# RESEARCH PROTOCOL:

# EFFECTS OF VAPORISED CANNABIS, WITH AND WITHOUT CBD, ON DRIVING AND COGNITION

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# LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

| | |
|---|---|
| **ABR** | **ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)** |
| **AE** | **Adverse Event** |
| **AR** | **Adverse Reaction** |
| **CA** | **Competent Authority** |
| **CBD** | **Cannabidiol** |
| **CB1** | **Cannabinoid receptor 1** |
| **CB2** | **Cannabinoid receptor 2** |
| **CCMO** | **Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek** |
| **CT** | **Cognitive tests** |
| **CV** | **Curriculum Vitae** |
| **DAT** | **Divided Attention Task** |
| **DS** | **Drug screen** |
| **DSMB** | **Data Safety Monitoring Board** |
| **DRM** | **Deese/Roediger-McDermott** |
| **ECG** | **Electrocardiogram** |
| **EMCDDA** | **European monitoring centre for drugs and drug addictions** |
| **EU** | **European Union** |
| **EudraCT** | **European drug regulatory affairs Clinical Trials** |
| **FC** | **Functional connectivity** |
| **GCP** | **Good Clinical Practice** |
| **GCS** | **Gudjonsson Compliance Scale** |
| **IB** | **Investigator's Brochure** |
| **IC** | **Informed Consent** |
| **GMP** | **Good manufacturing practice** |
| **IMP** | **Investigational Medicinal Product** |
| **IMPD** | **Investigational Medicinal Product Dossier** |
| **METC** | **Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)** |
| **PVT** | **Psychomotor Vigilance Task** |
| **SST** | **Stop-Signal Task** |

| | |
|---|---|
| **TOL** | **Tower of London** |
| **(S)AE** | **(Serious) Adverse Event** |
| **SDLP** | **Standard deviation of lateral position** |
| **SPC** | **Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)** |
| **SPM** | **Statistical parametric mapping** |
| **Sponsor** | **The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.** |
| **SUSAR** | **Suspected Unexpected Serious Adverse Reaction** |
| **THC** | **$\Delta^9$-tetrahydrocannabinol** |
| **VAS** | **Visual analogue scale** |
| **Wbp** | **Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)** |
| **WMO** | **Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen** |

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## SUMMARY

**Rationale:** There is a growing need to better understand the impact of medicinal cannabis use on driving. Although prior research suggests that cannabis impairs driving performance in a dose-dependent manner, it is largely with respect to the effects of Δ9-tetrahydrocannabinol (THC) in recreational cannabis users. It is not clear to what extent these results can be generalised to medicinal cannabis users. A recent pilot study suggests that there may be little difference between high and low CBD cannabis, despite anecdotal reports to the contrary, and that the effects of cannabis on driving may depend on the complexity of the task. This study will seek to validate these findings, primarily by using an on-road driving paradigm.

**Objective**: To examine and compare the effects of vaporized medicinal grade cannabis containing known concentrations and doses of the cannabinoids THC and CBD on on-road driving performance and cognitive function.

**Study design:** Within-subjects, double-blind and placebo-controlled. Occasional cannabis users (N=24) will attend four test sessions, each one week apart, in which driving and cognitive function will be assessed following vaporisation of (1) THC/CBD containing cannabis, (2) THC only cannabis, (3) CBD only cannabis and (4) placebo cannabis. The order of these conditions will be counterbalanced across participants.

**Study population:** Twenty-four healthy, occasional cannabis users, aged 20-50.

**Intervention (if applicable)**: Vaporized Bedrocan, Bedrolite and matched placebo cannabis (equivalent to 13.75 mg THC and CBD).

**Main study parameters/endpoints:** Driving performance will be assessed using the on-road driving task. Cognitive performance will be assessed using computerised cognitive tasks and subjective drug effects will be assessed by established self-report and clinician-administered measures.

**Nature and extent of the burden and risks associated with participation, benefit and group relatedness:** All participants will inhale cannabis and placebo vapor and will complete 2 on-road driving assessments in each session.

# 1. INTRODUCTION AND RATIONALE

Experimental studies indicate that cannabis impairs driving performance and certain aspects of cognitive function in a dose-dependent manner. However, to date, these studies have only considered the effects of the principal intoxicating component of cannabis - Δ9-tetrahydrocannabinol (THC) – and have largely involved recreational cannabis users. It is not clear to what extent these results can be generalized to medicinal cannabis users.

In areas where medicinal cannabis is readily accessible, patients have access to an extensive variety of cannabis chemovars ('strains') and pharmaceutical cannabinoid preparations, many of which contain a significant amount of Cannabidiol (CBD), such as Sativex, which contains a 1:1 ratio of THC and CBD. CBD is a non-intoxicating cannabinoid which shows therapeutic potential in several diseases and conditions, with demonstrated antioxidant, anti-inflammatory, anxiolytic, anticonvulsant, antipsychotic and analgesic properties [1-5]. CBD is well tolerated in humans even at doses of up to 1,500 mg/day [6] and has a very good safety and side-effect profile [7].

CBD has been sometimes found to modulate the pharmacological actions of THC and to dampen some of the adverse psychological effects of THC [8, 9]. There may be some receptor-level interactions between THC and CBD that mediate such effects, and it has been shown that CBD acts as a negative allosteric modulator of the CB1 receptor [10]. Additionally, fMRI studies have observed opposite patterns of activation in the amygdala, prefrontal cortex, anterior cingulate cortex and the cerebellum with THC and CBD [9, 11]. This may have relevance to driving performance and cognitive function.

Amongst recreational cannabis users, there is a growing trend toward high-THC chemovars and highly concentrated THC-rich cannabis extracts. Cannabis users typically prefer these products as they maximise the intensity and the duration of the 'high'. CBD, owing to its potential to dampen the effects of THC, is thus undesirable. Medicinal cannabis users, by contrast, typically wish to maximise the therapeutic effects of cannabis whilst minimising its psychotomimetic effects which can interfere with daily function. They are thus likely to prefer high-CBD chemovars which are also lower in THC. Additionally, clinicians are likely to recommend high-CBD chemovars to patients as they are thought to be more tolerable for patients who do not have experience with cannabis.

Accordingly, it is imperative to establish whether high-CBD chemovars impair driving in the same way as those containing THC alone. This information will allow clinicians to effectively tailor medicinal cannabis treatment regimens for patients, and to provide accurate patient advice concerning the impact of medicinal cannabis treatment on daily functioning. This is especially important given the dispensary model that is emerging in areas within the United States, where patients are being given advice on the relative effects of different chemovars by non-medical staff. Furthermore, this has relevance for therapeutic cannabinoid preparations such as Sativex, which is licensed in various countries for the treatment of spasticity associated with MS. At current there is only limited evidence to suggest that long-term use does not adversely affect standard driving ability in patients with moderate to severe MS spasticity [12].

Here we will examine whether vaporised GMP-grade medicinal cannabis containing a 1:1 ratio of THC and CBD impairs driving in the same way as cannabis containing an equivalent amount of THC with no CBD and compared with CBD alone. This novel study will examine on-road driving performance at acute (30 min) and post-acute (4 hours) timepoints following consumption of GMP-grade vaporised medicinal cannabis.

## 2. OBJECTIVES

Primary Objective:

- To assess the influence of cannabis containing varying ratios of THC and CBD and placebo on driving performance at 30 minutes (peak of acute intoxication phase) and 4 hours later (post-acute intoxication phase)

Secondary Objective(s):

- To assess the influence of cannabis containing varying ratios of THC and CBD and placebo on cognitive performance at 30 minutes (peak of acute intoxication phase) and 4 hours later (post-acute intoxication phase)
- To assess whether participants can accurately estimate their fitness to drive prior to driving tests
- To assess whether CBD alters the subjective drug effects of THC
- To examine whether CBD modulates the pharmacokinetics of THC, and whether this might be a relevant mechanism whereby CBD influences THC impairment.

# 3. STUDY DESIGN

The study will employ a within-subjects, double-blind and placebo-controlled design. Occasional (*N*=24) cannabis users will receive single doses of cannabis (Bedrocan, Bedrolite and Placebo) over four separate sessions (with each session separated by a minimum of 7 days) in a randomised and counter-balanced order.

# 4. STUDY POPULATION

## 4.1 Population (base)

Healthy, occasional users of cannabis will be recruited (20-50 years).

## 4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Occasional cannabis users (>10 lifetime exposures and <2x/week in the last 12 months)
- Age between 20-50
- Good physical health as determined by medical examination and laboratory analysis
- Absence of any major medical, endocrine and neurological condition
- Normal weight, body mass index (weight/height$^2$) between 20 and 28 kg/m$^2$
- In possession of a valid driver license with at least 2 years driving experience (having driven > 3000 km/yr)
- Written Informed Consent

## 4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- History of drug abuse (other than the use of cannabis) or addiction (determined by the medical questionnaire, drug questionnaire and medical examination)
- Pregnancy or lactation (pregnancy test, if needed)
- Hypertension (diastolic> 90; systolic> 140)
- Current or history of psychiatric disorder (determined by the medical questionnaire and medical examination)
- Liver dysfunction
- Use of medications that may impact upon driving ability (e.g. mood stabilisers, sedatives)

- Any serious prior adverse response to cannabis
- History of cardiac dysfunctions (e.g. arrhythmia, ischemic heart disease)
- QT syndrome

### 4.4 Sample size calculation

A priori sample size calculation was done by using G*Power. The effect size was calculated from a previous study which compared on-road driving performance after placebo, 10mg and 20mg dronabinol [13]. Although dronabinol is an oral THC product and its pharmacokinetic profile differs from that of vaporized cannabis, it is a prescribed medicinal cannabinoid product which produces similar subjective effects, and the dose range is similar to that which we will be using in this study. Given the partial eta value of 0.28 associated with a main effect of Dronabinol on SDLP and using a nonspherecity correction error value of 0.8 to allow for violation of the sphericity assumption, a sample size of 20 is needed for the probability of an α-error of .05 (β–error: 0.95). To allow for a drop-out rate of 15-20%, 24 participants will be recruited to the study. The power analysis protocol is shown below:

**F tests -** ANOVA: Repeated measures, within factors

| | | |
|---|---|---|
| **Analysis:** | A priori: Compute required sample size | |
| **Input:** | Effect size f(U) | = 0.6236096 |
| | α err prob = | 0.05 |
| | Power (1-β err prob) | = 0.95 |
| | Number of groups | = 1 |
| | Number of measurements | = 4 |
| | Nonsphericity correction ε | = 0.8 |
| **Output:** | Noncentrality parameter λ | = 17.7333354 |
| | Critical F = | 3.0151288 |
| | Numerator df | = 2.4000000 |
| | Denominator df | = 45.6000000 |

Total sample size = 20

## 5. TREATMENT OF SUBJECTS

### 5.1 Investigational product/treatment

Participants will receive a fixed dose of each of the following cannabis varieties:

- Bedrocan (THC 22% | CBD <1.0%)

- Bedrolite (THC<1% | CBD 9%)
- Placebo

The dose of each variety given will be sufficient to deliver 13.75 mg THC and 13.75 mg CBD. Because of the disparity between THC and CBD cannabinoid concentrations in Bedrocan and Bedrolite cannabis, active cannabis will be mixed with sufficient placebo material so that a total of 215 mg plant material is vaporised in each condition according to the following ratios:

1) THC:
62 mg Bedrocan (THC) + 153 mg placebo = 13.75 mg THC + Nil CBD
2) THC/CBD:
62 mg Bedrocan (THC) + 153 mg Bedrolite (CBD) = 13.75 mg THC + 13.75mg CBD
3) CBD:
153 mg Bedrolite (CBD) + 62 mg placebo = 13.75 mg CBD + Nil THC
4) Placebo:
215 mg Placebo = Nil THC / CBD

Details of the treatment procedure and described further in Section 6.1.

### 5.2 Use of co-intervention

Participants will be asked to refrain from any drugs during the study period. Subjects will not be allowed to use alcohol on the day prior to an experimental session.

### 5.3 Escape medication

Not applicable

## 6. INVESTIGATIONAL PRODUCT

### 6.1 Name and description of investigational product(s)

The following varieties of Bedrocan cannabis flos will be used:

- Bedrocan (THC 22% | CBD <1.0%)
- Bedrolite (THC<1% | CBD 9%)
- Placebo

- Bedrocan and Bedrolite placebo products retain the terpene profile of the original strains (i.e. they have the same flavor and smell) but the active cannabinoids have been extracted to <0.2% of the total weight. As such, they are not psychoactive. To ensure consistency across sessions, placebo plant material will be added to each active dose to ensure that participants vaporizer the same amount of total plant material in each session.

### 6.2 Summary of findings from non-clinical studies

*See also Specification Sheet and product information of Bedrocan and Bedrolite.*

Δ9-THC is the principal psychoactive constituent of cannabis. The pharmacological actions of THC result from its partial agonist activity at the cannabinoid receptor $CB_1$ located mainly in the central nervous system, and the $CB_2$ receptor, mainly expressed in cells of the immune system. THC has mild to moderate analgesic effects, and cannabis can be used to treat pain. Other effects include relaxation, alteration of visual, auditory, and olfactory senses, fatigue, and appetite stimulation. THC has marked antiemetic properties, and may also reduce aggression in certain subjects. CBD is not psychoactive, is well tolerated by humans even at very high doses and has a very good safety profile (Iffland & Grotenhermen, 2017).

Since the 1980s, THC (dronabinol, Marinol, Solvay Pharmaceuticals) and one of its synthetic analogues, nabilone (Cesamet, Valeant Pharmaceuticals), are being used for the suppression of nausea and vomiting produced by chemotherapy and, since 1992, Marinol is being used for the stimulation of appetite in AIDS. In the Netherlands, four types of medicinal cannabis are available through pharmacies: Bedrocan, Bedrobinol, Bediol and Bedica. The composition and strength varies from about 6% till 22% THC. Medicinal cannabis is prescribed for pain and muscle spasms/cramps associated with multiple sclerosis (MS) or spinal cord damage; nausea, reduced appetite, weight loss and debilitation associated with cancer and AIDS; nausea and vomiting caused by medication or radiotherapy for cancer and HIV/AIDS; long-term neurogenic pain and tics associated with Tourette Syndrome.

The psychological effects of cannabis can vary widely, depending on the dose, the route of administration, and personal conditions such as experience with the drug and mood. Use of cannabis can cause a feeling of euphoria which changes slowly into a pleasant feeling of calmness and tranquility. Other effects include sedation, cheerfulness, hunger, greater sensitivity to perceptions of color and music, distorted space-time perception, and lethargy.

The altered perception can induce feelings of anxiety, panic and confusion. Also, restlessness and insomnia have been reported. Cannabis can in rare cases provoke a psychotic reaction, characterized by delusions and hallucinations. The physical effects of Bedrobinol include: tachycardia, orthostatic hypotension, headache, dizziness, warmth or cold hands and feet, red burning eyes, muscular weakness, dry mouth. These effects are temporary and disappear a few hours after use.

### 6.3 Summary of findings from clinical studies

Not applicable

### 6.4 Summary of known and potential risks and benefits

At doses exceeding the psychotropic threshold, ingestion of cannabis usually causes enhanced well-being and relaxation with an intensification of ordinary sensory experiences. The most important acute adverse effects caused by overdosing are anxiety and panic attacks, and with regard to somatic effects increased heart rate and changes in blood pressure. Regular use of cannabis may lead to dependency and to a mild withdrawal syndrome.

### 6.5 Description and justification of route of administration and dosage

Each subject will receive a dose equivalent to 13.75mg THC and CB. This dose is similar to what was used in a previous study (Arkell et al., manuscript under review) testing the effects of high and low CBD cannabis on simulated driving performance. Participants in this study reported feeling ‘high’, and a clear reduction in performance was observed in laboratory tasks measuring working memory, divided and sustained attention, reaction time, tracking, and motor function. The administration of cannabis will occur through heating in the Storz and Bickel Mighty Medic vaporiser. Cannabis plant material will be positioned in the filling chamber of the device, which will then be heated to 200 °C. Participants will inhale through the mouthpiece according to a standardized procedure (i.e. inhale 5 seconds, hold 3 seconds, exhale and rest until 30s has elapsed) for a minimum of 8 inhalations. If vapor is still observable in exhaled breath after these 8 inhalations, this procedure will continue until vapor is no longer seen. Appropriate training of the volunteers for the use of a Mighty Medic vaporizer will be performed during the training session, using the placebo. The preparation of the vaporizer will be done in the drug administration room by one of the researchers, out of sight for the participant. This researcher will not be present during the administration or during the testing of the subjects. The administration will take place in the waiting room with one of the researchers present.

### 6.6 Dosages, dosage modifications and method of administration

Vapor of 215mg cannabis (containing 62 mg Bedrocan + 153 mg placebo OR 62 mg Bedrocan + 153 mg Bedrolite OR 153 mg Bedrolite + 62 mg placebo OR 215mg placebo) plant material as described in Section 5.1 will be inhaled via vaporisation. This amount of plant material is sufficient to provide 13.75mg of THC and CBD.

### 6.7 Preparation and labelling of Non-Investigational Medicinal Product

Bedrocan, Bedrolite and placebo cannabis will be delivered by the Office for Medicinal Cannabis, and the doses will be weighted and labelled in our drug storage room, using a calibrated digital MyWeigh scale (type i101).

### 6.8 Drug accountability

The Office for Medicinal Cannabis will deliver the cannabis to the University where it will be placed immediately in a safe, in a cool and dark locked room. In the trial master file, there will be a drug accountability log where information about distribution and return will be registered.

## 7. NON-INVESTIGATIONAL PRODUCT

### 7.1 Name and description of non-investigational product(s)

Subjects will also receive placebo, which is Bedrocan cannabis flos that has had the phytocannabinoids (including THC, the psychoactive component) removed.

### 7.2 Summary of findings from non-clinical studies and clinical studies

This section is not applicable. Bedrocan placebo retains the precise terpene profile of Bedrocan cannabis with all cannabinoids removed to <0.2% of dry weight i.e. to a negligible level. As such, the product is non-psychoactive. This makes it an appropriate placebo and blinding agent. To date there have been three clinical trials which have successfully used this product [14-16]. No adverse events with Bedrocan placebo cannabis have been reported. See also the Product Information Sheet of Bedrocan placebo.

### 7.3 Summary of known and potential risks and benefits

Not applicable

### 7.4 Description and justification of route of administration and dosage

The amount of Bedrocan placebo cannabis material administered will be equivalent to 215mg minus the amount of active plant material in each condition and it will be administered via the Mighty Medic vaporizer (i.e. the same way the Bedrocan is administered). Bedrocan placebo retains the precise terpene profile of the Bedrocan strain, with all cannabinoids removed to <0.2% of dry weight. As such, the product is non-psychoactive, but retains the taste of the original strain, which makes it indistinguishable from its active equivalent during vaporising. Placebo cannabis plant material will mixed homogenously with active cannabis plant material and will be positioned in the filling chamber of the device, which will then be heated to 200 °C. Participants will inhale through the mouthpiece according to a standardized procedure (i.e. inhale 5 seconds, hold 2 seconds, exhale and rest until 30s has elapsed) for a minimum of 8 inhalations. If vapor is still observable in exhaled breath after these 8 inhalations, this procedure will continue until vapor is no longer seen. Appropriate training of the volunteers for the use of a Mighty Medic vaporizer will be performed during the training session, using the placebo. The preparation of the vaporizer will be done in the drug administration room by one of the researchers, out of sight for the participant. This researcher will not be present during the administration or during the testing of the subjects. The administration will take place in the waiting room with one of the researchers present.

### 7.5 Dosages, dosage modifications and method of administration.

The amount of Bedrocan placebo (<0.2% THC & CBD) administered will be equivalent to 215mg minus the amount of active plant material required in each condition to deliver 13.75 mg THC / CBD.

### 7.6 Preparation and labelling of Non Investigational Medicinal Product

Bedrocan placebo (<0.2% THC & CBD) will be delivered by the Office for Medicinal Cannabis, and the doses will be weighted and labelled in our drug storage room, using a calibrated digital MyWeigh scale (type i101).

### 7.7 Drug accountability

The Office for Medicinal Cannabis will deliver the cannabis to the University where it will be placed immediately in a safe, in a cool and dark locked room. In the trial master file, there will be a drug accountability log where information about distribution and return will be registered.

# 8. METHODS

## 8.1 Study outcome measures

- Primary: Driving performance will be assessed using the on-road driving test. Outcome measures will include standard deviation of lateral position (SDLP), speed (MS) and standard deviation of speed (SDSP).
- Secondary: (1) Cognitive performance as assessed using the Divided Attention Task (DAT), Digit Symbol Substitution Task (DSST), Paced Auditory Serial Addition Task (PASAT), Tower of London (TOL) task; (2) Subjective drug effects and confidence in driving ability as measured by a series of Visual Analog Scales (VAS); Cannabis effects on anxiety as measured by the State Trait Anxiety Inventory (STAI) and an emotional Stroop task, and; (3) Plasma concentrations of THC, 11-OH-THC, THCCOOH and CBD.

### 8.1.1 Primary outcomes

**Driving performance**

Road tracking test

In the road tracking test (O'Hanlon, 1984), the participant operates a specially instrumented vehicle over a 100 km primary highway circuit in The Netherlands (Maastricht-Kelpen-Oler) while maintaining a constant speed (95 km/h) and a steady lateral position between the delineated boundaries of the right (slower) traffic lane. An electro-optical device mounted at the rear back of the car continuously measures lateral distance separating the vehicle and the left lane-line. This signal is digitized at a rate of 4 Hz and stored on an onboard computer disk file for later editing analysis. The off-line editing routine involves removal of all data segments that reveal signal loss, disturbance or occurrence of passing manoeuvres. The remaining data are then used to calculate means and variances for lateral position and speed. Standard deviation of lateral position (SDLP) is taken as the primary outcome variable. SDLP is a measure of road tracking error, in practical terms, a composite index of allowed weaving, swerving and overcorrecting. Another outcome variable is mean speed, and standard deviation of speed, which is a measure of the accuracy of performance. The test duration is 60 minutes.

### 8.1.2 Secondary outcomes

## Cognitive performance

Divided Attention Task (DAT)

The DAT measures the subject's ability to divide attention between two tasks performed simultaneously. The primary task consists of a tracking task with an individually determined level of difficulty, while the secondary task involves monitoring a display of numbers and responding to only a certain number. Mean absolute tracking error, number of correct detections and number of control losses are the main performance measures [17]. This takes about 12 minutes to complete.

Digit Symbol Substitution Task (DSST)

The DSST measures speed of processing [18]. A series of 10 symbols are matched with numbers (1-10) Individual symbols are presented one at a time on the bottom of the screen, and subjects are required to respond by pressing the appropriate number associated with that symbol using the numerical keypad of a computer keyboard. Dependent variables include the number of items correct and the response time. The DSST takes 3 minutes to complete.

Paced Auditory Serial Addition Test (PASAT)

This computerized version of the PASAT measures information processing speed and working memory [19] . In this task, numbers are presented one at a time on the screen. Participants are required to add each number to the preceding number and input the sum of these two numbers using the numerical keypad of a computer keyboard. Dependent variables include the number of items correct and the response time. It takes approximately 5 minutes to complete the PASAT.

Tower of London (TOL)

The Tower of London (TOL) is a decision-making task that measures executive function and planning (Shallice, 1982). The task consists of computer-generated images of begin- and end-arrangements of three colored balls on three sticks. The subject's task is to determine as quickly as possible, whether the end-arrangement can be accomplished by "moving" the balls in two to five steps from the beginning arrangement by pushing the corresponding number coded button (Veale et al., 1996). The total number of correct decisions is the main performance measure. Completion of the TOL takes between 10 and 15 minutes.

**Subjective drug effects, perceived driving ability and pharmacokinetic measures**

Emotional Stroop task

This task [22] looks at differences in information processing between anxious and non-anxious individuals. During the training session, participants will practice this task with 80 neutral words. On the test days, participants will be presented with 20 anxiety-related words and 20 anxiety-matched neutral words. All words will be presented twice in a mixed-trail (anxiety related/neutral at random). The colour the words are presented in are: blue, red, green, yellow. Outcomes include mean reaction time for the anxiety related words and neutral words and number of errors. Completion takes about 3 minutes.

Visual analog scales (VAS)

A series of 100mm VAS will ask participants to report:

1. Strength of drug effect (No effect – Very strong)
2. Liking of drug effect (Dislike very much – Like very much)
3. Stoned (Not stoned – Very stoned)
4. Sedated (Not sedated – Very sedated)
5. Relaxed (Not relaxed – Very relaxed)
6. Anxious (Not anxious – Very anxious)
7. Confident to drive (Not confident – Very confident)

Perceived Driving Quality

At the end of each driving task, a series of 100mm VAS will ask participant the following:

1. How would you rate the quality of your driving just now? (Very poor – Very good)
2. Compared to normal (i.e. when not stoned), how well do you think you drove? (Much worse – Much better)
3. Do you think your driving was impaired? (Not at all – Very much)

State Strait Anxiety Inventory (STAI)

This scale [20, 21] consists of two sections, Y-1 and Y-2, which assess state and trait anxiety, respectively. Section Y-2 (trait) will be administered during the training session, and section Y-1 (state) will be administered once during each research session. The outcome measure for both sections is the total score.

Groningen Sleep Quality Scale (GSQS)

This scale [23] will be used to assess sleep quality during the nights preceding the testing days. Measurements consist of a total score of 14 yes/no questions to score the number of sleep complaints (ranging from good sleep [score = 0] to worst possible sleep [score = 14] and specific questions about time needed to fall asleep, number of awakenings during the night, and sleep duration in hours.

Physiological measures

Blood pressure, heart rate and body temperature will be measured throughout each testing day.

Pharmacokinetic measures

On each test day, blood samples will be collected at baseline, immediately after, 30 m, 2h 15m, 3h 30m and 5h 30m after drug administration. 5 mL blood will be collected in purple top EDTA tubes and centrifuged for 10 minutes. Plasma will be extracted and stored at -20ºC until analysis. Plasma will be analyzed for THC, THCCOOH, 11-OH-THC and CBD.

## 8.2 Randomisation, blinding and treatment allocation

Cannabis and placebo will be administered according to a balanced randomisation schedule containing 4 blocks of 6 (i.e. 24 total allocations). Allocation of the treatment order will be done in a completely random order, by one experimenter who does not come in direct contact with the subjects. The study will be double blind. One experimenter will be responsible for preparing the cannabis. This experimenter will not be the one testing the subjects. If a subject is withdrawn from the study, that treatment allocation will not be further used and the following subject will be given the next treatment allocation. Following completion of all data collection the study will be fully unblinded. If necessary, the study physician will break the blind on a study day.

## 8.3 Study procedures

### 8.3.1 Pre-screening

Before subjects are invited for a medical examination, a brief pre-screening by email is conducted. This will include questions regarding the subject's frequency of cannabis consumption and driving history to determine potential eligibility for the study. If a subject appears eligible from the pre-screening, the information brochure for volunteers and the

informed consent form will be sent via email. The potential subject is given one week of time to read the information and decide whether or not to participate. If the decision is positive, the subject is invited for a medical screening.

### 8.3.2 Medical screening and training day

Before the medical screening commences, subjects must sign the informed consent form. After that, they are requested to fill out a drug and medical questionnaire. Eligible subjects are invited for a physical examination [including blood- and urine analyses (Haematology, Clinical Chemistry, Urinalysis and Virology) and ECG]. Subjects are informed that they will be notified about all incidental significant medical findings that occur during the study. In case participants do not want to be informed about these findings, they cannot participate in the study. When there is no medical objection for participation, subjects will be invited to participate in the research and a training day will be scheduled.

On the training day, participants will be asked to come in to the lab for approximately 2-3 hours. Participants will be introduced to the on-road driving task, involving a detailed explanation of the task itself and a 1-hour practice drive on the course that will be used on test days. This allows participants to become thoroughly familiar with the vehicle itself and to become familiarized with the driving instructor. Participants will then practice each of the cognitive tasks in the lab. Participants will also practice the emotional Stroop task and complete the Y-2 (trait) section of the STAI.

### 8.3.3 Test days

Subjects will participate in 4 separate test days, each separated by a minimum period of 7 days, and a maximum period of 28 days. Subjects will be asked to refrain from any drugs from 7 days prior to each test day, to make sure that subjects will no longer have a positive drug screen. Subjects are not allowed to use alcohol on the day prior to the experimental session and will be requested to arrive at the experimental session well rested. Subjects are requested to have a light breakfast at home and consume no more than their usual amount of caffeine. On the test day, participants will be picked up from their home in time to arrive at the lab at 9:00. Drug and alcohol screens will be performed first, using a saliva drug test and breathalyzer. In case of a positive screen for cocaine, alcohol, opiates, benzodiazepine, methamphetamine or amphetamine, subjects will be sent home to return to the laboratory at a later time. If the tests are negative, then the session will proceed.

Baseline measures will be administered, including the GSQS and VAS item. A cannula will be inserted into the participant's non-dominant arm, and the first blood sample will be taken. Approximately 45 minutes after arrival at the lab, participants will inhale Bedrocan, Bedrolite, Bedrocan/Bedrolite or placebo vapor. An investigator will be present in the room while the administration takes place. A second blood sample will be taken immediately after vaporizing, when THC plasma concentrations are maximal. Participants will then complete VAS items, the Y-1 section of the STAI, the three cognitive tests (DSST, PASAT and DAT), and the emotional Stroop task. A third blood sample will be taken after these tests, approximately 25 minutes after vaporizing. The first driving test will begin approximately 30 minutes after vaporizing (i.e. when plasma THC concentrations have declined considerably but during peak subjective drug effects) and will run for 90 minutes, including the time needed to leave and return to the lab. At the end of the driving test, a fourth blood sample will be taken. Participants will then complete VAS items and the TOL task. Participants may take short breaks in between tests when needed. Participants will then be given 45 minutes to rest and have a standardized lunch.

A fifth blood sample will be taken at 13:10, after which participants will complete the second cognitive test battery and VAS items. Following this, the second driving test will commence. Once this has been completed, participants will provide a final blood sample and complete the final set of VAS items. A saliva test will then be performed to confirm that the participants' saliva is negative for THC. Participants will be discharged from the lab at approximately 15:30 and will be driven back to their home. In the case that this final saliva test is negative, participants will remain at the lab and saliva testing will be repeated every 30 minutes until such time as the test result is negative. If the researcher deems the participant unfit to leave the lab safely, the participant will be reviewed by a medical practitioner and asked to remain at the lab until such time as they are fit to go home. At the end of the fourth session, a short debriefing will take place in which the aims of the study may be explained, and the participants is asked whether he/she noticed on which days the cannabis/placebo were received. An overview of the sessions is presented below:

| Activity | Time post-drug | Duration (minutes) | Time Start | Time End |
|---|---|---|---|---|
| Drug and alcohol screen | -40m | 10 | 9:00 | 9:10 |

| | | | | |
|---|---|---|---|---|
| Baseline questionnaire, GSQS, VAS | -30m | 10 | 9:10 | 9:20 |
| Cannulation & blood sample (1) | -20m | 10 | 9:20 | 9:30 |
| **Drug administration** | **0** | **10** | **9:40** | **9:50** |
| Blood sample (2) | Immediately | 5 | 9:50 | 9:55 |
| VAS, STAI, DAT, DSST, PASAT, Stroop | 5 min | 20 | 9:55 | 10:15 |
| Blood sample (3) | 25 min | 5 | 10:15 | 10:20 |
| VAS, Driving task (1) | 30 min | 90 | 10:20 | 11:50 |
| Blood sample (4) | 2 h 10 min | 5 | 12:00 | 12:05 |
| VAS, TOL | 2 h 15 min | 20 | 12:05 | 12:25 |
| Lunch and rest | 2 h 35 min | 40 | 12:25 | 13:10 |
| Blood sample (5) | 3 h 20 min | 5 | 13:10 | 13:15 |
| VAS, DAT, DSST, PASAT | 3 h 25 min | 15 | 13:15 | 13:30 |
| Driving task (2) | 3 h 50 min | 90 | 13:40 | 15:10 |
| Blood sample (6), VAS, saliva sample, review and discharge | 5 h 20 min | 20 | 15:10 | 15:30 |

### 8.4 Medical supervision during the study and emergency plan

The medical supervisor will medically check all participants before they are included in the study (see 8.3.1). During the test days, a researcher will always accompany the participant during their time at the testing facilities. In case the participants report any side effects, the researcher will take the necessary steps:

- In case it requires no further action, the side effects will be noted (e.g. headache, feeling high).
- In case the side effect causes some minor discomfort (e.g. feeling dizzy), the subject will be asked to lie down, while a nearby staff member with first aid training will check out the subject. If needed, the medical doctor will be called to determine what action should be taken. It will be determined by the participant and the medical doctor whether the participant can continue the test day.
- In case of more severe side effects (e.g. losing consciousness), the medical doctor will be informed immediately, a nearby staff member with first aid training will be called

upon, and if needed, the participant will be brought to the first aid department of the Maastricht Hospital or an ambulance will be called. The testing day will be stopped and it will be evaluated by the medical doctor and principal investigator whether the study can continue.

**Additional safety measures:** A list with phone numbers of all researchers involved, the medical doctor, and staff member with first aid training will be clearly visible in all rooms used during the experiment. In addition, the researcher who will accompany the participant will always carry his mobile phone with these phone numbers. All researchers will be informed about the emergency plan.

### 8.5 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

### 8.6 Replacement of individual subjects after withdrawal

If a volunteer drops out of the study, that treatment allocation will have been used and the subsequent volunteer will be assigned to the next treatment allocation. 24 participants will be recruited to the study in total, allowing for a potential drop-out rate of ~15% to ensure that at least 20 participants finish the entire study. Any test day on which a subject has been administered study medication and on which tests cannot be conducted, due to unforeseeable technical failures (e.g. computer malfunction) that occurred after drug administration, can be repeated on the next visit of the subject using spare medication. When this will occur, another person, not directly involved in this research will unblind the code for this subject and take spare medication.

### 8.7 Follow-up of subjects withdrawn from treatment

In case a subject withdraws or is withdrawn from the study due to an AE or SAE the usual procedures will be followed as stated in section 9 of this protocol.

### 8.8 Premature termination of the study

Study termination is defined as a permanent discontinuation of the study due to unanticipated concerns of safety to the study subjects.

# 9. SAFETY REPORTING

## 9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

## 9.2 AEs, SAEs and SUSARs

### 9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to [the investigational product / the experimental intervention]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

### 9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse reactions.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

#### 9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable

### 9.3 Annual safety report

Not applicable

### 9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

### 9.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]

Not applicable for this study.

## 10. STATISTICAL ANALYSIS

Statistical analyses of drug effects on driving, cognitive test performance and subjective measures will be conducted in SPSS using a linear mixed model design with treatment (THC, THC/CBD, CBD, placebo) and time (time since drug administration) as fixed factors. The appropriate covariance structure for each model will be chosen based on model fit criterion (e.g. AIC). Bonferroni pair-wise comparisons will be used to test for differences between treatment means at each timepoint. Separate models will test the influence of plasma THC concentrations on driving and cognitive test performance at each individual timepoint by including treatment and plasma THC at fixed factors. Associations between perceived driving ability and actual driving will be analysed using correlational analyses. All data will enter statistical analyses, including incomplete datasets due to missing data. Data will only be left out of analyses in the case where a participant withdraws his/her consent and requests that his/her data will not be used.

# 11. ETHICAL CONSIDERATIONS

## 11.1 Regulation statement

This study will be conducted according to the code of ethics on human experimentation established by the declaration of Helsinki (1964) and amended in Fortaleza (Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO). This implies that all subjects will participate voluntarily and will be fully informed of all procedures, possible adverse reactions to drug treatments, legal rights and responsibilities, expected benefits of a general scientific nature, and their right for voluntary termination without penalty or censure. All subjects shall give their informed consent, in writing, and the individual subject's anonymity shall be maintained in all communications from the project. Approval for the studies shall be obtained from the Academic Hospital and University's Medical Ethics committee.

All data will be treated confidentially using codes and only the researchers involved in the study will have access to the data. All human tissue that is gathered during the study will be destroyed 6 months after completion of the study. An independent physician is at the subjects' disposal for additional information. Subjects are offered the possibility to be informed about the results of the study.

## 11.2 Recruitment and consent

Participants will be recruited through various mediums from Maastricht and the surrounding area. Advertisements will be put up in the University buildings (e.g. in Maastricht: FPN, SBE, inner city library), and a call for participants will also be published in local newspapers (Maastricht: e.g. "De Limburger", "1Maastricht"). Online enrolment systems (SONA) will also be used as well as social media channels (e.g. Facebook, Twitter). It is anticipated that participants will also be notified of the study via word of mouth. When potential subjects react to the advertisement, they will be pre-screened by email/phone for eligibility. If they appear eligible, they receive the brochure 'information for volunteers' and informed consent form, which they are requested to read carefully. From this point, they have one week of time to decide whether they want to participate or not, and if they do they are invited for a medical screening. Before the medical screening starts, subjects will be fully informed of all procedures, possible adverse reactions to drug treatments, legal rights and responsibilities, expected benefits of a general scientific nature, and their right for voluntary termination without consequences. Subjects will then be asked

to sign the informed consent and to fill in the medical questionnaire and drug questionnaire. One of the researchers and the medical doctor will check all in- and exclusion criteria. Subjects are subsequently informed whether they fulfil the criteria or not. In case they are suited for participation, a physical examination is conducted. All subjects shall give their informed consent, in writing, and the individual subject's anonymity shall be maintained in all communications from the project. After consent has been given, data will be collected by experimenters and will be encoded. All collected and encoded urine and blood samples will be destroyed after 6 months. The blood and urine samples will be labelled with codes of the study ID, date, testing day, and participant number.

### 11.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable

### 11.4 Benefits and risks assessment, group relatedness

A workshop on pharmacology challenge studies convened by the National Institute of Mental Health (NIMH) concluded that drug studies can be considered ethical provided that two conditions are met [24]:

1) *there must be sufficient and clear scientific merit to the study in the form of testable hypotheses that will provide new knowledge.* We think that for the present study this is sufficiently met. In many criminal cases (occasional) drug use plays a role; however, the implications for witnesses' and perpetrators' testimony have not been sufficiently investigated.

2) *the risks must be minimized and justified in terms of potential scientific gains*. We believe that the risk is kept to a minimal in this study. The acute effects of Bedrobinol are well known, and similar doses have been used in our previous studies.

Cannabis: The effects of THC occur very rapidly after inhalation and disappear within 2 to 3 hours. The given dose has been given to participants in previous studies with nil adverse events and is well tolerated in recreational cannabis users. Expected effects include mild relaxation, alteration of visual, auditory, and olfactory senses, fatigue, and appetite stimulation. Serious acute adverse effects of cannabis may include anxiety and panic attacks, tachycardia and an increase in blood pressure, however these are typically induced at much higher doses that what will be administered in this study. Placebo cannabis is not

expected to cause any side effects, given that the concentrations of present active cannabinoids are at negligible levels.

### 11.5 Compensation for injury

In accordance with the provisions of the law Maastricht University has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 650.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 5.000.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 7.500.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

### 11.6 Incentives (if applicable)

Subjects will be compensated for their participation by means of a monetary reward. Participants will receive € 400 for their participation in the study. This is based on € 75 per test day, plus € 30 for their time coming in for the medical assessment and training day. Upon completion of all 4 test days they will receive a bonus of € 70. In case of premature termination of the study will be based on the number of test days on which it is paid. In addition, participants will be brought to and from their home to the lab on test sessions, and will be provided with lunch on study test days.

## 12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

### 12.1 Handling and storage of data and documents

All data and blood samples will be labelled with a code that consists of the following information:

- Project number: 112
- Subject number: assigned based on order of inclusion
- Test day: test day 1 is labelled A; test day 2: B; test day 3: C, test day 4: D
- In case a test is repeatedly administered on a test day, the repetitions will be labelled: 1-….

All data is collected in electronic and paper format. Data from the questionnaires is collected on paper. These (paper) source data will be kept in a locked cabinet to which only researchers involved in the project have access. Electronic source data is stored on a partition of a server (hosted in the University Building) which is only accessible to the research team. The key code is safeguarded by the principal investigator. Data will also be accessible by the IGJ and monitors. The data will be kept for 15 years. Blood and urine samples from the medical screening and those collected on test days are destroyed after 6 months. Only anonymous data will be shared with The University of Sydney. This data will be transferred electronically via CloudStor (an enterprise level secure file sharing platform that is used by Australian research and educational institutions) once data collection is complete and stored on a secure University of Sydney server where it will be password protected and accessible only to members of the Sydney research team.

### 12.2 Monitoring and Quality Assurance

Monitoring of the study will take place. The monitor (Nadia Hutten) will conduct two visits in which she will (for details: see monitoring plan):

- do the verification of the source documentation
- check the drug accountability plan
- check the trial master file
- discuss the results of the visit and write a report

### 12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

### 12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

### 12.5 Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited METC and of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

### 12.6 Public disclosure and publication policy

All results from this research will be disclosed unreservedly in a scientific paper aimed for publication in a peer reviewed scientific journal. Research data collected in the current study will be owned by Maastricht University.

## 13. STRUCTURED RISK ANALYSIS

### 13.1 Potential issues of concern

a. Level of knowledge about mechanism of action

The mechanism of action of THC is well known. THC exerts its most prominent effects via its actions on two types of cannabinoid receptors, the $CB_1$ receptor and the $CB_2$ receptor. The CB1 receptor is found primarily in the brain, and the CB2 receptor is found primarily in peripheral tissues. THC alters mood and cognition through its agonist actions on the CB1 receptors, which inhibit a secondary messenger system in a dose dependent manner.

Via CB1 activation, THC indirectly increases dopamine release and produces psychotropic effects.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

The effects of THC on humans are well classified, and we have used similar doses to look at the effects of THC on cognition and driving previously [25-28]

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

No, we are specifically interested in drug effects on driving and cognition.

d. Selectivity of the mechanism to target tissue in animals and/or human beings

We will study changes in driving and cognitive performance during and after THC intoxication in humans.

e. Analysis of potential effect

The effects of THC occur very rapidly after inhalation and disappear within 2 to 3 hours. The given dose is well tolerated in recreational cannabis users, and will induce effects such as relaxation, alteration of visual, auditory, and olfactory senses, fatigue, and appetite stimulation. The most important acute adverse effects of a high dose of cannabis are anxiety and panic attacks, and with regard to somatic effects increased heart rate and changes in blood pressure.

f. Pharmacokinetic considerations

THC is very rapidly absorbed in the blood stream and reaches peak concentration (Tmax) within minutes after smoking [29]. THC is also rapidly eliminated as evidenced by a 50% reduction a THC concentration in blood within 1.5 hrs after cannabis smoking [30].

g. Study population

Participants will be occasional cannabis users (cannabis use <2x/week in previous 12 months and >10 lifetime exposures) aged between 18 and 65 years. All subjects will be medically screened. Inclusion and exclusion criteria are mentioned under section 4.2 and 4.3.

h. Interaction with other products

Participants are not allowed to use any psychoactive medication within 5 days before each test day until the end of the study. Use of drugs like painkillers (e.g. ibuprofen, aspirin, paracetamol) and oral contraceptives will be allowed during the study. Therefore, there will be no risk of drug interactions.

i. Predictability of effect

The effects of cannabis on driving are well documented [31]. At low doses, cannabis' effects on driving are nominal, and typically do not exceed those associated with 0.05% BAC. At high doses and in naïve users, the effects are more pronounced and can be significantly impairing.

j. Can effects be managed?

Effects will disappear as the drug is eliminated from the body.

### 13.2 Synthesis

This will be the first study to investigate the effects of different cannabis chemovars (with and without CBD) on real-world driving performance. Occasional cannabis users will receive cannabis (equivalent to 13.75mg THC and CBD) and will complete two on-road driving tasks and a series of cognitive tests and subjective measures during acute and post-acute intoxication phases. This is the first study of its kind, and is highly relevant given the increasing prevalence of medicinal cannabis use globally.

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