

PROTOCOL: Cannabidiol for Fibromyalgia

AUTHOR: Marianne Uggen Rasmussen, The Parker Institute, Copenhagen University Hospital

DATE: 2020-12-14

Protocol number P142; **Version:** 4; **EudraCT:** 2019-002394-59, **Regional Ethical Committee Journal Number** H-20047715. **ClinicalTrials.gov Identifier:**

CLINICAL TRIAL PROTOCOL

Cannabidiol for Fibromyalgia

The CANNFIB trial

Protocol for a randomized, double-blind, placebo-controlled, parallel-group, single-center trial

Sponsor Investigator

Marianne Uggen Rasmussen (MUR) RN, MPH, PhD; Post-doctoral fellow

Primary Investigator and Supervisor

Kirstine Amris (KA) MD, DMSc; Senior Rheumatologist

CO-investigator and statistical advisor

Robin Christensen (RC) MSc, PhD; Professor of Biostatistics and Clinical Epidemiology

CO-investigator and advisor

Eva Ejlersen Wæhrens (EEW) OT, DMSc; Senior Researcher

CO-investigator and advisor

Henning Bliddal (HB) MD, DMSc; Professor of Rheumatology

Sponsor contact details

Marianne Uggen Rasmussen
The Parker Institute, Bispebjerg and Frederiksberg Hospital,
Nordre Fasanvej 57,
DK-2000 Frederiksberg
Phone: +45 38164197
Email: marianne.uggen.rasmussen@regionh.dk

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LIST OF ABBREVIATIONS

ACR	American college of rheumatology
ADL-Q	Activities of daily living questionnaire
AE	Adverse events
AMPS	Assessment of Motor and Process Skills
BIA	Bioelectrical impedance analysis
CBD	Cannabidiol
DASS	Depression anxiety and stress scale
DUN	Dispensing unit number
EQ5D	EuroQol Group self-rated health questionnaire
FDA	USA food and drug agency
FIQ-R	Fibromyalgia impact questionnaire-revised
FPFV	First patient first visit
GCP	Good clinical practice
hCG	Human chorionic gonadotropin
ICMJE	International Committee of Medical Journal Editors
ITT	Intention to treat
LPFV	Last patient first visit
LPLV	Last patient last visit
NRS	Numeric rating scale
PROM	Patient reported outcome measures
PRP	Patients Research Partners
PSEQ	Pain self-efficacy questionnaire
PSQI	Pittsburgh sleep quality index
PSS	Perceived stress scale
SAE	Serious adverse events
SNAQ	Simplified Nutritional Appetite Questionnaire
THC	Delta-9-tetrahydrocannabinol
WHR	Waist-to-hip ratio

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1. PROTOCOL SYNOPSIS

Location	The Parker Institute, Copenhagen University Hospital Bispebjerg and Frederiksberg Hospital.
Title	Medical cannabis for fibromyalgia.
Design	A randomized, double-blind, placebo-controlled, parallel-group, single-center trial.
Compound	Medical cannabis; cannabidiol (CBD).
Key dates	First patient first visit: 4 th quarter 2020. Last patient first visit: 4 th quarter 2021. Last patient last visit: 3 rd quarter 2022.
Duration	Trial duration is 40 weeks; including a up to four-week screening period (week -4 to 0), a 24-week main trial period (weeks 0 to 24), and a 12-week post-intervention observation period (weeks 24 to 36).
Participants	Patients fulfilling the 1990 ACR-criteria for Fibromyalgia above 18 years of age.
Sample size	200 patients.
Objectives	To establish the efficacy of cannabidiol compared to placebo after 24 weeks on pain intensity, and other relevant outcomes including sleep quality, sleep duration, activities of daily living, quality of life, and energy level.
Safety	To monitor the safety and tolerability of cannabidiol use over 24 weeks in patients with fibromyalgia.
Procedures	Patients will be randomized to receive either cannabidiol (CBD) 50 mg, or an identically appearing cannabidiol - placebo daily, after a 4-week screening period prior to randomization.
End points	Primary endpoint is change in pain intensity on a Numeric Rating Scale 0-10 from week 0 to week 24. Key secondary outcomes are changes in sleep quality, sleep duration, activities of daily living and quality of life from week 0 to week 24. Supportive (exploratory) secondary objectives include changes in sleep latency, pain self-efficacy, stiffness, energy level, physical activity, feeling rested, depression, anxiety, stress, memory problems, tenderness, balance problems, environmental sensitivity, pressure pain threshold and tolerance, muscle fatiguability, appetite, body weight, body composition and pain reduction 30% and 50% from week 0 to week 24.

2. INTRODUCTION

2.1. Background

Fibromyalgia is a serious chronic pain condition affecting 2-5 % of the background population, according to European studies [1–3]. The disease burden in most affected individuals is substantial; the typical patient presenting with widespread musculoskeletal pain, high pain intensity, few pain-free intervals, and often the pain is accompanied by sleep disturbances, fatigue, cognitive dysfunction, and considerable emotional distress [4–6]. Fibromyalgia is strongly associated with disability and muscle fatigue [7], affecting daily life activities [8], leading to poor social participation and incapacity for normal employment which incurs high direct medical costs as well as significant indirect costs, e.g. sick leave and disability compensation [9]. Studies have shown that a substantial number of patients, are not satisfied with the treatments offered, and rate their health and quality of life after treatment as poor [9,10].

Recognizing, that there currently is no cure for fibromyalgia, symptom-based management aiming at symptom reduction and maintenance of optimal functioning is recommended by most clinical guidelines, and ideally management should include both non-pharmacological and pharmacological treatment strategies [11]. All recommendations for the pharmacological treatment of fibromyalgia now propose classes of medications, such as antidepressants and anticonvulsants, which target central pain processing mechanisms [12–14]. Several of these drugs have been tested in controlled trials for their efficacy in fibromyalgia, and meta-analyses have been written on most of these interventions [15–21]. Generally, these meta-analyses have revealed that overall effect sizes are modest; a minority of patients will have substantial benefit (patient reported pain relief of 50% or greater), and more will have moderate benefit (patient reported pain relief of 30% or greater). Many will have no or minimal benefit or will discontinue because of adverse events. However, it appears that even moderate reductions in pain may lead to considerable increase in self-reported quality of life and other outcome domains in this specific patient population [22,23].

Medical cannabis is popularly advocated for in Denmark, both among politicians and in the general population [24], for different health conditions including chronic pain. However, no evidence exists on what types of medical cannabis to use and what dosages to prescribe for the different conditions. In addition, safety issues such as adverse events and serious adverse events remain underexplored. Thus, physicians are reluctant to prescribe medical cannabis to their patients. Nevertheless, patients living with chronic pain are known to self-administer unlicensed medical cannabis. The extent of actual cannabis use is unknown, although, one study has documented that 13% of patients with fibromyalgia use cannabis regularly with a more extensive use among male patients compared to females [23]. Numbers from a Danish context show that only 17 out of 286 (6%), patients with fibromyalgia participating in a multidisciplinary rehabilitation program in Bispebjerg and Frederiksberg hospital during 2018, stated that they were using self-administrated cannabis on a regular basis (unpublished data). Since self-administrated off-label use of

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cannabis is illegal in Denmark, this number may well be underreported. Still, individuals diagnosed with fibromyalgia who do admit to cannabis use, are sharing stories with health professionals about how unlicensed cannabis has improved their coping with everyday life, functional ability, pain, sleep, fatigue, mood and overall health related quality of life. Such compelling stories of individuals cannot be ignored and underline the necessity of exploring the efficacy of medical cannabis in a proper research design (i.e. with good internal validity).

2.2. Relevance of investigation

The use of the cannabis plant for medical purposes is limited in Europe. The European addiction societies stresses the need for further studies on the efficacy of medical cannabis and warrants for possible dangers associated with the increasing popularity of medical cannabis. Regulations are lacking concerning registration and medical indications, as well as the development of uniform compounds with regard to strength and types of products and rules concerning sales and marketing [25].

In Denmark, production and distribution of medical cannabis is illegal. However, starting from January 1st, 2018, a four year pilot scheme has been legalized and approved by the Danish Medicines Agency [26], allowing for medical cannabis in the treatment of conditions such as multiple sclerosis, spinal injuries and nausea after chemotherapy and neuropathic pain. Although patients suffering from fibromyalgia have few treatment options for management of their disabling condition, this group is not included in the pilot scheme. However, under the pilot scheme, it is legal for physicians to prescribe cannabis for this and other patient groups.

3. RATIONALE AND EVIDENCE TO DATE

3.1. Medical cannabis

Medical cannabis is the term for medications derived from dried cannabis plants in the form of capsules, pills or extracts/oils. The top shoot of the plant contains 100 cannabinoids that are divided into two subgroups; Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), affecting the CB1 receptors located in the central nervous system, and CB2 cannabinoid receptors located outside of the central nervous system [27]. While the TCH cannabinoids have psychoactive, appetite stimulating and nausea reducing effects, cannabidiol has anti-inflammatory, anti-convulsive and immune modulating effects [28]. Studies are inconclusive with regard to the effect of cannabidiol on appetite and food intake [29] Cannabinoids are known to be highly lipophilic and to accumulate in fatty tissue, and may influence the metabolism, fat distribution and accumulation in users [30]. It has been implicated that both TCH and CBD have pain reducing effects [31,32]. CBD is confirmed to have a favorable safety profile compared to THC [29].

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The US Food and Drug Administration (FDA), has recently approved Epidiolex® as the first prescription cannabis drug derived from the cannabis plant, for treating rare and severe forms of epilepsy [33]. Synthetically manufactured cannabis such as dronabinol (USA) [34] and nabilone (USA and UK), have been approved earlier in the treatment of nausea after chemotherapy [35]. The only synthetic cannabis based approved drug in Denmark is Sativex® for the treatment of multiple sclerosis [36]. However, none of the synthetic cannabis drugs are currently approved for the treatment of chronic pain conditions.

3.2. Medical cannabis and fibromyalgia

Evidence is sparse on medical cannabis in the treatment of fibromyalgia. In a Cochrane review on herbal cannabis (hashish, marihuana), plant-based and synthetic cannabinoids for fibromyalgia, only two out of four identified studies on the topic were included, due to small sample sizes, short-term duration and poor reporting of the other studies. The two studies were both on synthetic cannabinoid (nabilone). No high-quality studies on plant-based cannabis could be identified. Evidence for efficacy was inconsistent as one study favored nabilone on pain and quality of life, compared to placebo, and the other study favored nabilone on sleep compared to Amitriptyline (anti-depressant). However, the quality of the studies was low and tolerability was low due to adverse events [37].

Recent systematic reviews, have investigated the existing evidence on the effectiveness of cannabinoids for chronic non-cancer pain, including fibromyalgia. No impact on physical and emotional functioning was found, and only low-quality evidence found improved sleep and patient global impression of change. Thus, it was concluded to be unlikely that cannabinoids are effective in the treatment of non-cancer pain [38], as findings were inconsistent for the effect of medical cannabis for fibromyalgia [39]. Surveys however, have showed favorable effect on fibromyalgia symptoms and health-related quality of life [40], and improved pain management and sleep, among users of unlicensed cannabis compared to non-users [41], although no information on type and dosages of cannabis was given in the surveys. Negative patients' perspectives themes such as the high cost, the negative effects of cannabis and the "views of others", including their health care professionals, were also identified [41]. A recent retrospective study showed significantly favorable outcomes on fibromyalgia symptoms among medical cannabis users, and only mild adverse events. However, the retrospective design, the relatively small sample size and short duration reduced the quality of the study [42].

3.3. Rationale for a randomized trial

Based on the high demand and an increasing popularity of medical cannabis - which is currently used unlicensed among many patients with fibromyalgia, despite the lack of high-quality evidence on efficacy and safety, a well-designed randomized trial with a large sample size and clinically relevant duration is warranted.

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4. OBJECTIVES

The aim of this trial is to assess the efficacy and safety of cannabidiol use compared to placebo.

4.1. Primary objective

To assess the effect of cannabidiol 50 mg compared to cannabidiol-placebo, on change in pain intensity from baseline to week 24.

4.2. Secondary (key) objectives

To assess the effect of cannabidiol 50 mg, compared to cannabidiol-placebo, on changes in the following secondary key endpoints:

- Sleep quality
- Sleep duration
- Activities of daily living
- Quality of life

4.3. Supportive (exploratory) secondary objectives

For each group we will report changes in the following exploratory secondary endpoints:

- Energy level
- Sleep latency
- Pain self-efficacy
- Depression
- Anxiety
- Stress
- Hair cortisol level
- Stiffness
- Feeling rested
- Memory problems
- Anxiety level
- Tenderness (tenderness to touch)
- Balance
- Environmental sensitivity
- Assessment of pressure pain threshold and tolerance

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- Assessment of muscle fatiguability
- Appetite
- Body weight
- Body composition
- Body fat distribution
- Number of patients (in each group) with a 30 % and 50% reduction in pain intensity
- To examine if observed ADL ability at baseline may predict treatment outcomes

4.4. Safety

To evaluate the safety and tolerability of cannabidiol 50 mg compared to cannabidiol 50 mg placebo in patients with fibromyalgia over 24 weeks.

5. HYPOTHESES

The primary hypothesis of the study is that pain intensity will be significantly reduced in participants receiving cannabidiol 50 mg compared to those receiving identically appearing placebo after 24 weeks.

Secondary hypotheses are that sleep quality and duration, activities of daily living and quality of life, will be improved in participants receiving cannabidiol 50 mg compared to those receiving cannabidiol 50 mg placebo after 24 weeks. It is also hypothesized that participants receiving cannabidiol will improve on the supportive exploratory secondary outcomes, and that a higher proportion of those receiving cannabidiol will have a substantial benefit (50 % pain reduction) and a moderate benefit (30 % pain reduction).

6. STUDY PLAN

6.1. Design

The trial is designed as a single-center, randomized, placebo-controlled, double blind and parallel-group trial.; the trial contains three periods: A pre-randomization screening period (week -8 to 0), a main trial period (week 0 to 24), and a post interventional observation period (week 24 to 36). The trial is designed to determine the efficacy and safety of cannabidiol use for patients with fibromyalgia, (see Figure 1).

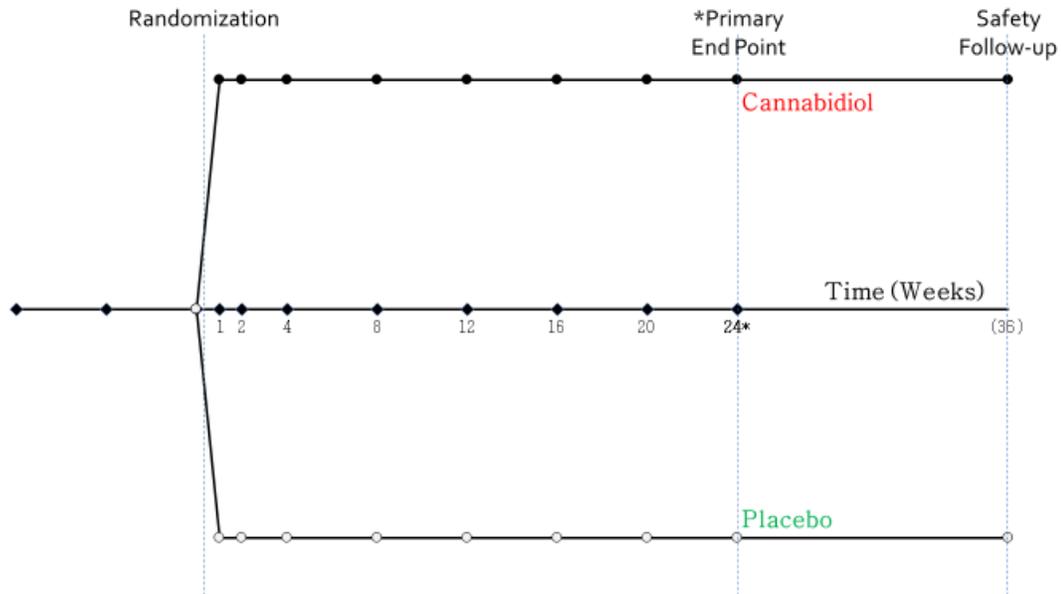


Figure 1: Illustration of the trial design

The trial is scheduled to start inclusion of first patient first visit, primo November 2020 or as soon as possible thereafter, and the study period will go on for two year and end with the last patient last visit in September 2022.

6.2. Randomization and treatment allocation

Eligible participants, who are included at screening, will be randomized in a 1:1 manner to receive either cannabidiol 50 mg or placebo. Allocation will also be stratified based on sex (male vs. female), age and pain intensity (over vs. under 7 on the FIQ-R pain numeric rating scale) to ensure that the two groups are as alike as possible. A computer-generated randomization sequence will create subject identification numbers and allocate the subjects to treatment arms. The subject number will be written on the medication label upon dispensation. This will ensure that participants receive the correct study drug or placebo according to treatment allocation. The randomization sequence will be created by an independent biostatistician using a random number generator (SAS Proc Plan), and subsequently entered in the electronic Case Report Form (e-CRF), that will be developed specifically for the study, by an independent data manager. If unblinding of a participant is required due to an adverse event, the primary investigator can request to break the randomization code for the individual patient, via the independent data manager. The unblinding will always be performed at patient level and unblinding can take place any time during the day (24/7).

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Randomization and concealed allocation are done electronically in the e-CRF at the randomization visit (week 0).

6.3. Site

The study will be conducted at the Parker Institute, Bispebjerg and Frederiksberg Hospital, University of Copenhagen. The Parker Institute is a well-established research institute and clinical department with secretariat, data managers and Good Clinical Practice (GCP) trained health care professionals including physicians and study nurses. Monitoring will be conducted from the initiation and throughout the trial by the GCP unit at Bispebjerg and Frederiksberg hospital, in accordance with the GCP rules and regulations.

6.4 End of trial

The trial will end when the last patient has completed the last visit as well as the 12-week post interventional observation period, or prematurely discontinued the intervention or withdrawn from the trial, which comes last.

7. PARTICIPANT SELECTION: ELIGIBILITY CRITERIA

7.1. Inclusion criteria

- Informed consent obtained
- Clinical diagnosis of fibromyalgia according to the American College of Rheumatology (ACR) 1990 criteria [43]
- Adult individuals (Age ≥ 18 years and < 75 years)
- Average pain intensity ≥ 4 on a Numeric Rating Scale (NRS)
- No use of medical cannabis (THC/CBD) within the last six months
- Proficiency in spoken Danish language and able to read and write in Danish

7.2. Exclusion criteria

- On-going participation in other medical trials for pain management of fibromyalgia
- Diagnosis of Rheumatoid Arthritis or other inflammatory diseases
- Diagnosis of other serious chronic diseases
- Impaired liver and kidney function
- Pregnancy or insufficient anti-conception therapy for fertile female participants
- Planning pregnancy or insufficient anti-conception use in fertile female partners of male participants

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- Breast feeding
- Surgery scheduled for the trial period or within 3 months prior to enrollment
- History of or current diagnosis of cancer
- History of or current epilepsy and seizures
- History of or major depressive disorder
- History of a suicide attempt or any suicidal behavior
- A mental state that may impede compliance with the program
- History of severe psychiatric disorders
- History of or current cannabis abuse
- History of or current drug abuse
- History of or current alcohol abuse
- Severe personality disorder
- Current use of opioids, opioid antagonists (LDN) or similar strong analgesics
- Allergic reactions to the active ingredients in cannabidiol

Participants who are using mild analgesics (e.g. NSAIDs, acetaminophen, paracetamol), on a regular or as-needed (PRN) basis, may continue this treatment if needed during the study. Any changes in the participants concomitant medications will be monitored and documented.

7.3. Participant enrolment

Participants will be recruited from the multidisciplinary patient education and rehabilitation program of the fibromyalgia outpatient clinic at Bispebjerg and Frederiksberg hospital. Patients enrolled in this program have previously given their consent to be included in a national database (DanFib), and they have agreed to be contacted for the purpose of participation in potential studies and given permission for researchers to obtain relevant information regarding eligibility for studies, from the patients' electronic hospital files (Sundhedsplatformen). Study recruitment will also be advertised on the Parker Institute website and the websites of the Danish Fibromyalgia Association and the Danish Rheumatism Association, and in the newspaper for Copenhagen metropolitan area. All potential trial participants who express an interest in the study, will be contacted by telephone by the study nurse, and given information about the purpose and the design of the trial. They will be informed that the design is placebo-controlled with two treatment arms, and that allocation to active treatment or placebo is random. Potential participants will also be asked a series of standardized questions to assess eligibility for study inclusion. At this point, potential participants who have not previously consented to this, will be asked if they approve that information from the patients' electronic hospital files, may be obtained and disclosed to the investigators and study nurses, to assess their eligibility for study inclusion. Written information about the trial and mandatory information on study participants rights will be sent by mail or e-mail.

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After a minimum of 24 hours after the potential participant has received oral and written information, a screening visit will be scheduled with the study physician (primary investigator or sub-investigator) and the study nurse. If the participant wishes, they are welcome to bring a bystander to the screening visit. Study information is repeated without interruptions, in a private consultation with the study physician, to make sure that information is understood regarding the study aim, plan, visits, potential risks, adverse events, and complications. The participants will have the opportunity to ask questions and will be informed that they may have more time to consider their participation if needed, before informed consent is obtained and signed by the participant and the investigator.

Participants are informed that by signing informed consent, they consent to allowing the investigators and controlling authorities direct access to the patients' chart and electronic hospital files, to obtain study relevant information the such as medical history, laboratory results and medicinal history. This information is obtained to evaluate the efficacy of the project medicine and to ensure the safety and well-being of the participants throughout the study. Participants are also informed that this information will be disclosed to the sponsor investigator, primary investigator, sub-investigators, and study nurses, as well as representatives from the independent monitoring organization: The GCP unit at Copenhagen University Hospital. The study will be performed in compliance with the Data Protection Act (Databeskyttelsesloven).

Participants will be informed that they may withdraw from the study at any time during the study, if they no longer wish to participate, and that they also can withdraw their informed consent. After the signed informed consent is obtained, inclusion and exclusion criteria are reviewed. Then a physical examination is performed, information regarding medical history and prior and concomitant medications is collected and blood samples are drawn. Patient Reported Outcome Measures (PROMs) are answered electronically on touch screens and transferred into the e-CRF. There will be no remuneration given to trial participants.

7.4. Baseline pregnancy test and contraception

Females of childbearing potential will have a urine pregnancy test (hCG) performed at the screening visit. This will not be required for menopausal women who have been without menstrual period for at least 1 year. A negative pregnancy test is required for females of childbearing potential to be included in the study. Fertile women must use highly effective birth control methods during the entire period of the trial, unless their partner is vasectomized or in the case of sexual abstinence. Highly effective methods include hormonal contraception (birth control pills, intravaginal or transdermal patch or injection), intrauterine device (IUD), and intrauterine hormone-releasing system (IUS). Fertile male participants should use condom during the entire period of the trial.

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In the event of subjects becoming pregnant during the trial, they are instructed to notify the investigator immediately. If a partner of a male participant becomes pregnant, the investigator should be notified immediately.

8.INTERVENTIONS AND OBSERVATION

8.1 Examinations and testing

Participants will be subjected to a variety of examinations, questionnaires and testing during screening, enrolment and allocation, medical intervention visits, end of treatment and end of trial visits, (see table 1; visit schedule). Blood testing with standard biochemistry (C-reactive protein, Alanine Aminotransferase, Alkaline phosphatases, bilirubin, calcium, creatinine, potassium, sodium and hematology (hemoglobin, leucocytes, differential cell count, erythrocyte, erythrocyte volume fraction, erythrocyte middle volume, erythrocyte middle cell hemoglobin concentration, thrombocytes, reticulocytes), will be performed at screening visit, week 12 and week 24. Blood samples are drawn in order to monitor participants' liver and kidney function, inflammation markers and overall hematology, for safety. The sample will contain 10 ml of blood and will be destroyed after analysis. Urine samples for pregnancy tests and screening for Cannabinoid (THC) and opioid concentration in the urine, will be performed for safety and to ensure that participants are complying with the study protocol. The sample will contain 100 ml of urine and will be destroyed after analysis. Vital signs including blood pressure, systolic and diastolic and resting pulse (sitting down) will be monitored at all visits. ECG (12-lead) will be assessed at the screening visit. Participants will also undergo screening for potential psychiatric side effects including suicide risk, at the screening visit.

8.2. Pre-randomization run-in-period

After the screening visit, a pre-randomization run-in-period of up to 4 weeks starts (week -4 to 0), to ensure that potential participants fulfill all the inclusion criteria and have none of the exclusion criteria. Participants may continue with other prior medications for their pain if they wish (except for opioids).

8.3. Drug intervention period

Eligible participants will be randomly assigned 1:1 to receive cannabidiol 50 mg or an identically appearing placebo. All participants (independent of group) will be titrated up to 50 mg following a dose escalation scheme: Initial dosage of 10 mg daily (week 0), escalated every third day by 10 mg up to week 2. Subsequently participants will stay on 50 mg dosage until the week 24 end of treatment visit. Visits will be conducted weekly during the up-titration period (week 0, 1 and 2), and subsequent visits will take place at week 4, 8, 12, 16, 20 and 24, (see figure 1, Trial design and table 1. Visit schedule). Visits 1, 8 and 16 will be

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performed as a telephone visit. Medical monitoring of vital signs and clinical and laboratory evidence of potential adverse events will be conducted throughout the study.

8.4. Study drug use, content and handling

Cannabidiol will be administered to the participants orally in tablet form. Participants will start with 10 mg daily and the dose will be escalated every third day until the maximum dosage of 50 mg is reached (after two weeks). Dose escalation will be based on safety and tolerability, and if dose escalation is not feasible, then delayed increments are allowed. Subjects will be maintained at the highest tolerated dose level. However, reduction of the achieved maintenance level will lead to study discontinuation. The dosage of 50 mg as the daily intake during the study period, is decided based on clinical experience from private pain clinics from where medical cannabis is prescribed in Denmark (Clinic Horsted), and on dialogue with the pharmacists at Glostrup pharmacy, who will supply the investigational medicinal product and placebo. Glostrup pharmacy is experienced in producing cannabidiol pills for research purposes, and “cannabidiol” placebo pills that are identical in appearance, taste, and smell. Glostrup pharmacy will be responsible for the labelling of the cannabidiol and placebo tablet packages with a unique Dispensing Unit Number (DUN). The investigating site will ensure proper storage of the trial products, in a locked and secure temperature-controlled room. A non-blinded, non-investigator will ensure that participants are receiving the study drug or placebo according to the treatment allocation by parring DUN numbers and the recipient patient numbers in the e-CRF system. One investigator will be responsible for drug accountability. For each patient treated, the DUN number of the package will be documented, and the patients will be asked to return the empty packages after use for accountability. Proper destruction of unused drugs will be ensured.

8.5 Post-interventional observation period

After the termination of treatment, a post-interventional observational period of 12 weeks will be initiated. This period is essential for the assessment and monitoring of the effects of drug cessation on pain, sleep quality, pain self-efficacy, activities of daily Living, quality of life and the overall burden of fibromyalgia symptoms, as well as potential adverse events.

9. ENDPOINTS

Endpoints are selected based on the fibromyalgia core domains, identified by the OMERACT 9 (Outcome measures in Rheumatology) initiative [44].

9.1 Outcome measures

The following validated Patient Reported Outcomes (PRO's) are applied in this study:

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- The Fibromyalgia Impact Questionnaire Revised (FIQ-R) [45]
- The Pittsburgh Sleep Quality Index (PSQI) [46]
- The EuroQol Group Self-Rated Health Questionnaire (EQ5D) [47]
- The Activities of Daily Living Questionnaire ADL-Q [48]
- The Pain Self-Efficacy Questionnaire (PSEQ) [49,50]
- The Depression, Anxiety, Stress Scale (DASS-21)[51]
- The Perceived Stress Scale (PSS)[52]
- Columbia-Suicide Severity Rating Scale (C-SSRS) [53]
- The Simplified Nutritional Appetite Questionnaire (SNAQ) [54]
- The Fibromyalgia Sensory Hypersensitivity Scale (FSHSS) [Developed at the Parker Institute]

In addition, a basic information questionnaire will be applied at the screening visit to collect data on demography, medical and medication history.

Observation-based outcomes are also applied in the study. The Assessment of Motor and process skills (AMPS) [55], is an observation-based, standardized evaluation of the individual's ability to perform and complete activities of daily living. The AMPS motor ability measure reflects the level of effort, fatigability and clumsiness observed during performance of a task, whereas the AMPS process ability measure reflect how timely and well organized the tasks are performed [55]. Assessment of pressure pain threshold and tolerance is performed using computerized cuff pressure algometry [56]. Pain threshold is defined as the pressure of the cuff at the subjects first sensation of pain when applying constantly rising pressure. Pain tolerance is defined as the worst tolerable pain caused by the pressure stimulation and the pressure is switched off by the patient [56]. To assess muscle fatiguability, a static muscle exhaustion test is performed during which surface electromyography is recorded (non-invasively). From the surface electromyography signal, the degree of peripheral (muscular) and central (central nervous system) fatigue is quantified [7]. Hair clippings will be sampled from all participants and analyzed to assess cortisol contents as a biomarker for prolonged stress [57]. Objectively measured information on sleep and physical activity will be collected using the triaxial accelerometer device SENS MOTION® activity measurement system [58]. Body weight (± 0.1 kg) will be measured using an electronic scale. To estimate body composition, bioimpedance measurement (BIA) will be conducted using the ImpediMed, model SFB7 [59], produced in Queensland, Australia, which measures impedance over a spectrum of frequencies. Waist and hip circumferences (WHR) will be measured using a tape measure to the nearest 0.1 cm, from which WHR will be calculated (waist circumference / hip circumference) are included as a measure of bodyfat distribution.

9.2 Primary endpoint

The primary endpoint is change in pain intensity from baseline to week 24, measured on a 0-10 Pain Numeric Rating scale (NRS) included in the FIQ-R. To facilitate interpretation of the pain intensity measure,

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the findings will also be communicated as the proportion of patients achieving more than 30% and 50% pain reduction on the FIQ-R Pain Numeric Rating scale.

9.3 Key secondary endpoints

1. Change in sleep quality: PSQI subjective sleep quality domain
2. Change in sleep duration: PSQI, sleep duration domain
3. Change in objectively measured sleep duration and patterns: accelerometer data
4. Change in activities of daily living: AMPS and ADL-Q total
5. Change in Quality of life: EQ5D total

9.4 Exploratory secondary endpoints

1. Change in sleep latency: PSQI, sleep latency domain
2. Change in pain self-efficacy: PSEQ total
3. Change in stiffness: FIQ-R stiffness subscale
4. Change in energy level: FIQ-R energy subscale
5. Change in objectively measured physical activity: accelerometer data
6. Change in feeling rested: FIQ-R rested subscale
7. Change in depression: FIQ-R depression subscale
8. Change in depression, anxiety and stress: DASS depression anxiety and stress scale
9. Change in anxiety level: FIQ-R anxiety subscale
10. Change in perceived stress: PSS perceived stress scale
11. Change in cortisol concentration in hair: hair clipping analysis
12. Change in memory problems: FIQ-R memory subscale
13. Change in tenderness level (tenderness to touch): FIQ-R tenderness subscale
14. Change in balance problems: FIQ balance subscale
15. Change in environmental sensitivity: FIQ environmental sensitivity subscale and FSHSS
16. Change in pressure pain threshold and tolerance: Cuff algometry
17. Change in muscle fatiguability
18. Change in appetite: SNAQ
19. Change in body weight
20. Change in body composition: BIA
21. Change in body fat distribution: WHR

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10. STUDY PROCEDURES

10.1 Visit description

Prescreening (week -8 to-4)

- Exchange of oral information and general eligibility screening; done by telephone by study nurse or secretary
- Written trial information material and information on trial subjects' rights is sent to potential participants

Screening visit (week -4 to 0)

- Information about the trial and participants' rights is repeated
- Signed informed consent is obtained by the study physician (primary investigator or sub investigator)
- Eligibility, inclusion and exclusion criteria are reviewed
- Physical examination to assess for eligibility and ensure safety
- Medical history
- Medication history
- Vital signs (blood pressure and pulse), body weight and height
- Electrocardiogram (ECG 12-lead)
- Blood testing for standard biochemistry and hematology (see section 8.1)
- Urine test (pregnancy, opioids, cannabinoid (TSH))
- Vital signs
- Body weight
- ECG
- Accelerometer data
- Adverse events

Randomization (week 0)

- Medical history
- Medication history
- PROMs
- AMPS
- Cuff Algometry

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Identifier:

- Muscle fatiguability
- Vital signs
- Body weight
- Body composition (BIA)
- Body fat distribution (WHR)
- Hair cortisol level
- Accelerometer data
- Adverse events
- Blinded allocation to cannabidiol 50 mg or placebo
- Medicine dispense

Drug intervention (week 0 to 24)

Up titration period (week 2) and telephone visits (weeks 1, 8 and 16)

- Adverse events
- Compliance assessment
- Accelerometer data
- Vital signs (week 2)

Follow-up visits (Week 4, 12 and 20)

- PROMs
- Vital signs
- Body weight
- Blood testing with standard biochemistry and hematology (week 12)
- Urine test (pregnancy, opioids, cannabinoid (TSH)) (week 12)
- Adverse events
- Compliance assessment
- Medicine handout

End of trial (week 24)

- Physical examination
- PROMs
- AMPS
- Hair cortisol level

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Identifier:

- Cuff algometry
- Muscle fatiguability
- Vital signs
- Blood testing with standard biochemistry and hematology
- Urine test (pregnancy, opioids, cannabinoid (TSH))
- Body weight
- Body composition (BIA)
- Body fat distribution (WHR)
- Accelerometer data (collection start one week prior to end of trial)
- Adverse events
- Compliance assessment

End of follow-up (week 36)

- PROMs
- Vital signs
- Body weight
- Adverse events

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10.2 Visit schedule

Study phases	Prescreening	Screening	Randomization	Drug intervention							End of trial	End of follow-up
				Up-titration			Follow-up visits					
Week no.	-8 - -4	-4 - 0	0	1*	2	4	8*	12	16*	20	24	36
Information	x	x	x									
Eligibility screening	x	x										
Informed consent		x										
Physical examination		x									x	
Medical history		x	x									
Medication history		x	x									
Blood testing		x						x			x	
Urine test		x						x			x	
PROMs			x			x		x		x	x	x
AMPS			x								x	
Cuff algometry			x								x	
Muscle fatiguability			x								x	
Vital signs (BP, pulse)		x	x		x	x		x		x	x	x
Body weight		x	x			x		x		x	x	x
Body composition			x								x	
Body fat distribution			x								x	
Height		x										
ECG (12-lead)		x										
Hair clipping (Cortisol)			x								x	
Accelerometer data		x	x								x	
Adverse events		x	x	x	x	x	x	x	x	x	x	x
Medicine allocation			x									
Medicine dispense			x			x		x		x		
Compliance assessment				x	x	x	x	x	x	x	x	

* Visits to be performed via telephone call

Visit window is \pm 7-days.

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11. SAFETY CONSIDERATIONS

11.1. Potential side effects, risks, and discomforts for study subjects

Common side effects (1-10%) of drugs containing both THC and CBD (Sativex), are overall feeling of weakness and uneasiness, reduced or increased appetite, diarrhea, nausea, dryness in the mouth, constipation, apathy, balance problems, depression, euphoria, feeling of intoxication, problems with memory and concentration, confusion, personality disorders, sleepiness, difficulty speaking, blurred vision. Rare side effects (0,1-1%) are abdominal pain, hypertension, hallucinations, psychosis, suicidal behavior and fainting. THC and CBD may interact with and enhance the effects of sedatives and alcohol [60]. According to the current legal practice in Denmark, it is not allowed to drive a car when using medical THC. CBD alone is shown to have a favorable safety profile compared to the CBD + THC combined or THC alone.

The most commonly reported side effects of CBD (seen in at least 10%), are tiredness/fatigue, problems sleeping, feeling weak, changes in appetite and weight, infections, diarrhea and rash [61]. More serious and rare side effects (seen in at least 1 %), are hypersensitivity reactions, hepatocellular injury and suicidal behavior and ideation [62]. However, these serious side effect have been reported in patients diagnosed with epilepsy who have been undergoing treatment with daily Cannabidiol dosages of 5 mg per kilogram body weight [62], which could be six times the dosages prescribed in the current CANNFIB study.

11.2 Adverse events

Potential adverse events (AE) will be assessed for at every visit throughout the study, and all evidence of a clinical and/or laboratory AE will be documented in the patient's medical file and recorded in the patient e-CRF. The primary investigator or sub investigator will assess the seriousness of the AE and the probability of the AE being related to the study drug. Subsequently the AE will be followed up on its duration and whether it is resolving or not to a satisfactory conclusion, and any concomitant medication taken in relation to the AE, will be recorded in the patient's medical file and. All adverse events will be documented from the start of the study drug administration to 12 weeks after the discontinuation of the study drug.

The Parker Institute as the investigator of the study, will be responsible for the reporting of all Serious Adverse Events (SAE), which is defined as an AE resulting in death, being life-threatening, requiring hospitalization or resulting in significant disability. If a SAE occur, the investigator will report it within 24 hours of the site being made aware of the SAE, to the sponsor. The Parker Institute will as the sponsor of the study, be responsible for the reporting of any deadly or life-threatening Suspected Unexpected Serious Adverse Reactions (SUSARS) that may occur, to the Danish Medicines Agency, as soon as possible and no later than 7 days after being made aware of the SUSAR. The Parker Institute will also be responsible for reporting any additional information regarding the SUSAR, within 8 days of the initial reporting. The Parker

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Institute will be responsible to report any other SUSARs to the Danish Medicines Agency within 15 days after being made aware of the SUSAR.

The Reference document to be used to assess whether a reported SAE is suspected or unexpected, is the product resume of Epidyolex in which the active ingredient is Cannabidiol [63].

12. STATISTICAL CONSIDERATIONS

12.1 Sample size and Power considerations

For a two-sample pooled t-test of a normal mean difference with a two-sided significance level of 0.05 ($p < 0.05$), assuming a common standard deviation of 2 on a 0-10 pain numeric rating scale, a total sample size of 200 assuming a balanced design (1:1), will have the statistical power of 0.94 (94%) to detect a difference between the means of 6 and 7. Even with a smaller sample of 128 patients assuming a balanced design (1:1), the statistical power of the required 80 % will be obtained, to detect a difference between of 1 on a 0-10 pain numeric rating scale.

12.2 Statistical analyses

The details for the statistical analyses plan (SAP) will be determined prior to the completion of data collection and before the data analyses are initiated [64]. The prespecified efficacy analyses will be based on the data for full analysis set; the intention-to-treat (ITT) population, which includes all participants that are assessed and randomized at baseline. In the case of missing data at week 24, the baseline values will be carried forward and included in the of trial analyses.

The primary analyses will be the comparison between cannabidiol 50 mg and placebo, using a mixed linear repeated-measures ANCOVA model with treatment, stratifying factors, and weeks from baseline as fixed effects; in order to reduce the random variation, we will adjustment for the level at baseline as a covariate. From this model the potential observed differences in pain intensity (FIQ-R NRS) and the secondary continuous outcomes will be estimated together with the associate 95% confidence interval and the p-value corresponding to the test of the hypotheses of no difference between treatments (i.e. the null hypothesis).

To establish the efficacy of cannabidiol 50 mg compared to placebo in patients with fibromyalgia, the key secondary endpoints are tested in a hierarchical manner in the order in which endpoints are presented. Cannabidiol will be considered statically significantly better than placebo with respect to change in pain intensity FIQ-R NRS if the null hypothesis is rejected ($p < 0.05$). Categorical changes for dichotomous end points will be analyzed with the use of logistic regression with the same fixed effects and covariates as

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the respective ANCOVA for continuous outcomes (see above). Sensitivity analyses will be performed to assess the robustness for the primary analyses, including a 'non-responder imputation', 'multiple imputation techniques', and a 'per protocol analysis'.

The SAP will also include explicit details on how we will handle/adjust for multiplicity: Multiplicity, as a consequence of many secondary outcome comparisons in the clinical trial, increases the likelihood that a chance association could be deemed causal. This problem commonly arises in clinical trials that have several clinical objectives based on the evaluation of multiple end points. In this trial, P values will be narratively adjusted for the key secondary outcomes (e.g., Bonferroni adjustments).

13. DATA MANAGEMENT

13.1 Data handling

The collection, preservation and dissemination of the clinical data abide to the standard requirements for GCP-compliant data management in clinical trials. Before commencement of any clinical activity, approval from the Danish Medicines Agency, The Regional Health Research Ethics Committees for the Capital Region (De Videnskabetiske Komiteer for Region Hovedstaden) and the National Data Protection Agency, will be obtained. A secure database will be established for the collection of clinical data via the e-CRF platform through a secure connection at the clinical research facility. All data obtained during the study will be documented in the individual eCRF. In the case of missing data, the reasons for this will be noted in the e-CRF.

Participant information collected in the e-CRF but not recorded in the patient files, will be regarded as source data. However, the patients' participation and any SAE related to the study treatment will be documented in the patient hospital files. No patient information such as medical history and medication history will be collected from the patient hospital files, before informed consent has been obtained from the patient.

Information obtained directly from potential participants prior to obtained signed informed consent (i.e. during the telephone eligibility screening), will be recorded in the e-CRF, and this information will be made available to the researchers, upon permission from the patients.

In the process of ensuring data completeness and accuracy, source data verification (SDV), will be performed. The patients will be informed in writing about the need for SDV. The GCP-unit, investigators, sponsors and study coordinators will perform SDV, after informed consent is obtained, and require the following data to get information about the subjects' health condition from the patients' electronic hospital files (Sundhedsplatformen): Admission to hospital for any reason including diagnoses, surgical procedures,

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medical history and medication history. SDV will be performed as a required part of the project not only to get information about the subjects' health condition, but also for the required control purposes, including site self-monitoring, quality control and GCP- monitoring. The dissemination of relevant information from patient files will be conducted in accordance with the Danish health act § 46. Data collection may continue for participants who wish to stop the intake of the study drug or discontinue from the study for other reasons, and these participants will be invited to attend the end-of-trial and follow-up, unless they have withdrawn their informed consent.

The Parker Institute will ensure adherence to the EU-wide data protection instrument, the General Data Protection Regulation, ("the Regulation"), of May 25th, 2018. Consequently, all data will be handled in alignment with the following principles:

- Personal data is fairly and lawfully processed
- It is processed for limited and specified purposes
- Data collection is adequate, relevant and not excessive
- Data are kept accurate and up to date
- Personal data are not kept longer than necessary
- The data are processed in line with subjects' rights
- All reasonable measures are used to ensure data protection
- Data is not transferred to other countries without adequate protection
- An internal project handling process will ensure that the technical procedure for delivering data and the legal procedure for permitting data delivery are handled separately
- All software installations are kept under surveillance for security related updates
- Staff having data-handling task are governed by strict rules for known security breaches
- Decoded data will only be delivered under written signed security-instructions and will normally be delivered without possibility to identify the person
- Participants have a right to get insight in their own personal data

13.2 Data ownership

All data obtained during this study belongs to the Parker institute. All investigators will have full access (except for the described blinding) to all data before, during and up to 10 years after the study is completed.

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14. SPONSORSHIP

The CannFib trial is a sponsor/investigator-initiated trial, initiated by Marianne Uggen Rasmussen (Sponsor Investigator), in close cooperation with Kirstine Amris (Primary Investigator) and the Parker Institute, thus, the status of the sponsor is non-commercial. The trial has received a grant from the Danish Rheumatism Association (Gigtforeningen) of 285.000 DKK, and additional grants have been given from The Erna Hamilton Foundation: 100.000 DKK, The Aase and Ejnar Danielsen's foundation: 100.000 DKK and an internal research grant from the Copenhagen University Hospital, Bispebjerg and Frederiksberg: 100.000 DKK. In addition, the project investigational medicinal product will be partly sponsored with 600.000 DKK by Nordic Cannabis Research, and Linnea Switzerland who are supplying the plant-based cannabidiol for production to Glostrup pharmacy.

Financial support to cover for study operational costs including study medicine and placebo as well as the salary of the researcher, are applied for from various external grants, that will be transferred to the Parker Institute. The Regional Health Research Ethics Committees for the Capital Region and the study participants will be notified if future financial support is granted. The overall study expenses in Danish kroner, are estimated to be the following:

• Cannabidiol 50 mg and cannabidiol 50 mg placebo:	885.000
• Salary sponsor investigator (nurse) 2 years:	800.000
• Clinical examinations	200.000
• Hair cortisol analyses	100.000
• Lab technician	140.000
• Occupational therapist (AMPS tests)	140.000
• Hair cortisol measurements	180.000
• Accelerometers	40.000
• Database assistance	30.000
• Statistical advisor	25.000
• Cuff algometry	75.000
• Publication expenses	20.000
• Total budget	2.635.000

If external funding is not obtained to cover all the expenses, the Parker Institute will cover all excess costs of the study. The Parker Institute, Bispebjerg and Frederiksberg Hospital is supported by a core grant

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from the Oak Foundation (OCAY-13-309). Neither Marianne Uggen Rasmussen or any other member of the project group has financial interest in the conduct of the trial or the results of the trial.

15. DISSEMINATION AND TRANSPARENCY

15.1 Registrations

The trial will be subject to registration according to the specifications from the International Committee of Medical Journal Editors (ICMJE), and the trial will be uploaded and registered at ClinicalTrials.gov prior to patient enrolment. A notification will be submitted to the national authorities before commencement of the trial as applicable according to the Danish Medicines Agency. The sponsor will apply for permission to conduct the trial from the Danish Medicines Agency, the national committee on health research ethics as well as the local data protection agency.

15.2 Protocol publication and patient research partners

The full protocol will be published and will be freely available in open access. This project follows the EULAR recommendations [65] for the inclusion of patient representatives in the contemporary scientific process. Thus, the study is designed with the assistance of two Danish patient research partners (PRPs) of the Parker Institute; (Trine Leth [TL] and Elena Andersen [EA]). The two PRPs have participated in the process of designing and acknowledging the protocol in its current form. Collaboration between patients and health care professionals is developing and disseminating in the planning of research projects, to ensure that patient perspectives are fully taken into consideration in the trial and to ensure external validity. The results of the study will be submitted into EudraCT and thereby published on clinicaltrialregister.eu.

15.3 Publications and communication

Several manuscripts will be prepared for publication in scientific journals, starting with the protocol article. At the end of the trial the main article based on this protocol, will be prepared for publication in a high impact scientific journal. Subsequently, other studies will be conducted based on the data collected and prepared for publication, including a paper on predictive factors for a positive outcome of the intake of cannabidiol, and a separate paper on safety and adverse events associated with long-term use of cannabidiol. Both potential positive and negative findings, as well as inconclusive results will be published in ClinicalTrials.gov and in scientific journals. In addition to the scientific communication planned, the project has already gained general interest and has been mentioned in the newspaper (Børsen) and on several Danish websites (Gigtforeningen.dk, Sundhedspolitisk tidsskrift.dk and Cannabis Danmark.dk). A television

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team from Denmark's Radio (DR1), will follow the study throughout the project period until the results are available, as part of a planned documentary series on chronic pain and medical cannabis.

16. ETHICAL CONSIDERATIONS

Unlicensed medical cannabis is known to be self-administered among patients suffering from fibromyalgia, despite the lack of evidence on efficacy and safety of long-term cannabis use in patient with chronic widespread pain. Therefore, it is highly warranted, to investigate the efficacy and safety of medical cannabis intake, in a proper controlled research design to obtain high quality evidence on the already ongoing medical cannabis use in patients with fibromyalgia. In this study, the efficacy and safety of cannabidiol intake, is assessed by comparing cannabidiol to identical "cannabidiol" placebo pills that contains no active ingredients, in a double-blinded randomized design. This trial will be conducted in accordance with this protocol and applicable regulatory requirements, and the ethical criteria of the Helsinki declaration [66], to ensure the well-being of the participants of the trial. Cannabidiol has a low adverse event profile compared to other components of medical cannabis. However, throughout the study, participants will be monitored closely to make sure they are safe and with a minimum of discomforts. Patients will be made aware of their right to withdraw from the study, and that withdrawal will not affect their possibility to receive future treatment. Thus, the health, well-being and rights of the individual research subjects will take precedence over the study objective to generate evidence on efficacy and safety on cannabidiol use over time. However, once the study results are obtained and regardless of the outcomes, the evidence obtained will benefit all patients with fibromyalgia as results can be used in future guidelines and recommendations in the administration of medical cannabis in the treatment of fibromyalgia. As the study is investigator-initiated, the sponsor and the site are the same, and there is no sponsor-site contract. The trial is covered by the patient compensation insurance as it is originating from the capital region of Copenhagen, Denmark.

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