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Appetite stimulation with cannabis-based medicine and methods for assessment of glomerular filtration in older patients with medical illness

A study protocol

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Appetite stimulation with cannabis-based medicine and methods for assessment of glomerular filtration in older patients with medical illness: A study protocol

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Abstract

Background and aim: Malnutrition in older patients is linked to poor appetite. Cannabis-based medicine may have orexigenic properties in older patients, but this has to our knowledge never been investigated. In older patients, uncertainty applies to the accuracy of estimated glomerular filtration rate (eGFR) based on creatinine, which is crucial for medication prescribing. In older patients with poor appetite, the study aims (1) to assess the efficacy of Sativex® (8.1-mg delta-9-tetrahydrocannabinol [THC] and 7.5-mg cannabidiol [CBD]) to stimulate appetite and (2) to compare the performance of various GFR-estimates and measured-GFR (mGFR) for determining gentamicin clearance utilizing population pharmacokinetic (popPK) modelling methods.

Methods and objectives: This study is composed of two substudies. Substudy 1 is an investigator-initiated single-center, double-blinded, randomized, placebo-controlled, superiority, cross-over study. Substudy 1 will recruit 17 older patients with poor appetite, who will also be invited to substudy 2. Substudy 2 is a single-dose pharmacokinetics study and will recruit 55 patients. Participants will receive Sativex® and placebo in substudy 1 and gentamicin with simultaneous measurements of GFR in substudy 2. The primary endpoints are as follows: Substudy 1—the difference in energy intake between Sativex® and placebo conditions; substudy 2— the accuracy of different eGFR equations

Andersen A.L. and Houlind M.B. are sharing last authorship.

For affiliations refer to page 250.

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compared to mGFR. The secondary endpoints include safety parameters, changes in the appetite hormones, total ghrelin and GLP-1 and subjective appetite sensations, and the creation of popPK models of THC, CBD, and gentamicin.

KEYWORDS
appetite, cannabis-based medicine, kidney function, older patients, renal risk drugs

1 | INTRODUCTION

1.1 | Older patients with medical illness and malnutrition

Older patients with medical illness constitute approximately 45% of all acute admissions in Denmark and are often characterized by malnutrition and polypharmacy (≥5 prescribed medications).[1–10] Malnutrition is present in 8–33% of these patients and polypharmacy in approximately 75%.[4,5,7–12] Malnutrition is defined as "a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease."[13] Malnutrition is associated with a range of serious health problems including low quality of life, increased morbidity, hospital admissions, and mortality.[14] Consequently, malnutrition is a considerable societal burden costing EU governments up to €120 billion per year.[15] Anorexia of ageing is a major contributing factor in the development of malnutrition and is defined by reduced appetite and/or food intake in old age.[14] Anorexia of ageing is difficult to prevent, advances with age, and is of multifactorial origin.[16] Ageing is associated with reduced appetite and strength and increased cellular senescence, mitochondrial dysfunction, and chronic systemic inflammation.[17] Degradation of food-derived nutrients are utilized by mitochondria to produce ATP by oxidative phosphorylation. Both nutrient availability and functional mitochondria are required for sufficient ATP supply.[18] Malnutrition has been shown to impair mitochondrial function and to increase pro-inflammatory cytokines and elevated leukocyte activation.[19] Further, older patients with medical illness are at particularly high risk of adverse drug reactions due to polypharmacy, variations in ageing-related physiological changes, comorbidities, and altered pharmacokinetic and pharmacodynamic responses to medication.[20] Malnutrition and chronic inflammation can affect pharmacokinetics, with clinically relevant effects on both lipophilic and hydrophilic (often renally excreted) medications.[20,21] Altogether, there is an unmet need to treat poor appetite and for a better understanding of pharmacokinetics in these patients.

1.2 | The rationale for cannabis-based medicine as a pharmacological treatment for poor appetite

A recent review on the current best-practice nutritional interventions emphasizes that poor appetite poses a formidable challenge to healthcare providers in the management of malnutrition among community-dwelling older adults.[22] In patients who fail to respond to nonpharmacological nutritional interventions, a pharmacological intervention with an orexigenic drug may be indicated. However, there is currently no appropriate and effective pharmacological treatment for poor appetite.

Sativex® (cannabis-based medicine) is an oromucosal spray consisting of 2.7 mg/ml delta-9-tetrahydrocannabinol (THC) and 2.5 mg/ml cannabidiol (CBD) per spray. Sativex® is approved in Denmark and several other European countries for symptomatic relief of moderate to severe spasticity in multiple sclerosis.[23–25] The biological activity of the cannabinoids, THC and CBD, is conferred by modulating the endocannabinoid system (ECS).[26] The ECS is a complex cell-signalling system involved in numerous signalling processes such as appetite, digestion, metabolism, chronic pain, inflammation, mood, learning, memory, and motor control.[27,28]

Reduced secretion of appetite-stimulating hormones (ghrelin) and increased secretion of appetite suppressant hormones (glucagon-like peptide 1 [GLP-1]) have been shown in persons with anorexia of ageing compared to younger persons.[29] Interestingly, Riggs et al. found a positive association between treatment with cannabis-based medicine and plasma concentrations of ghrelin in patients

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with HIV.[30] Also, Farokhnia et al. reported that in healthy cannabis users, plasma-GLP-1 concentrations were lower after administration of cannabis compared to placebo.[31] These findings suggest that cannabis-based medicine (e.g. Sativex®) may possess appetite-stimulating properties through the modulation of appetite-regulating processes in the ECS and/or appetite hormone secretion, which could counteract the effects of anorexia of ageing. For evaluation of their effects, assessment of the patients' subjective appetite sensation will be important because of its relevance regarding food intake.

There are several human studies with cannabis-based medicines in patients with Alzheimer's disease/dementia, cancer, and HIV, and the studies that have investigated appetite stimulation have shown varying effects.[30,32–51] Brisbois et al. showed that THC increased premeal appetite in cancer patients.[50] Dejesus et al. showed that cannabis-based medicine improved appetite and reversed weight loss in HIV/AIDS-infected patients.[47] Beal et al. showed that cannabis-based medicine was associated with increased appetite in patients with AIDS.[42] On the contrary, Johnson et al. and Strasser et al. showed no significant treatment differences between placebo and cannabis-based medicine on appetite scores in patients with cancer.[48,49]

Despite methodological differences with regard to energy status, dosing schedules, drug administration methods, and social settings, these studies support that cannabis-based medicine may increase appetite and possibly food intake.

To date, no trials have examined the efficacy of Sativex® as an appetite stimulant and its pharmacokinetic profile in older patients with poor appetite. As such, we propose a study to examine the appetite-stimulating effect of Sativex® in older patients with poor appetite. As secondary objectives, we will examine the pharmacokinetics parameters of Sativex® and relate them to its pharmacodynamics. Additionally, we will assess the effects of Sativex® on the appetite hormones, total ghrelin and GLP-1, subjective appetite sensation, and safety parameters.

1.3 | Accurate methods for glomerular filtration to optimize medication dosing in older patients

Glomerular filtration rate (GFR) decreases with age, and this decline can be accelerated further by comorbidities such as cardiovascular diseases, diabetes, and chronic inflammation.[52] Accurate assessment of GFR is crucial since approximately 40% of all medications are excreted renally and require dose adjustment (renal risk medications) according to GFR.[53] Kidney function can be measured with exogenous tracers such as plasma technetium 99m-labelled diethylenetriaminepentaacetic acid (99mTc-DTPA [$mGFR_{STD}$]) clearance or plasma Iohexol clearance ($mGFR_{Ioh}$), but these procedures are time-consuming and expensive. Consequently, a simplified method for plasma iohexol clearance using blood collected by finger-prick, known as dried blood spot (DBS) testing ($mGFR_{Ioh\text{-}DBS}$), was developed recently. The dried blood spot method improves patient comfort, simplifies data analysis, and reducesthe costs. Importantly, it can be performed at bedside in a patient's own home, eliminating the need to visit a specialized facility.[54]

In clinical practice, GFR is usually estimated based on the endogenous marker, creatinine, a muscle waste-product heavily dependent on non-GFR factors such as sex, age, muscle mass, and nutritional status.[55]

Therefore, the use of a creatinine-based estimation of eGFR for prescribing renal risk medications in older patients with medical illness poses a risk of prescribing errors due to inaccurate GFR estimates.

Cystatin C, beta-trace protein (BPT), and beta-2 microglobulin (B2M) are modern plasma filtration markers less dependent on the same non-GFR factors as creatinine.[56,57] In that context, we have previously demonstrated that handgrip strength used as a proxy for muscle strength is associated with differences between creatinine and cystatin C-based GFR estimates in older hospitalized patients.[58] Although cystatin C, B2M, and BPT are considered modern filtration markers, plasma neutrophil gelatinase-associated lipocalin (NGAL) and plasma kidney injury molecule-1 (KIM-1) are new early responsive biomarkers for acute kidney injury (AKI) and medication-induced nephrotoxicity.[59–61] Therefore, NGAL and KIM-1 may be utilized for medication optimization by early identification of medication-induced nephrotoxicity.

A systematic review by Barreto et al. concluded that cystatin C-based eGFR was as accurate as or better than creatinine-based eGFR in predicting clearance of renally excreted medications.[62] Recently, we demonstrated that equations using the combination of creatinine and cystatin C outperformed estimates based on creatinine alone compared to $mGFR_{STD}$ in older patients with and without malnutrition.[63] In 2021, Inker and colleagues developed the four-marker panel eGFR equations based on creatinine, cystatin C, B2M, and BTP and suggested a higher performance compared to existing equations.[64]

For optimizing the dosing of medication in older patients, we also need knowledge about which method for assessing kidney function is best when predicting plasma concentrations for renally excreted medication. Thus, we propose a study with population pharmacokinetic (popPK) modelling of gentamicin as a model compound for an exclusively renally excreted medication to

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determine which measured or estimated GFR best explains inter-individual variability of gentamicin-clearance. Additionally, we wish to compare the predictive value of eGFR to mGFR in relation to gentamicin-clearance and study how gentamicin affects NGAL and KIM-1.

2 | OBJECTIVES

The primary objective is twofold and aims to determine (1) whether Sativex®, as an appetite-stimulant, is superior to placebo in improving energy intake and (2) to compare the performance of various GFR-estimates and mGFR for determining gentamicin clearance utilizing popPK modelling methods.

The secondary objectives in substudy 1 are to (1) determine to what extent age, body weight, body composition, and mGFR/eGFR (from substudy 2) as covariates affect popPK modelling of CBD and THC; (2) measure the difference in subjective appetite between Sativex® and placebo; (3) measure the difference in plasma concentrations of the appetite hormones total ghrelin and GLP-1 between Sativex® and placebo; (4) investigate the difference in safety parameters between Sativex® and placebo.

The secondary objectives in substudy 2 include the assessment of (1) the correlation coefficient between the clearance of gentamicin and the clearance determined as mGFR or eGFR and (2) the changes in kidney biomarkers between baseline and the day after administration of gentamicin.

3 | METHODS

3.1 | Study design

This study is composed of two substudies, where participants in substudy 1 are offered participation in substudy 2. The linkage between substudy 1 and 2 is, besides including the same patient population, the incorporation of patients' GFR and body composition measurements as covariates in both substudies' pharmacokinetic models. Both studies follow the ICH E6 (R2) Guideline for Good Clinical Practice (GCP) and are approved and monitored accordingly (see Table S1).[65] The study is reported in accordance with the SPIRIT guideline.[66]

3.1.1 | Substudy 1

Substudy 1 is an investigator-initiated single-center, double-blinded, randomized, placebo-controlled, superiority, cross-over study. Participants will be randomized to receive either Sativex® followed by placebo, or placebo followed by Sativex®.

3.1.2 | Substudy 2

Substudy 2 is a single-dose pharmacokinetics study of gentamicin as a model compound for a renally excreted medication. The GFR measurement from substudy 2 will be used in substudy 1 to provide basic knowledge about whether THC and CBD concentrations are affected by kidney function.

3.2 | Setting

Participants are recruited at the Emergency Department (ED) of Copenhagen University Hospital, Hvidovre, The Capital Region of Denmark. The ED has a 29-bed medical ward, handling all acute medical admissions, and a separate emergency room (ER) handling injuries and traumas. Trial days in substudy 1 are performed at the Zelo Phase 1 Unit at Copenhagen University Hospital, Bispebjerg, The Capital Region of Denmark. The Zelo Phase 1 Unit is responsible for medicine administration and registration, in concordance with GCP, as well as other trial–related tasks in substudy 1. The trial day in substudy 2 is performed at the Department of Clinical Physiology and Nuclear Medicine, Center for Functional Diagnostic Imaging and Research, Copenhagen University Hospital, Hvidovre, The Capital Region of Denmark.

3.3 | Eligibility criteria

All inclusion and exclusion criteria are listed in Table 1. The investigator may at any time exclude a participant if the participant's health status deteriorates or if a participant refuses to participate in study procedures.

3.4 | Recruitment

Trained trial staff including physicians will assess patients for eligibility based on a randomly ordered list of all patients admitted to the ED. If the investigator deems them suitable for the trial, the trial staff will approach potential participants during their stay at the ED. The trial staff will inform potential participants about the trial and a reflection period of 24 h is offered. If the potential participants wish to participate, a written informed consent is collected. After receiving written informed

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TABLE 1 Inclusion and exclusion criteria.

Inclusion criteria

- ≥65 years
- Admitted to the Emergency Department of Copenhagen University Hospital, Hvidovre
- Ability to read, understand and speak Danish
- Ability to cooperate cognitively and physically (e.g. no dementia or unconsciousness and ambulatory)
- Poor appetite, defined as a SNAQ score ≤14
- BMI ≤ 30
- Post-menopausal (defined as absent period for at least 12 months)

Exclusion criteria

- Regular use of cannabis
- Use of cannabis within 2 weeks at baseline
- Diagnosed or suspected psychotic disease, or a family history of diagnosed or suspected psychotic disease
- Severe personality disorders
- Significant psychiatric disorder beyond mild to moderate depression
- Allergy to any ingredient in Sativex®, placebo, and Hexamycin
- Terminal illness
- Active cancer treatment or disseminated cancer
- Known tumour in the brain or the kidneys
- Hepatic transplant
- Chronic eGFR ≤15 ml/min^2 or in dialysis treatment
- High risk of nephrotoxicity due to existing drug treatment
- Pacemaker
- Epilepsy
- Reoccurring convulsions
- Poorly controlled hypertension
- Angina pectoris or intermittent claudication
- Stroke, AMI or heart failure (NYHA class 3-4) within the past 5 years
- Food intolerance to any ingredient in the test meals
- Vegan
- Unwilling to avoid driving for up to 72 h after administration of Sativex®/Placebo
- Unwilling to avoid alcohol for 24 h up to the test days
- Ascites
- Significant oedema on test days
- In isolation room stay
- Observation for covid-19

Abbreviations: AMI, acute myocardial infarction; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; SNAQ, Simplified Nutritional Appetite Questionnaire.

consent, the potential participants will be prescreened in relation to poor appetite, and body mass index (BMI). Those who are still eligible after completing the prescreening are included in the study. The test days will be scheduled when baseline data are collected and will take place after the participants have been discharged from the hospital. A screening log will document all eligible patients that have been approached in the study including those who decline to participate.

All participants in substudy 1 are offered participation in substudy 2. To reach inclusion goals for substudy 2, additional participants will be included separately.

3.5 | Intervention

For an overview of substudy 1 and 2, see Figure 1.

In substudy 1, we will administer the approved cannabis-based medicine, Sativex®, and placebo (Table 2).

3.5.1 | Substudy 1

Participants will be scheduled to receive Sativex® and placebo on two separate test days with a two-week wash-out period in between. Sativex® is administered as an oromucosal spray in doses of 3 sprays per administration (8.1 mg THC and 7.5 mg CBD per dose).[23] The placebo consists of an alcohol base with peppermint and quinine flavouring mimicking the taste of Sativex®. It is an oromucosal spray identical in appearance, taste, and viscosity to that of Sativex® manufactured by the Capital Region Pharmacy, Denmark. Both Sativex® and placebo will be labelled by the Capital Region Pharmacy, Denmark. Participants are asked not to touch their oromucosal surface for the first 15 min after administration. Sativex® and placebo are administered by trial staff to ensure adherence to the intervention protocol and minimize the risk of unintentional overdosing.

3.5.2 | Substudy 2

In substudy 2, Hexamycin®, which contains gentamicin in a 40 mg/ml solution, will be administered according to body weight as measured on the morning of the test day. A dose corresponding to 5 mg/kg Hexamycin® is administered intravenously through a peripheral intravenous catheter.

Information on the administered doses in both substudies will be registered in the overall and individual medication registration documents. Adherence to all other measures is secured by members of the trial staff who initiate and complete all measurements.

3.6 | Outcomes

Primary and secondary outcomes for substudy 1 and substudy 2 are described in Tables 3 and 4, respectively.

Descriptive variables are described in Table 5 and include body composition, nutritional parameters, renal function, and handgrip strength, as well as inflammatory and cellular measures. Measures of chronic inflammation,

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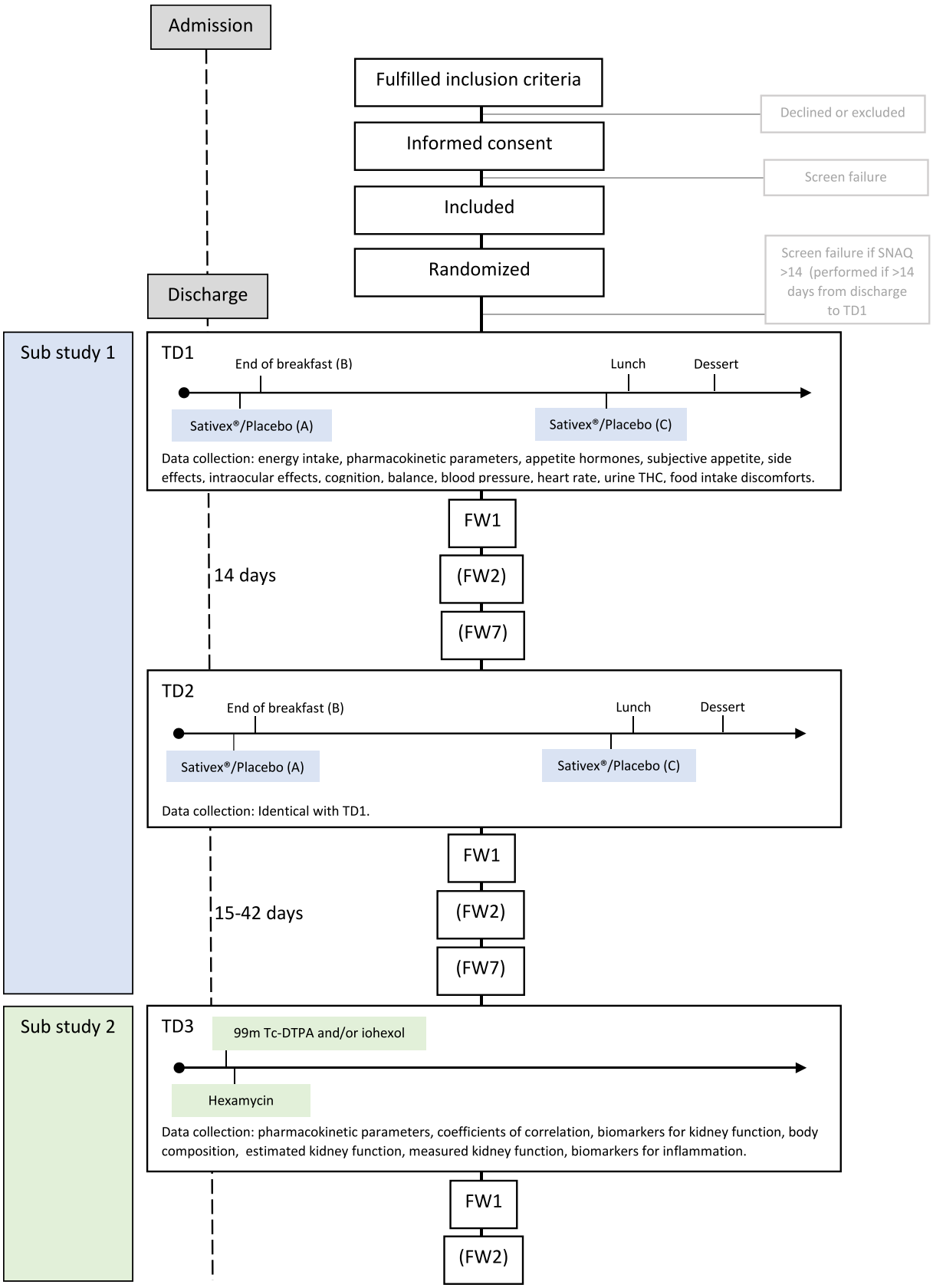

FIGURE 1 Overview of the study. (A) The timepoint of the first administration of Sativex®/placebo; (B) the timepoint for ended breakfast meal; (C) the timepoint of the second administration of Sativex®/placebo; TD1: test day 1; FW1: follow-up day 1; FW2: follow-up day 2; FW7: follow-up day 7; TD2: test day 2; TD3:test day 3.

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TABLE 2 Dosing regimen for substudy 1. A single spray of Sativex® contains 2.7/2.5 mg THC/CBD.

Dosing regimen ($n = 17$)	Experimental treatment (Sativex®)	Placebo treatment
Morning	3 sprays	3 sprays
Lunch	3 sprays	3 sprays
Accumulated	6 sprays	6 sprays

cellular senescence, and mitochondrial function are all hallmarks of ageing, and will be used for characterization of biological ageing in this patient group.[17]

3.7 | Sample size determination

3.7.1 | Substudy 1

To detect a clinically relevant difference of 500 kJ in energy intake between Sativex® and placebo, a total of 17 participants is needed. The clinically relevant difference is based on a trial on the effect of individualized nutritional support compared to control. The trial showed benefits from higher energy intake (1213 kJ a day) in the intervention group compared with the control group.[67] Therefore, we considered an increase of 500 kJ during one meal to be clinically relevant. The sample size calculation is based on a paired *t* test with a power of 80%, a significance level of 5%, and a standard deviation (SD) of 690 kJ. The SD is derived from a sample size estimate listed by Gregersen et al.[68]

3.7.2 | Substudy 2

Substudy 2 is a popPK study and therefore there is no sample size calculation. We aim to recruit 55 participants to conduct the popPK modelling with different covariates.

3.8 | Participant timeline

The duration of baseline data collection is estimated to last an hour.

3.8.1 | Substudy 1

Substudy 1 consists of two test days (TD1 and TD2) separated by a two-week wash-out period, with a follow-up phone call on day one after TD1 as well as TD2. If side effects are reported during this phone call another phone call will be made on day two after TD1 and TD2. If side effects are reported during this phone call another phone call will be made on day seven after TD1 and TD2. TD1 and TD2 each last for approximately 6 h.

3.8.2 | Substudy 2

Substudy 2 consists of one test day (TD3) with a follow-up visit on day one after TD3. If creatinine is elevated on this visit, another visit will be arranged 2 days after TD3. TD3 lasts for 8 h. See Figure 1 for an overview of the test days and Figure S1 for an example of timepoints and activities of TD1 and TD2.

3.9 | Randomization

3.9.1 | Substudy 1

After written informed consent is obtained and eligibility is confirmed by the investigator, participants will be randomly assigned to the sequence of Sativex® and placebo. The double-blinding in this study ensures that neither the participants nor the staff administering the investigational drugs and collecting the data will be aware of the sequence of Sativex® and placebo.

A statistician, who is not associated with the study, will generate a randomization schedule using the statistical software R. This schedule contains ID-numbers and their corresponding sequence of Sativex® and placebo. On a secure drive, each ID-number is given a separate folder, each with a unique password. These passwords are kept and administered by the statistician. Additionally, the Capital Region Pharmacy has access to the randomization schedule to be able to pack and label the investigational drugs accordingly. Further, the responsible physician can be granted access to the sequence of Sativex® and placebo in cases of adverse events (AE's). At the end of data analysis, the dataset will be unblinded. ID–number and sequence of Sativex® and placebo will be registered in the study-log placed on a secure drive which only the statistician can access.

3.9.2 | Substudy 2

Randomization and blinding are not relevant.

3.10 | Data collection methods

The methods and time points for data collection are described in Tables 3–5. Data collection for each patient is

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TABLE 3 Overview of outcomes, assessment methods, and time points for substudy 1.

Variable	Assessment	Timepoint reported as 'baseline' or in minutes after A, B and/or C.
Primary outcome		
The difference in energy intake between Sativex® and placebo	The difference between energy intake (kJ) from an ad libitum test meal (lunch and dessert) on test day 1 (TD1) and test day 2 (TD2) is compared by weighing the meals (with known energy content) before and after serving. At TD1, participants can choose between two and three different test meals for lunch and dessert respectively together with one cup of coffee/tea with/without milk and/or sugar. The test meal will be served 25 min after the second administration of Sativex®/placebo. The choice of test meal at TD1 will be applied for TD2. The participants can drink water ad libitum during TD1, but their intake on TD2 will be pursued identical to TD1 on amount and time of consumption. However, all participants are served one scheduled glass of water for lunch.	A: 270–295
Secondary outcomes		
Population pharmacokinetic parameters of THC, CBD and covariates explaining inter-individual variability	A population (pop) pharmacokinetic (PK) model will be developed for THC and CBD using serum concentrations over time measured from collected blood samples to characterize their respective pharmacokinetics and derive relevant PK parameters and identify inter-individual variability for this patient group. Potential covariates of interest will be identified and implemented on relevant PK parameters in the model in a covariate analysis, depending on the final form of the popPK model. The link between PK and pharmacodynamics (PD) will be characterized by the development of a popPK/PD model. The development of the popPK/PD model will be carried out in NONNEM (version 7,5 or newer; ICON Plc) and PopED. Blood samples are collected in nonadditive tubes and left for coagulation for min. 45 min at room temperature and then centrifuged. Ascorbic acid is added to the aliquoted serum to enhance stability and the samples are frozen at −80°C until analysis with Ultra-high performance liquid chromatography and tandem mass spectrometry (UHPLC-MS/MS). Following components will be quantitatively determined: Δ9-tetrahydrocannabinol (THC), 11-hydroxy-Δ9-tetrahydrocannabinol (THC-OH), Cannabidiol (CBD) and 11-nor-9-carboxy-Δ9-tetrahydrocannabinol (THC-COOH). Analysis will be performed at the Department of Clinical Biochemistry, North Denmark Regional Hospital.	Baseline + A: 15, 30, 75, 90, 150, 195, 240, 330, and 360
Appetite hormones	The difference in the appetite hormones, total ghrelin and GLP-1, between Sativex®/placebo will be measured before and after the consumption of a breakfast meal (125 ml Nutridrink Compact: 1255 kJ, 12 g protein). The breakfast meal is served 25 min after the first administration of Sativex®/placebo and must be finished within 15 min. The blood samples	Baseline + B: 15, 30, 45, 60, 90, 120, 180

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TABLE 3 (Continued)

Variable	Assessment	Timepoint reported as 'baseline' or in minutes after A, B and/or C.
	are collected in cooled EDTA tubes, which are immediately transferred to storage on ice and then centrifuged at 4°C. The samples are frozen at −80°C until analysis. Total ghrelin is measured with enzyme linked immunosorbent assay (ELISA) (Millipore) and GLP1 is measured with radioimmunoassay. The appetite hormones will be analysed at the Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark.	
Subjective appetite	100-mm standardized numerical Visual Analogue Scales (VAS) are used to measure the difference in subjective appetite between Sativex®/placebo. The subjects assess their appetite, by replying to five questions about hunger, desire to eat, satiety, future food intake, and satisfaction. A combined appetite score is calculated based on the five questions in accordance with Chaput et al.[70]	Baseline + A: 15, 60, 90, 120, 180, and 240 + C: 15, 60, and 90
Safety parameters		
Side effects	We will monitor differences in side effects between Sativex® and placebo. To collect data on the most common side effects of Sativex® (fatigue, dizziness, nausea, and euphoria), we will use 100-mm standardized numerical VAS.	Baseline + A: 15, 60, 90, 120, 180, and 240 + C: 15, 60, and 90
Intraocular effects	Changes in the intraocular pressure of the eye between Sativex® and placebo are measured with the iCare IC100 tonometer as literature discusses that THC and CBD can decrease intraocular pressure.[71,72] A tonometer measurement is a device-calculated average of 6 × 3 measurements.	Baseline + A: 75 and 320
Cognition	The proportion of participants with affected cognitive function between Sativex® and placebo is evaluated using the Hopkins Verbal Learning Test - Revised (HVLT-R).[73] It is a possibility not to perform the HVLT-R if the participant is too burdened.	Baseline + C: 70
Balance	The proportion of participants experiencing a change in balance after Sativex® and placebo is assessed using Berg's Balance Test. Poor balance is defined by a summated score of ≤45.[74] It is a possibility not to perform Berg's Balance Test if the participant is too burdened.	Baseline + C: 25 and 80
Blood pressure and heart rate	Changes in blood pressure and heart rate between Sativex® and placebo are measured in a sitting, relaxed position with Microlife, BP A3L Comfort, automatic monitor on the upper arm.	Baseline + A: 15, 60, 90, 120, 180, and 240 + C: 15, 60, and 90

Note: A: the first administration of Sativex®/placebo, B: consumption of the breakfast meal, C: the second administration of Sativex®/placebo.

performed by the same trial staff whenever possible and follows standard operating procedures to minimize variation. The study coordinators RLN, MBH, OB, and IKS will train and supervise the trial staff in data collection.

3.11 | Data management

All study-related information will be recorded, handled, and stored properly to allow for accurate trial reporting.

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TABLE 4 Overview of outcomes, assessment methods, and time points for substudy 2.

Variable	Assessment	Timepoints
Primary outcome		
Population pharmacokinetic parameters of gentamicin and covariates explaining inter-individual variability	A population (pop) pharmacokinetic (PK) model will be developed for gentamicin using plasma concentrations over time measured from collected blood samples to characterise the pharmacokinetics and derive relevant PK parameters such as clearance (CL) in this patient group. In a covariate analysis, measured glomerular filtration rate (mGFR) and estimated GFR (eGFR) based on different biomarkers and equations will be implemented on relevant PK parameters and compared and tested for significance based on the objective function value (OFV). The covariate analysis will be carried out as appropriate depending upon the final form of the base model. Blood samples are collected in EDTA tubes, and plasma is stored in a biobank at −80°C. Analysis of gentamicin will be performed with the Thermo Scientific™ QMS™ Gentamicin (GENT) immunoassay, a homogeneous particle-enhanced turbidimetric immunoassay (CV ≤ 10%) at the Department of Clinical Biochemistry, Copenhagen University Hospital, Rigshospitalet, Denmark.	t_3 (10, 15, 30, 180, 240, 330, 345, 360 min after administration of gentamicin) + t_4 (22 h after administration)
Secondary outcomes		
Coefficients of correlation between gentamicin clearance and estimated or measured GFR	Coefficients of correlation between gentamicin clearance as estimated by the popPK model for each individual subject and GFR either measured (mGFR) or estimated (eGFR) will give a simple measure of which estimate of GFR has the strongest correlation to gentamicin clearance.	$t_3 + t_4$
Change in plasma biomarkers for kidney function between baseline and 22 h after administration of gentamicin	Plasma biomarkers for kidney function (creatinine and cystatin C) and kidney damage (neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1)) will be measured from blood samples at baseline on test day 3 and on the follow-up visit on day 1 after the test day. The Department of Clinical Biochemistry, Copenhagen University Hospital, Rigshospitalet, Denmark, will perform the analysis of creatinine and cystatin C after internationally validated assays. NGAL and KIM-1 will be measured with ELISA at Department for Clinical Research, Copenhagen University Hospital, Hvidovre, Denmark.	$t_3 + t_4$

Note: Timepoints: Test day 3: t_3; follow-up day 1: t_4.

Data will be entered directly into REDCap (Research Electronic Data Capture, Vanderbilt University, Nashville, USA), which allows for high security, privacy, and data quality. In case of data collection using paper case report forms, these will be double–entered into REDCap and reviewed for disagreements to ensure data

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TABLE 5 Overview of descriptive variables, assessment methods and time points for substudy 1 and substudy 2.

Variable	Assessment	Timepoint
Descriptive variables		
Participant characteristics	Participant characteristics are based on self-report, measurements by trial staff, or from the medical journal and include: sex, age, smoking status, alcohol consumption, previous use of cannabis, civil status, living condition, body weight, diagnoses, medication, and drug–drug interactions.	t_0
Body composition	Total and segmented lean body mass and bone mineral content is measured with whole-body Dual-energy X-ray Absorptiometry (DXA) (GE Lunar Prodigy Primo, GE Healthcare Technologies, Madison, Wisconsin, US). DXA-scan is a validated method to assess body composition.[75] DXA–scan is only performed on t_3 Total and segmented body fat, fat free mass, soft lean mass, bone mineral content and intra and extracellular water is measured using Bioelectrical Impedance Analysis performed with InBody S10.[76] Information on fasting, physical activity and urination are collected prior to the measurement.	t_0, t_1; t_2; t_3
Food intake discomforts	Discomforts related to food intake is assessed using the Eating Symptom Questionnaire (ESQ).[77]	t_0, t_1; t_2
Nutritional status	Nutritional Status is assessed with Nutritional Risk Screening-2002. It consists of a primary screening with four yes/no questions. If one answer is yes, the secondary screening which evaluates the degree of illness and malnutrition is performed.[78]	t_0, t_1; t_2
Appetite	The Simplified Nutritional Appetite Questionnaire (SNAQ) is used to assess appetite. It identifies persons with anorexia and risk of weight loss by asking four questions on appetite, fullness, taste, and number of daily meals.[79]	t_0, t_1; t_2
THC in urine	THC is measured in a morning urine sample using a one-step Immunochromatographic Assay for the Detection of THC in urine (NanoSticka® THC). The measurement is performed to exclude participants who have used cannabis prior to the test days.	t_1; t_2
eGFR	Estimated kidney function (eGFR) by equations using either a panel of biomarkers ($CKDEPI_{panel}$[64] and FAS_{panel}[56]), a combination of creatinine and cystatin C (2012-$CKDEPI_{comb,}$[80] 2021-$CKDEPI_{comb,}$[57] and FAS_{comb}[56]) or creatinine alone (CG,[62] MDRD,[81] 2009-CKDEPI,[82] 2021-CKDEPI,[57] FAS,[56] and EKFC[83]).	t_3
mGFR	Measured kidney function (mGFR) determined by ^{99m}Technetium-diethylenetriaminepentaacetic acid (99mTc-DTPA) ($mGFR_{STD}$) and/or Iohexol plasma clearance by dried blood spot ($mGFR_{DBS}$). $mGFR_{STD}$ is determined by single-injection plasma clearance of 99mTc-DTPA. In short, 20 MBq of 99mTc-DTPA is injected intravenously, and samples are collected from venous blood at 180, 200, 220, and 240 min after injection for patients with eGFR >30 ml/min, or 180, 210, 240, 270, and 300 min after injection for patients with eGFR ≤30 ml/min. $mGFR_{Ioh}$ and $mGFR_{DBS}$ is determined by single-injection plasma clearance of Iohexol. In short, 5.0 ml (Omnipaque® 300 iodine/mL, GE Healthcare) is injected intravenously. $mGFR_{Ioh}$: Plasma EDTA tubes are used for the collection of plasma samples. $mGFR_{DBS}$: A volume of 2 × 10 µl (duplicate sample) finger-prick blood is collected with a capillary pipette and deposited on filter paper to each time point. $mGFR_{Ioh}$ and $mGFR_{DBS}$ samples are collected 120, 150, 180, 210, and 240 min after injection for patients with eGFR >60 ml/min/1.73m^2, or 120 180, 240, 300, and 360 after injection for patients with eGFR 59–30 ml/min/1.73m^2, or 120 180, 240, 300, 360, 420, and 480 after injection for patients with eGFR <30 ml/min/1.73m^2. $mGFR_{STD}$ will be analysed at the Department of Clinical Physiology and Nuclear Medicine, Centre for Functional and Diagnostic Imaging and Research, Copenhagen University Hospital Amager and Hvidovre following standard procedure. Iohexol from $mGFR_{Ioh}$ and/or $mGFR_{DBS}$ will be analysed by a high-performance liquid chromatography UV method (as described in details[54]) at the Department of Nephrology, Copenhagen University Hospital, Rigshospitalet, Denmark or Laboratory of Renal Function (LFR), Faculty of Medicine, University of La Laguna, La Laguna, Spain.	t_3

(Continues)

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TABLE 5 (Continued)

Variable	Assessment	Timepoint
Biomarkers for cellular senescence	Biomarkers for cellular senescence including expression of $p^{16Ink4a}$, $p21^{Cip1/Waf1}$, DPP4, and uPAR are measured in isolated peripheral blood mononuclear cells (PBMCs) with flow cytometry and qPCR. Biomarkers for cellular senescence will be analysed at the Department of Clinical Research, Acute CAG, Copenhagen University Hospital Amager and Hvidovre.	t_3
Biomarkers for dysfunctional mitochondria	Biomarkers for dysfunctional mitochondria, altered autophagic flux, and metabolic disturbances will be measured by ATP production, and electron transport chain activity by colorimetry, mitochondrial DNA copy number and DNA damage by PCR, mitochondrial DNA damage, membrane potential, fission, fusion, autophagy, and mitophagy by immunoblotting, microscopy, RT-qPCR or a combination. Analyses will be conducted at the Department of Clinical Research, Acute CAG, Copenhagen University Hospital Amager and Hvidovre.	t_3
Biomarkers for inflammation	Plasma levels of inflammation biomarkers including IL-1β, IL-6, IL-10, TNF-α, GDF15, suPAR, PAI-1, MCP-1, CXCL2, and CXCL9 are measured using standard immunoassays (ELISA, Luminex, and Ella Simple Plex assays). Plasma levels of inflammation biomarkers will be analysed at Department of Clinical Research, Acute CAG, Copenhagen University Hospital Amager and Hvidovre.	t_3
Handgrip strength	Maximal hand grip strength is measured with a hand dynamometer (Saehan, Digi-II) in three attempts.[84]	t_3

Note: Timepoints: Baseline: t_0; test day 1: t_1; test day 2: t_2; test day 3: t_3; CKDEPI: chronic kidney disease epidemiology. FAS: full age spectrum. CG: Cockcroft–Gault. MDRD: modification of diet in renal disease. EKFC: European Kidney Function Consortium.

accuracy. Further, the study is monitored regularly in accordance with GCP, whereby flaws and inaccuracies in data collection are detected continuously throughout the study.

3.12 | Statistical methods

The statistical methods pertaining to the primary endpoints are described for each substudy.

3.12.1 | Substudy 1

Data will be analysed with standard descriptive statistics in R (version 4.2.1, R Foundation for Statistical Computing, Vienna, Austria). Normally distributed data will be presented as means and SD, and non-normally distributed data as median and interquartile range. Per protocol analysis including all participants who are compliant during the study will be performed after the last patient has completed the last visit. Additionally, intention–to–treat analysis will be performed including all randomized participants. Missing data will be included by multiple imputation.

For the primary endpoint, the comparison of the difference in energy intake between placebo and Sativex® will be analysed using a paired *t* test. If data are not normally distributed, the nonparametric Wilcoxon sign-rank test will be performed. Adjusted analyses are performed with linear regression, and if model assumptions are not met, data will be logarithmically transformed for analysis and back-transformed for presentation. If the logarithmic transformation is insufficient, nonparametric bootstrap estimates will be used.

3.12.2 | Substudy 2

A nonlinear mixed-effects popPK model will be developed using the software NONMEM (version 7.5, ICON plc), and data preparation for analysis and goodness-of-fit plots based on model output is performed in R (version 4.2.1). The base model will consist of a structural and stochastic model. The final model will consist of the base model and the covariate model. Overall model evaluation and selection for further development is based on criteria including the objective function value (OFV), goodness-of-fit plots, robustness of the models, shrinkage of random effects parameters, visual predictive checks, and agreement between model-estimated PK parameter values and literature values and/or physiological functions. Results will be presented as population values for relevant PK parameters and covariate effects with relative standard errors (RSE), relevant inter-individual variability as coefficients of variance with RSE, and residual unexplained variability in relevant terms depending on the exact form of the final model.

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The primary endpoint, a comparison of popPK model goodness-of-fit utilizing measured and estimated GFR as covariates on gentamicin clearance, will be performed by the development of a covariate model from the popPK *base model*. In the development of the covariate model, OFV is the main criterion for model selection. The OFV is a representation of the overall goodness-of-fit of the popPK model to the data. Upon comparing two nested models, where one model has one additional degree of freedom than the previous model, a drop in OFV of 3.84 represents a significant improvement of model fit based on a p value of 0.05 in a chi-squared test.

3.13 | Data monitoring and auditing

The GCP unit of the University of Copenhagen has been appointed as an independent data monitoring committee. Missing or inaccurate data will be audited by trial staff. The trial staff will have scheduled progress meetings to confirm progress and ensure scientific quality.

3.14 | Harms and approval

Safety will be assessed at regular intervals on test days and follow-up visits as reported by participants and actively sought by trial staff. Furthermore, participants are encouraged to contact the trial staff if they suspect an event to be related to the study. All AEs will be evaluated by the investigator and documented on CRFs and in the annual and final safety report. Participants experiencing AEs will be monitored until the event is resolved. The AE reporting workflow will adhere to GCP regulations by the Danish Medicines Agency.

4 | ETHICS AND DISSEMINATION

4.1 | Research ethics approval

All participants receive verbal and written information, and written informed consent will be obtained before enrolment. All participants are informed that they can withdraw from the study at any time and that it will not have any consequences for their regular course of treatment. The study has been approved by the Ethics Committee of the Capital Region of Denmark (H-21044231), the Danish Medicines Agency (EudraCT nr.: 2021-002318-15), and the Danish Data Protection Agency (Journal nr.: P-2021-744). Protocol amendments will be approved by relevant authorities before they are implemented. The investigational drug, Sativex®, is registered in Denmark.[23]

Regardless of the outcome, results will be published at conferences and in international peer-reviewed journals in accordance with the CONSORT guidelines. The manufacturers of Sativex® and Hexamycin® have been notified about the study but have not contributed to the protocol, nor have they made financial contributions. The study will be conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies.[69]

4.2 | Protocol amendments

The following two protocol amendments have been approved by the Ethics Committee of the Capital Region of Denmark and are registered at ClinicalTrials.gov.

Amendment #1: Removal of the secondary endpoint, in substudy 1, concerning eating patterns to relieve participants of extensive data collection. Additionally, the measurement of intraocular pressure in substudy 1 on follow-up days 1, 2, and 7 was removed, and it was specified that the result of the randomization in substudy 1 is not revealed to the project staff. Further, with additional approval from the Danish Medicines Agency, the exclusion criteria were clarified. Handgrip strength and biomarkers of ageing were added to substudy 2. Lastly, the total amount of blood collected in substudy 1 was corrected.

Amendment #2: Follow-up visits and phone calls were optimized. The number of PK blood samples was reduced from 12 to 10 and the time points were adjusted. Re-screening with SNAQ was implemented if there were >14 days from discharge until TD1. The dietary diary before TD1 and TD2 was removed. The time-point for the dessert was expedited to fit with a shorter TD1 and TD2. Lastly, funding details and information about trial staff were updated.

4.3 | Consent

Written informed consent will be collected from all participants.

4.4 | Confidentiality and access to data

Access to the final dataset is limited to trial staff as the handling of data complies with Danish and European regulations to protect data. The dataset can be made available upon reasonable request.

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4.5 | Ancillary and post-trial care

Trial staff follow-up on AEs that occur on the trial days. Also, participants can contact trial staff in case of suspected AEs. In case of suspected AEs a physician will contact the participant to initiate treatment if relevant and to assess if the AE is related to the investigational drug. Subsequent follow-up will be made till the AE has ceased. Transportation and meals are provided on all study visits. The participants are not offered any other compensation for trial participation.

5 | DISCUSSION

This trial is the first to study the appetite-stimulating effect of cannabis-based medicine in older patients with poor appetite. A major strength of substudy 1 is its randomized and placebo-controlled design with an approved oromucosal spray, which ensures more precise dosing and bypasses the harmful pulmonary effects observed within smoking and vaporization. The linkage between substudy 1 and 2 is the inclusion of mGFR and body composition in the pharmacokinetic modelling in both substudies. This linkage is a pragmatic choice that results in fewer unique patients being included than if the studies were separated. However, this coupling of substudies also makes the design more complex. A limitation of the trial design in substudy 1 is the short treatment period with Sativex®, which limits the possibility to evaluate the long-term effects of treatment with cannabis-based medicine. The lengthy duration of test days in substudy 1 and 2 is another limitation and participants may be deterred from entering the trial or prematurely terminate their participation. A third limitation is the lack of evidence for the optimal dosage and timing of Sativex® for appetite stimulation, thus the dosage and timing were chosen based on a review of existing literature and opinions from experts within the field. Furthermore, we do not include groups of younger healthy participants and cannot compare the pharmacokinetics across age and patient groups.

In conclusion, this trial will provide new knowledge on the effectiveness of Sativex® as an appetite stimulant in older patients with poor appetite and the accuracy of different methods of determining eGFR compared to mGFR and gentamicin clearance.

6 | ADMINISTRATIVE INFORMATION

The protocol follows the second amendment of the original protocol for the study. Information on trial registration, funding, roles, and responsibilities can be found in Table S1.

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CONFLICT OF INTEREST STATEMENT

All authors declare no competing interests.

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REFERENCES

1. Danmarks Statistik. Statistikbanken. 2020. Accessed May 29, 2020. https://www.statistikbanken.dk/statbank5a/default.asp?w=1600
2. Data Use Agreement for HCUPnet|AHRQ Data Tools. Accessed January 19, 2023. https://datatools.ahrq.gov/hcupnet-dua
3. Wittenberg R, Sharpin L, McCormick B, Hurst J. Understanding emergency hospital admissions of older people.
4. Pereira GF, Bulik CM, Weaver MA, Holland WC, Platts-Mills TF. Malnutrition among cognitively intact, noncritically ill older adults in the emergency department. *Ann Emerg Med*. 2015;65(1):85-91. doi:10.1016/j.annemergmed.2014.07.018
5. Jensen LD, Andersen O, Hallin M, Petersen J. Potentially inappropriate medication related to weakness in older acute medical patients. *Int J Clin Pharmacol*. 2014;36(3):570-580. doi:10.1007/s11096-014-9940-y
6. Juul-Larsen HG, Andersen O, Bandholm T, et al. Differences in function and recovery profiles between patterns of multimorbidity among older medical patients the first year after an acute admission—an exploratory latent class analysis. *Arch Gerontol Geriatr*. 2020;86:103956. doi:10.1016/j.archger.2019.103956
7. Vanderwee K, Clays E, Bocquaert I, Gobert M, Folens B, Defloor T. Malnutrition and associated factors in elderly hospital patients: a Belgian cross-sectional, multi-centre study. *Clin Nutr*. 2010;29(4):469-476. doi:10.1016/j.clnu.2009.12.013
8. Griffin A, O'Neill A, O'Connor M, Ryan D, Tierney A, Galvin R. The prevalence of malnutrition and impact on patient outcomes among older adults presenting at an Irish emergency department: a secondary analysis of the OPTI-MEND trial. *BMC Geriatr*. 2020;20(1):455. doi:10.1186/s12877-020-01852-w
9. Gentile S, Lacroix O, Durand AC, et al. Malnutrition: a highly predictive risk factor of short-term mortality in elderly presenting to the emergency department. *J Nutr Health Aging*. 2013;17(4):290-294. doi:10.1007/s12603-012-0398-0
10. Burks CE, Jones CW, Braz VA, et al. Risk factors for malnutrition among older adults in the emergency department: a multicenter study. *J am Geriatr Soc*. 2017;65(8):1741-1747. doi:10.1111/jgs.14862
11. Damoiseaux-Volman BA, Medlock S, Raven K, et al. Potentially inappropriate prescribing in older hospitalized Dutch patients according to the STOPP/START criteria v2: a longitudinal study. *Eur J Clin Pharmacol*. 2021;77(5):777-785. doi:10.1007/s00228-020-03052-2
12. Thomas RE, Thomas BC. A systematic review of studies of the STOPP/START 2015 and American Geriatric Society Beers 2015 criteria in patients ≥ 65 years. *Curr Aging Sci*. 2019;12(2):121-154. doi:10.2174/1874609812666190516093742
13. Cederholm T, Barazzoni R, Austin P, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. *Clin Nutr*. 2017;36(1):49-64. doi:10.1016/j.clnu.2016.09.004
14. Landi F, Calvani R, Tosato M, et al. Anorexia of aging: risk factors, consequences, and potential treatments. *Nutrients*. 2016;8(2):69. doi:10.3390/nu8020069
15. Freijer K, Tan SS, Koopmanschap MA, Meijers JMM, Halfens RJG, Nuijten MJC. The economic costs of disease related malnutrition. *Clin Nutr*. 2013;32(1):136-141. doi:10.1016/j.clnu.2012.06.009
16. Wysokiński A, Sobów T, Kłoszewska I, Kostka T. Mechanisms of the anorexia of aging-a review. *Age (Dordr)*. 2015;37(4):9821. doi:10.1007/s11357-015-9821-x
17. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell*. 2013;153(6):1194-1217. doi:10.1016/j.cell.2013.05.039
18. Trifunovic A, Larsson NG. Mitochondrial dysfunction as a cause of ageing. *J Intern Med*. 2008;263(2):167-178. doi:10.1111/j.1365-2796.2007.01905.x
19. Bañuls C, de Marañon AM, Veses S, et al. Malnutrition impairs mitochondrial function and leukocyte activation. *Nutr J*. 2019;18(1):89. doi:10.1186/s12937-019-0514-7
20. Verrest L, Wilthagen EA, Beijnen JH, Huitema ADR, Dorlo TPC. Influence of malnutrition on the pharmacokinetics of drugs used in the treatment of poverty-related diseases: a systematic review. *Clin Pharmacokinet*. 2021;60(9):1149-1169. doi:10.1007/s40262-021-01031-z
21. Stanke-Labesque F, Gautier-Veyret E, Chhun S, Guilhaumou R. Inflammation is a major regulator of drug metabolizing enzymes and transporters: consequences for the personalization of drug treatment. *Pharmacol Ther*. 2020;215:107627. doi:10.1016/j.pharmthera.2020.107627
22. de van der Schueren MAE, Wijnhoven HAH, Kruizenga HM, Visser M. A critical appraisal of nutritional intervention studies in malnourished, community dwelling older persons. *Clin Nutr*. 2016;35(5):1008-1014. doi:10.1016/j.clnu.2015.12.013
23. Administrator. Produktresume.dk Lægemiddelstyrelsen. Accessed March 28, 2021. http://produktresume.dk/AppBuilder/search?utf8=%E2%9C%93&id=&type=&q=Sativex&button=S%C3%B8g
24. Lægemiddelstyrelsen. Hvad er medicinsk cannabis? Lægemiddelstyrelsen. Published 2019. Accessed June 10, 2020. https://laegemiddelstyrelsen.dk/da/special/medicinsk-cannabis/borgere/hvad-er-medicinsk-cannabis/
25. Public Assessment Report - GOV.UK/public-assessment-report-gov-uk.pdf/PDF4PRO. PDF4PRO. Published August 18, 2018. Accessed November 17, 2020. https://pdf4pro.com/view/public-assessment-report-gov-uk-15a25f.html
26. Sativex Oromucosal Spray - Summary of Product Characteristics (SmPC) - (emc). Accessed November 16, 2020. https://www.medicines.org.uk/emc/product/602/smpc
27. Dryburgh LM, Bolan NS, Grof CPL, et al. Cannabis contaminants: sources, distribution, human toxicity and pharmacologic effects. *Br J Clin Pharmacol*. 2018;84(11):2468-2476. doi:10.1111/bcp.13695
28. Jager G, Witkamp RF. The endocannabinoid system and appetite: relevance for food reward. *Nutr Res Rev*. 2014;27(1):172-185. doi:10.1017/S0954422414000080
29. Johnson KO, Shannon OM, Matu J, Holliday A, Ispoglou T, Deighton K. Differences in circulating appetite-related hormone concentrations between younger and older adults: a systematic review and meta-analysis. *Aging Clin Exp Res*. 2019;32(7):1233-1244. doi:10.1007/s40520-019-01292-6

17427843, 2023, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/bcpt.13914 by Aalborg University Library, Wiley Online Library on [19/09/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

30. Riggs PK, Vaida F, Rossi SS, et al. A pilot study of the effects of cannabis on appetite hormones in HIV-infected adult men. *Brain Res*. 2012;1431:46-52. doi:10.1016/j.brainres.2011.11.001
31. Farokhnia M, McDiarmid GR, Newmeyer MN, et al. Effects of oral, smoked, and vaporized cannabis on endocrine pathways related to appetite and metabolism: a randomized, double-blind, placebo-controlled, human laboratory study. *Transl Psychiatry*. 2020;10(1):71. doi:10.1038/s41398-020-0756-3
32. van den Elsen GAH, Ahmed AIA, Lammers M, et al. Efficacy and safety of medical cannabinoids in older subjects: a systematic review. *Ageing Res Rev*. 2014;14:56-64. doi:10.1016/j.arr.2014.01.007
33. Herrmann N, Ruthirakuhan M, Gallagher D, et al. Randomized placebo-controlled trial of nabilone for agitation in Alzheimer's disease. *Am J Geriatr Psychiatry*. 2019;27(11):1161-1173. doi:10.1016/j.jagp.2019.05.002
34. Shelef A, Barak Y, Berger U, et al. Safety and efficacy of medical cannabis oil for behavioral and psychological symptoms of dementia: an-open label, add-on, pilot study. *JAD*. 2016;51(1):15-19. doi:10.3233/JAD-150915
35. Ahmed AIA, van der Marck M, van den Elsen G, Rikkert MO. Cannabinoids in late-onset Alzheimer's disease. *Clinical Pharmacology & Therapeutics*. 2015;97(6):597-606. doi:10.1002/cpt.117
36. Walther S, Schüpbach B, Seifritz E, Homan P, Strik W. Randomized, controlled crossover trial of dronabinol, 2.5 mg, for agitation in 2 patients with dementia. *J Clin Psychopharmacol*. 2011;31(2):256-258. doi:10.1097/JCP.0b013e31820e861c
37. Volicer L, Stelly M, Morris J, McLAUGHLIN J, Volicer BJ. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *Int J Geriatr Psychiatry*. 1997;12(9):913-919. doi:10.1002/(SICI)1099-1166(199709)12:93.0.CO;2-D
38. Woodward MR, Harper DG, Stolyar A, Forester BP, Ellison JM. Dronabinol for the treatment of agitation and aggressive behavior in acutely hospitalized severely demented patients with noncognitive behavioral symptoms. *Am J Geriatr Psychiatry*. 2014;22(4):415-419. doi:10.1016/j.jagp.2012.11.022
39. Smith LA, Azariah F, Lavender VT, Stoner NS, Bettiol S. Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. *Cochrane Database Syst Rev*. 2015;2015(11):CD009464. doi:10.1002/14651858.CD009464.pub2
40. Haney M, Gunderson EW, Rabkin J, et al. Dronabinol and marijuana in HIV-positive marijuana smokers: caloric intake, mood, and sleep. *JAIDS J Acquir Immune Defic Syndr*. 2007;45(5):545-554. doi:10.1097/QAI.0b013e31811ed205
41. Beal JE, Olson R, Lefkowitz L, et al. Long-term efficacy and safety of dronabinol for acquired immunodeficiency syndrome-associated anorexia. *J Pain Symptom Manage*. 1997;14(1):7-14. doi:10.1016/S0885-3924(97)00038-9
42. Beal JE, Olson R, Laubenstein L, et al. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *J Pain Symptom Manage*. 1995;10(2):89-97. doi:10.1016/0885-3924(94)00117-4
43. Bedi G, Foltin RW, Gunderson EW, et al. Efficacy and tolerability of high-dose dronabinol maintenance in HIV-positive marijuana smokers: a controlled laboratory study. *Psychopharmacology (Berl)*. 2010;212(4):675-686. doi:10.1007/s00213-010-1995-4
44. Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. *Neuropsychopharmacology*. 2009;34(3):672-680. doi:10.1038/npp.2008.120
45. Struwe M, Kaempfer SH, Geiger CJ, et al. Effect of dronabinol on nutritional status in HIV infection. *Ann Pharmacother*. 1993;27(7–8):827-831. doi:10.1177/106002809302700701
46. Timpone JG, Wright DJ, Li N, et al. The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome. *AIDS Res Hum Retroviruses*. 1997;13(4):305-315. doi:10.1089/aid.1997.13.305
47. DeJesus E, Rodwick BM, Bowers D, Cohen CJ, Pearce D. Use of dronabinol improves appetite and reverses weight loss in HIV/AIDS-infected patients. *J Int Assoc Physicians AIDS Care*. 2007;6(2):95-100. doi:10.1177/1545109707300157
48. Strasser F, Luftner D, Possinger K, et al. Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the cannabis-in-cachexia-study-group. *JCO*. 2006;24(21):3394-3400. doi:10.1200/JCO.2005.05.1847
49. Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. *J Pain Symptom Manage*. 2010;39(2):167-179. doi:10.1016/j.jpainsymman.2009.06.008
50. Brisbois TD, de Kock IH, Watanabe SM, et al. Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial. *Ann Oncol*. 2011;22(9):2086-2093. doi:10.1093/annonc/mdq727
51. Jatoi A, Windschitl HE, Loprinzi CL, et al. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a north central cancer treatment group study. *JCO*. 2002;20(2):567-573. doi:10.1200/JCO.2002.20.2.567
52. Perkins RM, Bucaloiu ID, Kirchner HL, Ashouian N, Hartle JE, Yahya T. GFR decline and mortality risk among patients with chronic kidney disease. *Clin J am Soc Nephrol*. 2011;6(8):1879-1886. doi:10.2215/CJN.00470111
53. Wehling M (Ed). *Drug Therapy for the Elderly*. Springer-Verlag; 2013. doi:10.1007/978-3-7091-0912-0
54. Luis-Lima S, Gaspari F, Negrín-Mena N, et al. Iohexol plasma clearance simplified by dried blood spot testing. *Nephrol Dial Transplant*. 2018;33(9):1597-1603. doi:10.1093/ndt/gfx323
55. Inker LA, Levey AS, Coresh J. Estimated glomerular filtration rate from a panel of filtration markers—hope for increased accuracy beyond measured glomerular filtration rate? *Adv Chronic Kidney Dis*. 2018;25(1):67-75. doi:10.1053/j.ackd.2017.10.004
56. Pottel H, Schaeffner E, Ebert N. Evaluating the diagnostic value of rescaled β-trace protein in combination with serum creatinine and serum cystatin C in older adults. *Clin Chim Acta*. 2018;480:206-213. doi:10.1016/j.cca.2018.02.026
57. Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C–based equations to estimate GFR without race. *N Engl J Med*. 2021;385(19):1737-1749. doi:10.1056/NEJMoa2102953
58. Iversen E, Bodilsen AC, Klausen HH, et al. Kidney function estimates using cystatin C versus creatinine: impact on

17427843, 2023, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/bcpt.13914 by Aalborg University Library, Wiley Online Library on [19/09/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

medication prescribing in acutely hospitalized elderly patients. *Basic Clin Pharmacol Toxicol*. 2019;124(4):466-478. doi:10.1111/bcpt.13156
59. Luo Q, Chen ML, Sun FJ, et al. KIM-1 and NGAL as biomarkers of nephrotoxicity induced by gentamicin in rats. *Mol Cell Biochem*. 2014;397(1-2):53-60. doi:10.1007/s11010-014-2171-7
60. Luo QH, Chen ML, Chen ZL, et al. Evaluation of KIM-1 and NGAL as early indicators for assessment of gentamycin-induced nephrotoxicity in vivo and in vitro. *Kidney Blood Press Res*. 2016;41(6):911-918. doi:10.1159/000452592
61. Walls AB, Bengaard AK, Iversen E, et al. Utility of suPAR and NGAL for AKI risk stratification and early optimization of renal risk medications among older patients in the emergency department. *Pharmaceuticals (Basel)*. 2021;14(9):843. doi:10.3390/ph14090843
62. Barreto EF, Rule AD, Murad MH, et al. Prediction of the renal elimination of drugs with cystatin C vs creatinine: a systematic review. *Mayo Clin Proc*. 2019;94(3):500-514. doi:10.1016/j.mayocp.2018.08.002
63. Iversen E, Bengaard AK, Andersen A, et al. Performance of the Cockcroft-Gault, modification of diet in renal disease, and new chronic kidney disease epidemiology collaboration equations without race in older acute medical patients. *Kidney Int*. 2022;101(5):1087-1088. doi:10.1016/j.kint.2022.02.016
64. A New Panel-Estimated GFR, Including β2-Microglobulin and β-Trace Protein and Not Including Race, Developed in a Diverse Population - American Journal of Kidney Diseases. Accessed January 16, 2023. https://www.ajkd.org/article/S0272-6386(20)31126-4/fulltext
65. EMA. *ICH E6 (R2) Good Clinical Practice—Scientific Guideline*. European Medicines Agency; 2018. Accessed January 19, 2023. https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice-scientific-guideline
66. GUIDANCE FOR CLINICAL TRIAL PROTOCOLS. Accessed February 3, 2023. https://www.spirit-statement.org/
67. Schuetz P, Fehr R, Baechli V, et al. Individualised nutritional support in medical inpatients at nutritional risk: a randomised clinical trial. *The Lancet*. 2019;393(10188):2312-2321. doi:10.1016/S0140-6736(18)32776-4
68. Gregersen NT, Flint A, Bitz C, Blundell JE, Raben A, Astrup A. Reproducibility and power of ad libitum energy intake assessed by repeated single meals. *Am J Clin Nutr*. 2008;87(5):1277-1281. doi:10.1093/ajcn/87.5.1277
69. Tveden-Nyborg P, Bergmann TK, Jessen N, Simonsen U, Lykkesfeldt J. BCPT policy for experimental and clinical studies. *Basic Clin Pharmacol Toxicol*. 2021;128(1):4-8. doi:10.1111/bcpt.13492
70. Chaput JP, Gilbert JA, Gregersen NT, Pedersen SD. Comparison of 150-mm versus 100-mm visual analogue scales in free living adult subjects. *Appetite*. 2010;54(3):583-586. doi:10.1016/j.appet.2010.01.016
71. iCare. *IC100 Tonometer for All Eye Care Professionals*. iCare. Accessed January 17, 2022. https://www.icare-world.com/product/icare-ic100-tonometer/
72. Passani A, Posarelli C, Sframeli AT, et al. Cannabinoids in glaucoma patients: the never-ending story. *J Clin Med*. 2020;9(12):3978. doi:10.3390/jcm9123978
73. Shapiro AM, Benedict RH, Schretlen D, Brandt J. Construct and concurrent validity of the Hopkins verbal learning test-revised. *Clin Neuropsychol*. 1999;13(3):348-358. doi:10.1076/clin.13.3.348.1749
74. Kwan E, Straus SE. Assessment and management of falls in older people. *CMAJ*. 2014;186(16):E610-E621. doi:10.1503/cmaj.131330
75. Lee SY, Gallagher D. Assessment methods in human body composition. *Curr Opin Clin Nutr Metab Care*. 2008;11(5):566-572. doi:10.1097/MCO.0b013e32830b5f23
76. InBody USA|Body Composition Analysis: Muscle, Fat & Water. Accessed February 3, 2023. https://inbodyusa.com/
77. Nordén J, Grönberg AM, Bosaeus I, et al. Nutrition impact symptoms and body composition in patients with COPD. *Eur J Clin Nutr*. 2015;69(2):256-261. doi:10.1038/ejcn.2014.76
78. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z, Ad Hoc ESPEN Working Group. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. *Clin Nutr*. 2003;22(3):321-336. doi:10.1016/S0261-5614(02)00214-5
79. Wilson MMG, Thomas DR, Rubenstein LZ, et al. Appetite assessment: simple appetite questionnaire predicts weight loss in community-dwelling adults and nursing home residents. *Am J Clin Nutr*. 2005;82(5):1074-1081. doi:10.1093/ajcn/82.5.1074
80. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med*. 2012;367(1):20-29. doi:10.1056/NEJMoa1114248
81. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med*. 1999;130(6):461-470. doi:10.7326/0003-4819-130-6-199903160-00002
82. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612. doi:10.7326/0003-4819-150-9-200905050-00006
83. Pottel H, Björk J, Courbebaisse M, et al. Development and validation of a modified full age spectrum creatinine-based equation to estimate glomerular filtration rate: a cross-sectional analysis of pooled data. *Ann Intern Med*. 2021;174(2):183-191. doi:10.7326/M20-4366
84. Roberts HC, Denison HJ, Martin HJ, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age Ageing*. 2011;40(4):423-429. doi:10.1093/ageing/afr051

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