.ch **Subinvestigator** Janine Hotz Division of Cognitive Neuroscience University of Basel Birmannsgasse 8 4055 Basel Tel: +41 61 207 0249 Fax: +41 61 207 0241 Email: j.hotz@unibas.ch
Study Centre(s):	Division of Cognitive Neuroscience University of Basel
Statistical Considerations:	A significance level of $p < 0.05$ (two-sided) will be considered as significant. All analyses will be done in R. The differences between the experimental conditions will be analyzed using linear mixed models in combination with analysis of variance (SS II).

GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.

ABBREVIATIONS

AE	Adverse Event
BASEC	Business Administration System for Ethical Committees, (https://submissions.swissethics.ch/en/)
BMI	Body mass index
BP	Blood pressure
CA	Competent Authority (e.g. Swissmedic)
CB1 receptors	Cannabinoid 1 receptors
CB1 receptors	Cannabinoid 2 receptors
CBD	Cannabidiol
CEC	Competent Ethics Committee
CRF	Case Report Form
ClinO	Ordinance on Clinical Trials in Human Research *(in German: KlinV, in French: OClin, in Italian: OSRUm)*
eCRF	Electronic Case Report Form
CTCAE	Common terminology criteria for adverse events
DSUR	Development safety update report
EKNZ	Ethikkommission Nordwestschweiz
GCP	Good Clinical Practice
IB	Investigator's Brochure
Ho	Null hypothesis
H1	Alternative hypothesis
HRA	Federal Act on Research involving Human Beings *(in German: HFG, in French: LRH, in Italian: LRUm)*
IMP	Investigational Medicinal Product
IIT	Investigator-initiated Trial
ISO	International Organisation for Standardisation
ITT	Intention to treat
MADRS-S	Montgomery-Asperg Depression Self-rating Scale
MD	Medical Device
MedDO	Medical Device Ordinance *(in German: MepV, in French: ODim)*
NA	Not applicable
NG/ML	Nanogram per millilitre
PI	Principal Investigator
SD	Source Data
SDV	Source Data Verification
SOP	Standard Operating Procedure
SPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
THC	Delta-9-tetrahydrocannabinol
TMF	Trial Master File

VAS Visual analogue scales

STUDY SCHEDULE

Procedure	Visit	Duration (min)	Starting time Visit 1 1 day (+ 3 month) after Tel. Screening	Starting time Visit 2 2 week (+ 8 week) after Visit 1
Telephonescreening				
Inclusion / Exclusion criteria		10	-	-
Screening				
Informed consent	**Visit 1**	10	00:10	-
MADRS-S		5	00:20	-
Sociodemographic questionnaire		2	00:25	-
Mental - Health questionnaire		5	00:27	-
Concomitant medication		2	00:32	-
Inclusion / Exclusion criteria		1	00:34	-
Test battery 1, 2				
Urine sample	**Visit 1, Visit 2 (cross-over)**	8	00:35	00:00
AE / Medication Log		1	00:43	00:08
Primary Endpoint: Words learning and immediate recall		2	00:44	00:09
Vape		15	00:46	00:11
Secondary Endpoint: n-back		15	01:01	00:26
VAS of mood, arousal **Confounding factors:** VAS of motivation, tiredness, headache, tolerance		1	01:16	00:41
Primary Endpoint: Words short delay recall		3	01:17	00:42
Overall time			**80min**	**45min**
End Visit 1 and Visit 2				

1. STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor-Investigator

Principal Investigator / Sponsor	**Prof. Dominique de Quervain, MD** Division of Cognitive Neuroscience University of Basel Birmannsgasse 8 4055 Basel Tel.: +41 61 267 0237 Fax: +41 61 267 0241 Email: dominique.dequervain@unibas.ch

1.2 Subinvestigator

Subinvestigator	**Janine Hotz** Division of Cognitive Neuroscience University of Basel Birmannsgasse 8 4055 Basel Tel.: +41 61 207 0249 Fax: +41 61 207 0241 Email: j.hotz@unibas.ch

1.3 Statistician ("Biostatistician")

Statistician and data manager	**Nathalie Schicktanz, Dr.** Division of Cognitive Neuroscience University of Basel Birmannsgasse 8 4055 Basel Tel.: +41 61 267 0228 Fax: +41 61 267 0241 Email: Nathalie.schicktanz@unibas.ch

1.4 Laboratory

Not applicable

1.5 Monitoring institution

Monitor	**Bernhard Fehlmann** Division of Cognitive Neuroscience University of Basel Birmannsgasse 8 4055 Basel Tel.: +41 61 207 0226 Fax: +41 61 207 0241 Email: bernhard.fehlmann@unibas.ch

1.6 Data Safety Monitoring Committee

A data safety monitoring will not be formed due to the fact that no extended or unexpected safety concerns are anticipated.

1.7 Any other relevant Committee, Person, Organisation, Institution

Not applicable

2. ETHICAL AND REGULATORY ASPECTS

The decision of the CEC authority concerning the conduct of the study will be made in writing to the Sponsor-Investigator before commencement of this study. The clinical study can only begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities shall be implemented.

2.1 Study registration

The study will be registered on clinicaltrial.gov and kofam.ch.

2.2 Categorisation of study

This study is classified as other clinical trial with persons.

The use of CBD e-liquid classified as foodstuff and commodities (according to Swissmedics: https://www.swissmedic.ch/swissmedic/de/home/news/mitteilungen/produkte-mit-cannabidiol--cbd----ueberblick.html) in usual quantity and dose entails only minimal risks and burdens and justifies the risk categorization A. CBD e-liquids are available on the Swiss market. The experimental setting entails only minimal risks and burdens to the well-being of subjects.

2.3 Competent Ethics Committee (CEC)

The sponsor/investigator will obtain approval from CEC (EKNZ) before the start of the clinical trial.

The sponsor/investigator will report all changes in the research activity and all unanticipated problems involving risks to humans; including in case of planned or premature study end and the final report and no changes are made to the protocol without prior EKNZ approval, except where necessary to eliminate apparent immediate hazards to study participants.

Premature study end or interruption of the study is reported within 15 days. The regular end of the study is reported to the EKNZ within 90 days, the final study report shall be submitted within one year after study end. Amendments are reported according to chapter 2.10.

2.4 Competent Authorities (CA)

Not applicable

2.5 Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, in case of medical device: the European Regulation on medical devices 2017/745 and the ISO Norm 14155 and ISO 14971, the Swiss Law and Swiss regulatory authority's requirements. The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

2.6 Declaration of interest

The authors certify that they have no intellectual, financial or proprietary conflict and are independent.

2.7 Patient Information and Informed Consent

During the telephone screening the subinvestigator will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and

any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time.

The participant must be informed that his/her medical records may be examined by authorised individuals other than their treating physician.

All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study. The information will be sent by e-mail to interested voluntary participants after telephone screening. Details see chapter 9.3. The interested voluntary will be given time between telephone screening and screening (at least one day) for his/her decision to participate.

The participant information sheet and the consent form will be submitted to the CEC to be reviewed and approved. The formal consent of a participant, using the approved consent form, must be obtained before the participant is submitted to any study procedure.

The participant should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee) at the same time as the participant sign, and it will be retained as part of the study records.

2.8 Participant privacy and confidentiality

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files.

For data verification purposes, authorised representatives of the Sponsor-Investigator or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2.9 Early termination of the study

The Sponsor-Investigator may terminate the study prematurely according to certain circumstances, for example:

- Insufficient participant recruitment

2.10 Protocol amendments

Substantial amendments are only implemented after approval of the CEC.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the CEC. Such deviations shall be documented and reported to the sponsor and the CEC as soon as possible.

All non-substantial amendments are communicated to the CEC within the Annual Safety Report (ASR).

3. BACKGROUND AND RATIONALE

3.1 Background and Rationale

Cannabis is thought to be the most commonly used illicit substance (Hall & Degenhardt, 2007). Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the two major constituents of cannabis. THC is psychoactive and binds to cannabinoid 1 (CB1) receptors located in brain and the periphery, as well as to cannabinoid 2 (CB2) receptors which are located exclusively on nonneural tissue, such as immune cells (Pertwee, 1997) or glial cells (Nunez et al., 2004). In contrast, CBD has little affinity to CB1 and CB2 receptors (Bisogno et al., 2001; Showalter, Compton, Martin, & Abood, 1996) and is not psychoactive.

Prolonged frequent of THC, has been associated with deleterious effects on psychological functions, including increased risk of developing schizophrenia-related psychotic episodes (Di Forti et al., 2015; Moore et al., 2007), impaired cognition (Broyd, van Hell, Beale, Yucel, & Solowij, 2016; Solowij & Michie, 2007), and alteration in brain structure (Lorenzetti, Solowij, & Yucel, 2016) and function (Bhattacharyya, Crippa, Martin-Santos, Winton-Brown, & Fusar-Poli, 2009; Martin-Santos et al., 2012). Furthermore, acute exposure to high doses of THC can also produce psychotic episodes in healthy individuals that largely resemble positive symptoms of schizophrenia (Henquet, Di Forti, Morrison, Kuepper, & Murray, 2008).

In contrast, the primary “non-intoxicating” phytochemical in cannabis, CBD, is thought to have a broad range of therapeutic properties, including amelioration of the adverse psychological effects of THC. Moreover, CBD shows pro-cognitive effects and has, in multiple studies, been shown to protect against the detrimental cognitive effects of THC (Osborne et al., 2017; Zuardi, 2008). Regarding the effect of CBD on episodic memory, naturalistic human studies found that THC was associated with impaired learning and memory, but that the amount of CBD within cannabis was correlated with less impaired cognition (Morgan et al., 2012; Morgan, Schafer, Freeman, & Curran, 2010). A placebo-controlled between-subject study using participants with the diagnosis of schizotyp found reduced performance in an emotional recognition task in the THC groups as compared to a THC plus CBD group. Interestingly, CBD administration significantly improved accuracy in the emotional recognition task beyond placebo levels (Hindocha et al., 2015). However, an imaging study in healthy subjects found no effect of THC (10mmg), CBD (600 mg) or placebo on cognitive task performance, but only on brain activations (Bhattacharyya et al., 2010).

Although the precise pharmacological mechanisms and neurocircuitry responsible for the deleterious vs. therapeutic properties are still being investigated, it is assumed that CBD indirectly influence CB1 receptors as CBD has low affinity for CB1 and CB2 receptors (McPartland, Duncan, Di Marzo, & Pertwee, 2015). Moreover, CBD interacts with the 5-HT_{1A} as an agonist (Russo, Burnett, Hall, & Parker, 2005). In general, neurotransmission through the brain’s endocannabinoid system has been shown to influence emotional memory processing through changes in dopamine signaling within the mesolimbic system (for a review see (Hudson, Rushlow, & Laviolette, 2018)). Here, we aim at investigating the effects of CBD on episodic memory.

3.2 Investigational Product (treatment, device) and Indication

Refer to chapter 8.1.

3.3 Preclinical Evidence

N/A

3.4 Clinical Evidence to Date

Only a few studies investigated the effect of CBD alone on episodic memory (see 3.1). In summary, animals and a few human studies showed that CBD has the potential to limit THC induced cognitive impairments. However, we are interested to investigate the effect of CBD on episodic memory in

humans.

3.5 Dose Rationale / Medical Device: Rationale for the intended purpose in study (pre-market MD)

The CBD doses used in describes studies in chapter 3.1 varies from 16 mg to 600 mg of CBD. Due to practical reasons and reasons of compliance, we have chosen a dose of 12.5 mg dose of CBD based on the estimated time taking to vape such a dose (15 minutes).

3.6 Explanation for choice of comparator (or placebo)

We will use a placebo vaping product (does not include CBD) tasting similar to intervention vaping product as a comparator.

3.7 Risks / Benefits

Benefits: current evidences suggests that CBD has the ability to reduce psychotic, anxiety and withdrawal symptoms (Mandolini et al., 2018) and amelioration of the adverse psychological effects of THC (Osborne et al., 2017).

Risks: sedative actions like somnolence and increase of sleep duration (for review see (Zuardi, 2008)). Therefore, subjects will not be allowed to drive home by a vehicle after study participation.

3.8 Justification of choice of study population

This study aims to gain knowledge about memory processes in healthy participants. We will include male and female subjects between 18 and 30 years.

4. STUDY OBJECTIVES

4.1 Overall Objective

The purpose of this study is to evaluate whether CBD has an influence on episodic memory functions in healthy participants.

4.2 Primary Objective

The study seeks primarily to determine the effect of CBD on episodic memory functions.

4.3 Secondary Objectives

The secondary objects are to assess the Influence of CBD on working memory.

4.4 Safety Objectives

The study aims to assess tolerability of CBD in terms of incidence of side effects e.g. headache, gastrointestinal side effects etc.

5. STUDY OUTCOMES

5.1 Primary Outcome

The primary endpoint will be the performance in a **verbal memory task** (de Quervain, Henke et al. 2003), i.e. number of correctly recalled words (hits). Participants will view three series of five semantically unrelated nouns with the instruction to learn the words for immediate (after each series) and delayed (30 minutes after learning) free recall. Words are presented at a rate of 2 seconds.

5.2 Secondary Outcomes

Working memory will be assessed by means of a letter **0-back and 2-back task** (Papassotiropoulos et al., 2011). The 0-back condition serves as a low-load control condition, measuring general attention and does not require the manipulation of information within working memory. In the 2-back condition, participants have to compare the currently presented letter with the one presented 2 steps before and have to indicate whether they are identical or not. The 2-back condition requires online monitoring, updating and manipulation of remembered information and therefore is assumed to involve key processes of working memory (Owen, McMillan, Laird, & Bullmore, 2005). Accuracy and reaction time will be measured. The tasks lasts about 15 minutes.

5.3 Other Outcomes of Interest

Current mood and arousal will be assessed by means of 10 cm visual analog scales (VAS) with the two end points—"lowest level" (0) and "highest level" (10).

VAS of motivation, tiredness, headache and tolerance will be assessed to control for possible confounders ranging between 0 and 10 each.

5.4 Safety Outcomes

Safety outcome variables will consist of rate of adverse events in general.

6. STUDY DESIGN

6.1 General study design and justification of design

This is a single center clinical study comparing effects of CBD e-liquid versus a perfumed e-liquid on physiological processes (episodic memory) in healthy subjects using the following design

- Randomized
- Double-blind
- Placebo-controlled
- Cross-over design
- Approx. equal number of male and female subjects in each group

The duration of the study - from first participant in to last participant out - lasts approximately 6 months. The duration for a participant will be approximately 80 minutes for visit 1, and 45 min for visit 2. Dropouts will be replacement until data of total needed sample size is completed.

The wash-out period between the two testing days lasts 14 days (approximately 10 half-lives of CBD (Ujvary & Hanus, 2016)) to 56 days (due to flexible recruiting).

6.2 Methods of minimising bias

6.2.1 Randomisation

By time of visit 1 eligible participants will be randomly allocated to receive either CBD or placebo (perfumed e-liquid) first. To minimise allocation bias, a randomization list will be prepared by a team member of the division of cognitive neuroscience. Block randomization will be used to achieve balance between number of participants starting with CBD and number of participants starting with placebo. A separate list will be used for males and females. The randomization number will be listed in the SD and in the eCRF.

6.2.2 Blinding procedures

CBD e-liquid and perfumed e-liquid will be filled in identically looking vaporization tanks and labelled with a randomization number. Furthermore, tanks are wrapped with transparent colorized tape to cover e-liquid colour. Both vapes taste like citrus fruits. Participants will vape under supervision of a study member on a quiet balcony to avoid contaminating the air in the examination room with CBD vapours.

6.2.3 Other methods of minimising bias

The investigators of the test days will be trained personal and will follow detailed instructions to ensure that each test day will be conducted in a highly standardized way.

All study team members will be blinded to ensure that task evaluation by raters will be unbiased.

In order to minimise time of days effect, the time of day of all main visits will be keep constant (e.g. morning or afternoon) for each participant.

6.3 Unblinding Procedures (Code break)

Unblinding will be permitted under these circumstances

- SAE
- AE if knowledge is crucial for further medical approach

Unblinding procedures:

Randomization list containing unblinding information of each participant will be kept under the responsibility of the Sponsor-Investigator and unblinding of the participant can be performed by the Sponsor-Investigator at any time. The Sponsor-Investigator documents the unblinding. The

subinvestigator and other members of the team will not be informed about the result.

7. STUDY POPULATION

7.1 Eligibility criteria

Participants fulfilling all of the following inclusion criteria are eligible for the study:

- Healthy
- Normotensive (BP between 90/60mmHg and 140/90mmHg)
- BMI between 18 and 30 kg/m2
- Male or female
- Aged between 18 and 30 years
- Native or fluent German-speaking
- Able and willing to give written informed consent as documented by signature and comply with the requirements of the study protocol
- Willing to donate urine sample to control for pre-Visit CBD/THC consume

The presence of any one of the following exclusion criteria will lead to exclusion of the participant, for example:

- Acute or chronic psychiatric disorder including drug or alcohol abuse
- Women who are pregnant or breast feeding
- Intention to become pregnant during the course of the study
- Smoking (> 5 cigarettes per day)
- Participation in one of our previous studies using the same verbal test in the past 2 years
- Participation in a study with CBD / THC within the 30 days preceding and during the present study
- Known hypersensitivity or allergy to propylene glycol
- Intake of CBD / THC within the 7 days preceding and during the present study in any application form
- Long-term systemic medication or topical steroids to treat an underlying disease within last 3 months
- Inability to follow the procedures of the study, e.g. due to language problems, psychological disorders, dementia, etc. of the participant
- Enrolment of the investigator, his/her family members, employees and other dependent persons

7.2 Recruitment and screening

Study participants will be searched at the University of Basel, Bern and Zurich by mean of flyers as well as advertisements via the websites psycho.unibas.ch, markt.unibas.ch and marktplatz.uzh.ch, newspapers, Basler Verkehrsbetriebe (BVB) and Facebook. We will also invite former participants of unrelated studies in our Division of Cognitive Neuroscience by e-mail.

After contacting our subinvestigator via e-mail, a study team member will call the volunteer to inform him/her about the study. If the person meets all inclusion criteria and none of the exclusion criteria and is interested in participating, a date for the first visit will be fixed, the informed consent (Probandeninformation und Einverständniserklärung) will be sent, and the telephone screening documents will be filed as part of the SD in the participant's dossier. The telephone screening documents of participants, who are not eligible for the screening, will be shredded.

A study compensation of CHF 70 including travel expenses will be paid during visit 2.

7.3 Assignment to study groups

After informed consent, each participant will be assigned to a participant number. Eligible participants will be randomly allocated to either receive CBD or placebo first at visit 1 (see 6.1.3).

7.4 Criteria for withdrawal / discontinuation of participants

Participants have the right to withdraw from the study at any time for any reason without being obliged to give reason. There will be a final interview regarding their actual wellbeing after withdrawal for whatever reason. The subinvestigator also has the right to withdraw participants from the study if it is in the best interest of the participant.

The following reasons result in withdrawal:

- Adverse events prohibiting cognitive testing (e.g. nausea, headache)
- Single administration of psychoactive drug within 5 days before visit 2
- Non-Compliance
- Severe protocol violations
- Administrative problems
- Impossibility to vape 0.25mL e-Liquid
- Alcohol intake within 12 hours before visit 2

Withdrawal date and reason (if known) will be listed in the participant enrolment log. Safety data will be analysed for all participants, who received study medication.

A team member, who is not involved in the data sampling procedure, will provide the study leader with replacement e-liquid tanks, in case drop-outs have to be replaced. This way, the randomization order of the randomization list can be maintained. Drop-outs will be replaced until data of 34 participants are completed.

8. STUDY INTERVENTION

8.1 Identity of Investigational Products (treatment / medical device)

8.1.1 Experimental Intervention (treatment / medical device)

Single vape of 0.25mL of CBD e-Liquid containing: 5% CBD (low-temperature extracted Cannabidiol from Cannabis sativa L., purity 99%), Glycerine (vegetable), Propylene glycol, water

Brant: Pharma Hemp, Slovenia, https://pharmahemp.store/shop/e-liquids/cbd-e-liquid-5-10ml/

Label: CBD E LIQUID 5% Citrus Fruits

Color: Light orange

Taste: Citrus Fruits

Vaporizer: Canna Vape Kit

8.1.2 Control Intervention (standard/routine/comparator treatment / medical device)

Single vape of 0.25mL of La Baronne Jaune e-Liquid containing: Foodstuff fragrance additives, 80% Glycerine (vegetable), 20%Propylene glycol

Brant: BORDO2, France, https://www.bordo2.com/oh-my-god/la-baronne-jaune-oh-my-god

Label: LA BARONNE JAUNE

Color: Colorless

Taste: Lemon and madeleines

Vaporizer: Canna Vape Kit

8.1.3 Packaging, Labelling and Supply (re-supply)

We will use commercially available e-liquids:

- **CBD e-liquid** provided with a Certificate of Analysis containing 5.079% w/w CBD and < 0.05% w/w THC

- **La Baronne Jaune e-liquid**

In preparing the Vaporization tanks we shall adhere to the Schweizerische Hygieneverordnung: https://www.admin.ch/opc/de/classified-compilation/20143394/index.html, concerning especially:

- Cleanliness of work surface and all used utensils
- Use of products before date of expiry
- New vaporization tanks for each participant
- Protection from contamination by using new syringes to fill the tanks
- Temperature control

8.1.4 Storage Conditions

Filled tanks are kept at room temperature between 15°C and 25°C (controlled by Logtag® data logger) in a dark with badge restricted room until consumption.

8.2 Administration of experimental and control interventions

8.2.1 Experimental Intervention

It takes approximate 15 minutes to vape 0.25mL of an e-Liquid. We use a CBD e-Liquid with a high amount of CBD to reach a low dose (12.5mg CBD). This vape time is reasonable for e.g. students vaping before an exam.

Pharma Hemp produces CBD-Liquids with CO2 fluid extraction. This procedure gentle extract CBD from Cannabis sativa L. yielded purest CBD oil.

8.2.2 Control Intervention

Bord'O2 is a French e-Liquid brand from Bordeaux. It is rated as the top 3 e-Liquid brands according to the website vapoteurs.net. La Baronne Jaune tastes similar to CBD e-Liquid. So the use of this e-Liquid seems very suitable as comparator.

8.3 Dose / Device modifications

The filled tank (0.25mL) has to be vaped.

8.4 Compliance with study intervention

Participants will vape e-liquid under supervision of a study member.

8.5 Data Collection and Follow-up for withdrawn participants

Withdrawn participants will be paid off the compensation. In case of an AE it will be followed up until resolution.

8.6 Trial specific preventive measures

One week before and during the entire Study participants are not allowed to consume CBD in any form like smoking, vaping, eating (e.g. sweets, ice cream, chocolate containing CBD, CBD capsules), drinking (e.g. teas, beer, milk containing CBD), or using CBD lotions, massage oil, tinctures, sprays or joss-sticks.

We will register possible consumption. Coffee and black tea is permitted in the individual amount. Subjects should keep regular sleep habits.

Alcohol, psychoactive drugs are not permitted within the above (7.4) specified time period.

8.7 Concomitant Interventions (treatments)

Concomitant medication other than psychoactive medication and alcohol are not allowed but will not result in withdrawal.

8.8 Study Drug / Medical Device Accountability

Not applicable

8.9 Return or Destruction of Study Drug / Medical Device

Not applicable

9. STUDY ASSESSMENTS

9.1 Study flow chart(s) / table of study procedures and assessments

See study schedule.

9.2 Assessments of outcomes

9.2.1 Assessment of primary outcome

See primary outcome 5.1.

9.2.2 Assessment of secondary outcomes

See secondary outcome 5.2.

9.2.3 Assessment of other outcomes of interest

See chapter 5.3.

9.2.4 Assessment of safety outcomes

9.2.4.1 Adverse events

All (S)AEs occurring after IC confirmation until visit 2 will be fully recorded in the participants eCRF. Description of (S)AE includes time of onset, duration and resolution, assessment of intensity, relationship to study drug, and measures taken. All (S)AEs are post-investigated until resolution.

9.2.4.2 Laboratory parameters

No laboratory parameters will be assessed.

9.2.5 Assessments in participants who prematurely stop the study

If participants stopped the study prematurely for whatever reason, a final examination will take place. The examination aims at recording any adverse events.

9.3 Procedures at each visit

9.3.1 Screening visit

During the screening – that is the first part of the first visit- the subinvestigator will again explain the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits, and any discomfort it may entail. Furthermore, each subject will be informed that participation in the study is completely voluntary and that they can withdraw from the study at any time. Subjects will be informed that authorized individuals, other than the investigators, may analyse the observational data.

Thereafter, participants must read and confirm the informed consent. They will be given a copy of the signed document. The consent form must also be signed and dated by the investigator. It will be kept as part of the participants study records.

Written informed consent will be obtained from all participants without limiting time for signature. Participants who are candidates for enrolment into the study will be evaluated for eligibility during the screening visit (inclusion, exclusion criteria). Screening visit will consist of

- Assessment of medication history

- Vital signs (blood pressure / heart rate) will be taken with the participant having been in a seated position for at least 5 minutes.
- Height / weight (for calculation of BMI)

A pregnancy test will follow in case participants are not sure whether they are pregnant or not. Pregnancy testing will be performed in a urine sample according to instructions of AxaClear®, Axapharm.

The following questionnaires will be used to assess possible psychiatric disorders:

- Sociodemographic questionnaire
- Mental health questionnaire
- Depressive symptoms will be assessed with the self-rating questionnaire MADRS-S (Schmidtk1988). This scale consists of 9 items assessing participants' mood, feelings of unease, sleep, appetite, ability to concentrate, initiative, emotional involvement, pessimism and zest for life. Each item is scored between 0 and 3. The total score is calculated by summing the answers of the nine items, ranging between 0 and 27 (higher scores indicate increased impairment).

Screening failures equal to participants not meeting all inclusion criteria or meeting one or more of the exclusion criteria. Excluded participants will be listed on a screening failure log.

9.3.1 Cognitive testing visit 1 and visit 2

There will be a short examination consisting of a THC test, concomitant medication and adverse events. A THC test will be performed in a urine sample according to instructions of THC-Test, MedicTest. The test strip detects THC consummation with a sensitivity of 25 NG/ML. The detection time from last consummation least 3-5 days depending of the consumed amount. (The THC tests will be stored with IMP at the same conditions). Participants eligible for the study will start with the verbal memory task, i.e. learning a list of 15 words (for details see chapter 5.1), followed by an immediate free recall.

Then the participant vape 0.25mL of the e-Liquid (CBD or perfumed e-Liquid on visit 1 or visit 2 according to the randomization list). After approx. 15 minutes of vaping he/she will perform on the 0-, and 2-back task, followed by some VAS (for details see chapter 5.2). Then, short delay recall of the words will be assessed (for detail see study schedule table).

At the end of each test day participants will be interviewed regarding their actual wellbeing. If there are no complaints / symptoms they can be dismissed. In case of minor health problems, the participant will have to stay in the study centre under medical control until recovery.

The same memory/cognitive test battery will be administered in test days 1 and 2 using parallel versions of the primary and the main secondary outcome measures.

A study compensation of CHF 70 will be paid at the end of visit 2. Screening Failures and Drop-Outs receive a pro rata compensation.

10. SAFETY

10.1 Drug studies

Not applicable.

10.2 Medical Device Category C studies

Not applicable.

10.3 Medical Device Category A studies

Not applicable.

10.4 Other clinical studies Category A

10.4.1 Serious adverse events

A serious adverse event is defined as any adverse event where it cannot be excluded that the event is attributed to study, and which

- Requires inpatient treatment not envisage in the protocol or extends a current hospital stay;
- results in permanent or significant incapacity or disability; or
- is life-threatening or results in death.

The Sponsor Investigator is immediately notified (within 24 hours) if urgent safety and protective measures have to be taken during the conduct of the study. If a serious event occurs, the research project will be interrupted. The Ethics Committee will be notified via BASEC of these measures and of the circumstances necessitating them within 15 days.

10.4.2 Adverse events

We will document all adverse events following the vaporization of the e-Liquids until end of visit 2 assessing causality and severity.

11. STATISTICAL METHODS

A within-subject design is performed to achieve more Power than a between-subject design by partitioning between-subject variance out of the error variance. No carryover-effects (e.g. practice, fatigue) are expected.

A significance level of $p < 0.05$ (two-sided) will be considered as significant. As there is only one primary outcome measure, no Bonferroni correction will be applied.

11.1 Hypothesis

Cannabidiol has an influence on episodic memory.

11.2 Determination of Sample Size

We are interested to detect cannabinol effects with at least medium effect sizes. The estimation of N=34 is based on a power analysis using dependent t-tests assuming to detect a medium effect size (dz = 0.5) with a power of 80% at α =0.05 (software: G-power 3).

11.3 Statistical criteria of termination of trial

The study will be terminated, as soon as 34 participants will have completed the entire study.

11.4 Planned Analyses

All analyses will be done in R. Episodic memory performance (memory free recall) and secondary variables of interest will be analyzed by calculating linear mixed models with subject as random effect, experimental condition (Cannabidiol versus placebo) as contrast of interest (fixed effect) as well as the interaction term between experimental condition and covariates (sex, age). In case of significant interactions between covariates and experimental condition, post-hoc tests will be applied to describe the interaction.

Furthermore, to control for possible confounders, possible confounders (words immediate recall, MADRS-S, sociodemographic variables, VAS for mood / arousal / motivation / tiredness / headache / tolerance), subjects' believe about group allocation, will be entered into the model as covariates (each covariate entering the statistical analyses separately).

In case of no significant influence of covariates on dependent variables and in case of no significant interaction of covariate and experimental condition, we will consider to remove covariates out of the statistical model in order to reduce model complexity as far as possible (calculate t-tests in the simplest case).

To illustrate the influence on episodic memory change between experimental conditions, the delta values will be calculated and used dependent variable in an additional analyses. The delta values correspond to the difference in task performance between experimental conditions.

For interim analyses refer to 11.4.3.

11.4.1 Datasets to be analysed, analysis populations

Analysis of the primary and secondary outcome measures will be only performed with those participants, who completed all tests and investigations. There will be replacement of Drop-Outs until data of 34 participants are completed. Furthermore, subject performance will be analysed regarding

statistical outliers and might be removed from analyses. Drop-outs and statistical outliers will be thoroughly described.

11.4.2 Primary Analysis

Primary outcome analyses will be performed after completed data sampling (see 11.3, 11.4) by study statistician.

11.4.3 Secondary Analyses

Secondary outcome analyses will be analysed analogue to primary analyse (see 11.3, 11.4). Subgroup analyses will be performed in case of significant interactions between covariates and experimental condition in order to describe the interaction (see 11.4).

Interim analyses

No interim analyses will be applied.

11.4.4 Safety analysis

Safety analyses will be performed after data sampling completion analogue to the analyses of primary and secondary analyses.

11.4.5 Deviation(s) from the original statistical plan

Deviation from the original statistical plan will be performed, if reviewers demand specific analyses. If in the meantime other studies find important effects or confounding effects related to our study, we will include these found confounders (if we have those) as an additional analysis in our statistical plan beside our planned analyses.

All encoded data from participants who withdraw after enrollment are evaluated and anonymized afterwards.

11.5 Handling of missing data and drop-outs

Missing data will be recorded as NA. For drop-outs will be replaced (see 11.4.1).

12. QUALITY ASSURANCE AND CONTROL

The Principal investigator has an overall responsibility for the implementation and conduct of the study. He is allowed to delegate tasks to the research team as specified in the authorization list. Adequate information and training of the involved staff is in his charge and will be documented.

For quality assurance the Ethics Committee may visit the research sites. Direct access to the source data and all project related files and documents must be granted on such occasions.

12.1 Data handling and record keeping / archiving

Documentation of all study relevant source data of every study participant will be done by completing the project specific electronic case report forms (eCRF). Entries in the CRF must be consistent with information recorded in the source documents. CRF data should be accurate, consistent, complete and reliable. For confidentiality reasons CRFs must not contain any personal data of study participants.

12.1.1 Case Report Forms

As eCRF we will use LabKey®, a validated software provided with an audit trail. Words are imported from logfiles and automatically rated. Rated words are checked for correctness by the subinvestigator. Single data entry for the other parameters.

12.1.2 Specification of source documents

Source data will consist of telephone screening forms, screening questionnaires and checklists, demographic data, visit dates such as memory test dates and scales, Informed Consent Forms, randomisation number, SAEs, AEs and concomitant medication.

12.1.3 Record keeping / archiving

All study data must be archived for a minimum of (10 years) after study termination or premature termination of the clinical trial. Study data will be archived in the archives of Division of Cognitive Neuroscience.

12.2 Data management

12.2.1 Data Management System

Each subject will be assigned to a numeric code in the following way: 58-0001-BS. The first two digits identify the study, the 4 four digits in the middle the subject number and the last two digits are reserved for marking the centre. First subject will receive the number 58-0101-BS as the first 100 numbers are kept for testing purposes.

The coding list will be kept under lock and key.

12.2.2 Data security, access and back-up

Study team members will have access only to anonymized source data. All source data will be kept under lock and key. Electronical data will be stored on the server with back-up of the Division of Cognitive Neuroscience accessible only for study team members. The access to the sever room is a batch restricted only for authorized people.

12.2.3 Analysis and archiving

The log-files (data) will be stored on a linux or macintosh file-system with restricted user access (main file-system). The meta-information of each log-file (SHA-1 hashes as file id, file modification time, path

to the file on the file-system, date and time information logged in the log-file) is stored in LabKey (https://www.labkey.com/) in a study specific folder (main study folder). The relevant content of the log-files that is necessary for creating an analytical database is additionally uploaded to LabKey (main study folder). Data that needs a manual data entry is entered directly in LabKey (data entry folder); after quality control the final data will again be stored in the main study folder within LabKey, and additionally as text-files in the file-system.

The analytical database is created based on the uploaded or manually entered raw data as text-files with time-stamps. These text-files are stored within the LabKey file-system in the main study folder.

LabKey is a SQL database in combination with a file-system (linux file-system) with a web-based graphical user interface (GUI). LabKey provides a user-management and a data-access management. Within LabKey each study has its own study folders (main study folder, data entry folder) with restricted user access. Subject specific data is stored in these study folders only. Within these study folders the access to the LabKey file-system is also handled. Additional information (like design tables of tasks, no subject specific information) is stored also in common folders within LabKey.

The LabKey instance is deployed by SciCORE (https://scicore.unibas.ch/) within a virtual machine, the main file-system is deployed by the IT-department of Psychology.

For log-files we don't expect that any changes will be done. Therefore, we store the meta-information of each log-file to be able to verify that the file is in the original state. All other information is documented and stored within LabKey. LabKey provides an audit trail that allows the tracking of changes over time.

After database closure all eCRF will be printed and archived in paper form. Archiving for all data (electronic or paper form and film sequences) will be for at least 10 years.

12.2.4 Electronic and central data validation

For log-files we use different levels of validation: As a first step we evaluate for each subject, visit and computer if all expected log-files are available and stored in the correct sequence; this check is done via the modification time of the files. We furthermore check if the log-files have an expected number of lines (if applicable, fixed task designs only). If the basis checks fail, we manually curate the log-files, if possible; manual data curation is documented in text-files stored together with the log-files or in LabKey. After performing these basic checks, the data is copied and stored in the final storage space of a study in the main file-system (see above). At the same time-point the meta-information of each file (see above) is stored in LabKey. When uploading the relevant content of the raw data, we further validate if the file-content corresponds to the expected design of a task, if possible (this is task-dependent). Furthermore within LabKey we track for each subject, visit and task if there are exclusion reasons (filter-variables). While creating the final analytical database we apply these filter-variables to the data.

12.3 Monitoring

The aim of monitoring is to evaluate the progress of the study, to verify the accuracy and completeness of CRFs, to ensure that all protocol requirements, applicable local authority regulations and investigator's obligations are being fulfilled, and to resolve any inconsistencies in the study records. The investigator will allow the sponsor to periodically monitor the study.

Monitoring will be performed by an independent team member. Monitoring will consist of 20% of safety parameters, primary endpoint, inclusion and exclusion criteria, and 100% informed consent. (See Monitoring Plan).

12.4 Audits and Inspections

Audits by the CEC during study or after study closure may be performed to ensure proper study conduct and data handling procedures according to ICH-GCP guidelines and regulatory requirements.

Audits and inspections may include verification of all source documents, check of CRFs and site files and a visual inspection of the study site. Direct access to all documents and places at study site is mandatory. In case of an announced audit or inspection immediate notification of the respective other party is necessary.

12.5 Confidentiality, Data Protection

Participant's confidentiality will be maintained at all times. Personnel from the sponsor, members of CEC are obliged to respect medical secrecy and to refrain from divulging the participant's identity or any other personal information they might fortuitously be aware of.

12.6 Storage of biological material and related health data

Not applicable.

13. PUBLICATION AND DISSEMINATION POLICY

The main publication will be created by Prof. Dominique de Quervain. Subsequent publications of subgroups can follow thereafter and will have to be approved by Prof. de Quervain.

No unpublished data given to the investigator may be transmitted to a third party without prior written approval by Prof. de Quervain. No publication or communication involving the results of the study is authorized without prior written consent from the Prof. de Quervain. In view of patent and confidentiality issues, however, the investigator must accept requirements on the timing of early publication. The investigator's name should not be used in any publication without the prior written permission of Prof. de Quervain.

14. FUNDING AND SUPPORT

14.1 Funding

Funding of trial conduct phase: Funds of the Division of Cognitive Neuroscience, University of Basel.

14.2 Other Support

Not applicable

15. INSURANCE

In the event of study-related damage or injuries, the liability of the University Basel provides compensation, except for claims that arise from misconduct or gross negligence.

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