Statistical Analysis Plan

Cannabidiol for Fibromyalgia: The randomized, double-blind, placebo-controlled, parallel-group, single-center CANNFIB trial

Marianne Uggen Rasmussen[1], Robin Christensen[1,2], Eva Ejlersen Wæhrens[1,3], Marius Henriksen[1], Henning Bliddal[1], Kirstine Amris[1]

Affiliations

[1] The Parker Institute, Bispebjerg and Frederiksberg Hospital, Frederiksberg, Danmark

[2] Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark

[3] Institute of Public Health, University of Southern Denmark, Odense, Denmark

[4] Department of Rheumatology, Bispebjerg and Frederiksberg Hospital, Frederiksberg, Denmark

Correspondence to: Marianne Uggen Rasmussen, PhD.

The Parker Institute, Bispebjerg and Frederiksberg Hospital, Frederiksberg, Danmark;

marianne.uggen.rasmussen@regionh.dk

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Roles and responsibility:

Authors of the SAP: Marianne Uggen Rasmussen and Robin Christensen

Biostatistician responsible: Robin Christensen BSc, MSc, PhD

Primary investigator: Kirstine Amris MD, DMSc; Senior Rheumatologist

Sponsor: Marianne Uggen Rasmussen RN, MPH, PhD; Post-doctoral fellow

SUMMARY

Aim and Objectives

The aim of this randomized, placebo-controlled trial was to establish the efficacy and safety of cannabidiol (CBD) compared to placebo after 24 weeks of treatment in patients with fibromyalgia. The primary objective is to compare the effect of CBD, relative to placebo, on change in FIQ-R pain intensity assessed from baseline to week 24. In addition, comparison between groups for changes in the following key secondary outcomes will be assessed 24 weeks from baseline: sleep quality, sleep duration, objectively measured sleep duration, objectively measured sleep patterns, Activities of daily living, and Health-related quality of life.

Methods

The CANNFIB trial was designed as a single-center, permuted block randomized, placebo-controlled, double-blind, parallel-group study conducted in Copenhagen, Denmark. In the trial 200 patients diagnosed with fibromyalgia aged 18-74 years were randomized 1:1 to be treated with either CBD or placebo for 24 weeks, including an initial two-week titration phase. Our main analyses will estimate between-group differences in the continuous outcomes after 24 weeks for the primary and key secondary outcomes in the intention-to-treat (ITT) population. Data collection includes multiple repeated measurements of each patient's outcomes to assess change over time; for safety monitoring data collection run up to 36 weeks from baseline (i.e., including the 12 weeks without any study medication). The analyses will be based on the ITT population (all patients randomized with baseline measures successfully collected). For continuous outcome data, missing data after baseline will be handled indirectly using Mixed Models for Repeated Measures Data. All *P*-values and 95% confidence intervals will be two-sided; statistical significance among the secondary outcomes will loosely be defined as an observed effect that is unlikely ($P<5\%$) to occur due to chance alone. We will not apply explicit adjustments for multiplicity; we will instead analyze all the key secondary outcomes and interpret the findings based on the Hochberg sequential procedure. Secondly, to ease interpretation, analyses of responders will be performed, based on participants with more than one unit improvement the FIQ-R pain numeric rating scale, as well as 30% and 50% improvement in FIQ-R pain after 24 weeks. The responder criteria will be

analyzed based on the ITT population with missing data replaced by a simplistic non-responder imputation.

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INTRODUCTION

Background

Fibromyalgia is a serious chronic generalized pain condition associated with a substantial disease burden in the most affected individuals. In addition to widespread musculoskeletal high intensity pain with few pain-free intervals, the pain is often accompanied by sleep disturbances, fatigue, cognitive dysfunction, and considerable emotional distress. Fibromyalgia is strongly associated with muscle fatigue and disability which is affecting the patients' daily life activities and quality of life. As there is no cure for fibromyalgia at present, management aiming at symptom reduction and maintenance of optimal functioning including both non-pharmacological and pharmacological treatment strategies is recommended in clinical guidelines. However, the overall effect sizes of the currently recommended and available pharmacological treatments for fibromyalgia are modest and 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.

Due to the lack of efficacy of the available pharmacological treatment options, medical cannabis is in high demand among patients suffering from fibromyalgia. However, as evidence is sparse on the efficacy of medical cannabis, what types to use and dosages to prescribe, as well as safety issues, physicians are naturally reluctant to prescribe medical cannabis to patients. Thus, fibromyalgia patients that want to try this treatment are often on their own in using unlicensed medical cannabis, self-administered and at their own risk and cost.

Rationale for this trial

In recent systematic reviews, the existing evidence on the effectiveness of cannabinoids for chronic non-cancer pain, including fibromyalgia has been assessed, but only low-quality evidence has shown improved sleep and patient global impression of change and otherwise inconstant findings for the effect of medical cannabis for patients with fibromyalgia. Surveys have showed favorable effects on fibromyalgia symptoms, health-related quality of life, and improved pain management and sleep, among users of unlicensed cannabis compared to non-users. A recent retrospective study showed significantly favorable outcomes on fibromyalgia symptoms among medical cannabis users, and only mild adverse events. However, the designs in these studies, i.e., the relatively small sample size and short duration reduced the quality of the studies. Thus, based on the high demand and an increasing popularity of medical cannabis – 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 trial duration is warranted. In this RCT we investigate the efficacy and safety of Cannabidiol (CBD) 50 mg for treating patients with fibromyalgia. We will explore the effect of CBD on pain intensity and other key symptoms associated with fibromyalgia.

Aim and Objective(s)

The aim of this trial is to investigate whether treatment with CBD is safe and has a superior effect compared to placebo on relevant outcomes in patients with fibromyalgia. The primary objective is to assess the effect of CBD 50 mg compared to placebo, on change in pain intensity (FIQ-R) from baseline to week 24. Key secondary objectives include assessing the effectiveness of CBD compared to placebo on changes in sleep quality, sleep duration, objectively measured sleep duration, objectively measured sleep patterns, Activities of daily living, Health-related quality of life, and energy level.

METHODS

Trial design

The CANNFIB trial was designed as a single-center, randomized, placebo-controlled, double-blind, parallel-group trial. Participants were randomized in a 1:1 manner to receive either cannabidiol 50 mg or placebo. Allocation was stratified based on sex (male *vs*. female), age (<45 *vs*. ≥45 years at enrolment) 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**.**

Framework

A superiority trial: The hypothesis testing framework of this trial is to assess if CBD is superior to placebo in reducing FIQ-R pain in patients with fibromyalgia when assessed 24 weeks from baseline. The *P*-value will represent the probability of obtaining results as extreme as the ones observed, assuming that the null hypothesis is true (i.e., that there is no difference between groups). A smaller *P*-value indicates stronger evidence against the null hypothesis and will be applied as a threshold for determining statistical significance (1). If the two-sided *P*-value for the primary endpoint is below an α level of 5% ($P<0.05$), we will reject the null hypothesis, suggesting that the observed effect is unlikely to have occurred by random chance alone.

Randomization, allocation concealment and blinding

Stratified randomization was based on permuted blocks of up to 8 individuals; stratification was used to ensure good balance of participant characteristics in each group based on three clinically important factors. A computer-generated randomization sequence was created for each of the 8 eight strata, and consecutively patients enrolled were allocated to the corresponding treatment arms. The randomization sequence was created by an independent biostatistician using a random number generator (SAS Proc Plan), and subsequently entered in the electronic Case Report Form (e-CRF) subdivided by strata, that was developed specifically for the study, by an independent data manager. Investigators, sponsor, and outcome assessors were blinded to the permuted blocking strategy.

Sample size and power considerations

Integral to the structure of a randomized trial is the pre-established calculation of sample size, ensuring that the study is well-positioned to attain its predetermined primary objective with a high likelihood of success. In a randomized trial, the target difference refers to the desired difference between the experimental intervention and control comparator group regarding the outcome being measured (2). We decided that a difference between groups corresponding to one FIQR pain unit would correspond to a Minimal Important Difference in a population of fibromyalgia patients (3).

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 the 0-10 FIQR pain numeric rating scale, a total sample size of 200 assuming a balanced design (1:1), will have statistical power of 0.94 (94%) to detect a difference between the means of say 6 and 7. Even with a smaller sample of 128 patients in the ITT population assuming a balanced design (1:1), the statistical power of the suggested minimum 80 % will be obtained, to detect a difference between means of 1 on the 0-10 pain numeric rating scale. Since some attrition, drop-outs and missing data was expected during the 24-week intervention period, we decided to include 200 participants (approximately 100 in each group), in the ITT population, corresponding to a statistical power of more than 90% to detect a difference between groups that patients in the ITT population will perceive as important (4).

Statistical interim analyses and stopping guidance

No interim analyses are carried out. Due to the Covid-19 pandemic and long-term illness among the project staff, the inclusion period was extended by an extra year to allow for the inclusion of 200 participants and better ensure achieving the prespecified sample size of 200 patients in the ITT population.

Timing of final analyses

The primary and key secondary outcomes are analyzed collectively and will be reported in the primary manuscript. Final analyses will be performed blinded to group allocation and after the last patient- last- visit has been performed and all week-36 follow-up data are collected (expected in February 2024).

Box 1: Visit schedule for enrolment, interventions, and assessments. Visit "window" +/- 7 days

	STUDY PERIOD										
	Enrolment	Allocation	Post-allocation								Follow-up
Week	-8 - 0	0	1*	2	4	8*	12	16*	20	24	36
ENROLMENT:											
Informed consent	x										
Eligibility screen	x										
Medical/medicine history	x										
Physical examination	x									x	
INTERVENTIONS:											
Cannabidiol (CBD)		⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷	
Placebo		⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷	
Medicine dispensation		x			x		x		x		
ASSESSMENTS:											
Vital signs: BP, pulse ECG	x x	x		x	x		x		x	x	x
Safety tests: Hematology, Electrolytes, ALAT, Alkaline phosphatases, Bilirubin, CRP, Urine HCG, Opioids, THC	x						x			x	
Proms: FIQ-R, PSQI, EQ5D, ADL-Q, PSEQ, DASS-21, PSS, C-SSRS, SNAQ, FSHSS		x			x		x		x	x	x
Observation-based outcomes: AMPS, Cuff algometry, Muscle fatiguability, Hair Cortisol, Weight/Height, Bioimpedance, Body fat distribution, SENS		x								x	
Compliance			x	x	x	x	x	x	x	x	
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x	x	x	x	x

*Telephone visit
BP Blood pressure, ECG Electrocardiogram, ALAT Alanine Aminotransferase, CRP C-reactive protein, Urine Human Chorionic Gonadotropin, THC Tetrahydrocannabinol, FIQ-R Fibromyalgia Impact Questionnaire Revised, PSQI Pittsburgh Sleep Quality Index, EQ5D EuroQol Group Self-Rated Health Questionnaire, ADL-Q Activities of Daily Living Questionnaire, PSEQ Pain Self-Efficacy Questionnaire, DASS-21 Depression, Anxiety, Stress Scale, PSS Perceived Stress Scale, C-SSRS Columbia-Suicide Severity Rating Scale, SNAQ Simplified Nutritional Appetite Questionnaire, FSHSS Fibromyalgia Sensory Hypersensitivity Scale, AMPS Assessment of Motor and process skills, SENS MOTION® activity measurement system.

Statistical principles

Confidence intervals and P-values

All 95% confidence interval and *P* values will be two sided, and the level of statistical significance for the primary endpoint was *a priori* defined as a *P*-value < 0.05. We will not apply explicit adjustments for multiplicity; instead, we will analyze and interpret the key secondary outcomes using the Hochberg sequential procedure: All the multiple tests for secondary outcomes are performed, and the resultant *P*-values are ordered from largest to smallest on a list (5). If the largest observed *P*-value is less than 0.05, then all the tests are considered statistically significant. Otherwise, if the next largest *P*-value is less than 0.05/2 (0.025), then all the tests except the one with the largest *P*-value are considered significant. If not, and if the third *P*-value in the list is less than 0.05/3 (0.017), then all the tests except those with the largest 2 *P*-values are considered significant. This will be continued until all the comparisons are made. This approach uses progressively more stringent statistical thresholds (i.e., the most stringent one being the Bonferroni threshold).

Adherence and protocol deviations

The treatment period begins with a two-week titration phase, starting with a daily dosage of 10 mg CBD or placebo at week 0. Subsequently the dosage is titrated up by 10 mg every third day until a daily dosage of 50 mg is reached. Dose escalation is based on safety and tolerability, and if the planned dose escalation is not feasible, then delayed increments are allowed. Subjects will be maintained at the highest tolerated dose level, through-out the study. The per-protocol population is represented by participants who have been compliant with the schedule of activities and has ingested the project medication throughout the study at the highest tolerated level. Compliance is monitored by counting the number of non-ingested tablets. Compliance is calculated as % compliance number of tablets ingested from week 2 to week 24/ (number of days week 2-24 x maintenance dose/50 mg) x 100%. In addition, the use of opioids during the intervention period will be considered a protocol deviation.

Analysis populations

Intention-to-treat population

The appropriate use of a randomized trial design enables estimation of the average causal effect. The main analyses in the CANNFIB trial will be based on the Intention to Treat (ITT) population. In the context of a randomized trial, the average causal effect is estimated through statistical analysis, comparing the average outcomes of the treatment group with those of the control group. Randomization in trials helps ensure that observed differences in outcomes between the groups can be attributed to the treatment rather than confounding variables. The ITT population includes all participants according to their randomized treatment assignment, while the average causal effect measures the average impact of a treatment on the outcome of interest in a study population. Thus, the ITT principle asserts the effect of a treatment policy (the pre-planned treatment regimen), rather than the actual treatment given, thus, it is independent of treatment compliance. Accordingly, participants in the CANNFIB trial allocated at baseline will be followed-up, assessed, and analyzed as members of their respective allocated group, regardless of their compliance and adherence to the planned course of treatment, and even independent of withdrawals (i.e., the ITT Population) (6).

Per Protocol Population

The Per Protocol (PP) population is the subset of participants in the CANNFIB trial who strictly adhere to the study protocol without any major protocol violations. In other words, these are participants who have received the assigned interventions as per the study protocol, completed the trial without significant deviations, and have data available for analysis. Although the PP population highly likely correspond to a biased sample, since excluding participants who did not adhere to the protocol may result in a non-randomized selection, we will consider the PP analyses secondary to the main analyses.

Screening data

Published screening data comprises: the number of days recruiting, the number of people screened, the number of participants included, the number of participants screened but not included, and the reason for screen failure.

Eligibility

The following inclusion criteria were applied:

- Informed consent obtained
- Clinical diagnosis of fibromyalgia according to the American College of Rheumatology (ACR) 1990 criteria
- 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

The following exclusion criteria were applied:

- 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
- 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

Recruitment

The CONSORT flow diagram (Figure 1), includes information about the number of people recruited, screened, eligible, consented, randomized, allocated to treatment, withdrawal from treatment and lost to follow-up from baseline to week 36.

Withdrawals and follow-up

The CONSORT flow diagram (Figure 1) displays the number of participants lost to follow-up for the following time points; week 4 visit, week 12 visit, week 20 visit, week 24 visit (primary endpoint assessment), and week 36 visit. The reason for loss to follow-up will be reported as either due to adverse event or due to other reasons. The level of withdrawal will be categorized as withdrawal from the intervention, withdrawal from follow-up, or complete withdrawal.

Baseline characteristics

Baseline characteristics for each treatment arm will be summarized to visualize whether relevant demographic, pain-related, and other relevant characteristics appear balanced across the two groups. These data will be presented in the primary manuscript as shown in Table 1. Categorical data will be described using numbers and percentages. Normally distributed continuous data will be described using means and standard deviations (SDs), whereas continuous data that appear skewed will be described using medians and interquartile ranges.

Analysis

Outcome measures

A clinical trial's endpoints measure the outcomes in the trial. The following outcomes are applied in this study assessed 24 weeks from baseline.

Primary endpoint

Change in the pain intensity subscale of the Fibromyalgia Impact Questionnaire Revised (FIQ-R) from baseline to week 24.

Key secondary outcomes

Changes from baseline to week 24

- Sleep quality measured with the Pittsburgh Sleep Quality Index, total score of overall sleep quality. Scores are ranging from 0 to 21, with lower scores indicating better sleep quality and higher scores indicating worse sleep quality.
- Sleep duration measured with the Pittsburgh Sleep Quality Index, sleep duration domain, with number of hours of actual sleep during the night.
- Objectively measured sleep duration with number of minutes of nightly rest, measured with the Sens triaxial accelerometer device; MOTION® activity and rest measurement system.
- Objectively measured sleep patterns measured with the Sens triaxial accelerometer device; MOTION® activity and rest measurement system, in which movements during the night the number of times getting up during the night are indicated.
- Activities of daily living (ADL) measured with the Assessment of Motor and Process skills (AMPS) test, which is a performance-based, standardized evaluation of the individual's ability to perform and complete activities of daily living. The measure is based on 16 ADL motor skills and 20 ADL process skills. The obtained raw scores are transformed by a many-faceted Rasch-based computer-scoring program to provide 1 linear motor ability measure and 1 process ability measures expressed in logits (log-odds probability units) adjusted for rater severity as well as ADL task and skill item difficulty.

Activities of daily living is also measured with the Activities of Daily Living Questionnaire, in which the obtained raw scores are also transformed by the Rasch -based scoring program to yield an ability measure expressed in logits. For all ADL measures a higher ADL level, is indicated by a higher logits score.

- Health-Related Quality of Life measured with the EuroQol Self-Rated Health Questionnaire, developed by the EuroQual group and international network of multidisciplinary researchers. The scores range from 0 -100, with 0 indicating the worst possible health condition and 100 indicating the best possible health condition.
- Energy level measured with the Energy level subscale of the Fibromyalgia Impact Questionnaire Revised (FIQ-R).

Outcome definitions

The primary endpoint is the change in pain intensity outcome, measured with the 0-10 pain numeric rating scale, from the Fibromyalgia Impact Questionnaire Revised. The minimum value is 0, which is the best outcome, indicating no pain. The maximum value is 10, which is the worst outcome, indicating the worst possible pain. The primary outcome measure is change in pain intensity from baseline through week 4, 12, 20 to 24 weeks of treatment, with a subsequent 12-week follow-up measurement (week 36), using the level of pain item from the FIQR (measures the average pain the last seven days), on an 11-point rating scale (ranging from 0 = “no pain” to 10 = “unbearable pain”). The week 24 assessment is the primary timepoint of interest.

Key secondary outcome measures assessing change from baseline through week 4, 12, 20 to 24 weeks of treatment, with the 24-week assessment being of primary interest and with a subsequent 12-week follow-up measurement (week 36), are the following:

- Change in sleep quality: assessed by the PSQI subjective sleep quality domain
- Change in sleep duration: assessed by the PSQI, sleep duration domain
- objectively measured sleep duration: assessed by the triaxial accelerometer device SENS MOTION®

- objectively measured sleep patterns: assessed by the triaxial accelerometer device SENS MOTION®
- Change in activities of daily living: assessed by AMPS ADL motor and ADL process ability measures, and ADL-Q total
- Change in Quality of life: assessed by the EQ5D total
- Change in energy level: assessed by the FIQ-R energy subscale

Finally, another secondary objective is to investigate the number of responders in both treatment groups. The following two responder categories are defined:

- Number of responders with 30 % improvement of the primary outcome
- Number of responders with 50 % improvement of the primary outcome

Analysis methods

The pre-specified efficacy analyses are based on the ITT population, which include all participants randomized and assessed at baseline. By applying repeated measures, mixed effects models for the continuous outcome measures, we assume that missingness (among the outcomes), is independent of unobserved measurements but dependent on the observed measurements i.e., assuming that data is *'Missing At Random' (MAR)*. Reasonably valid estimates of treatment effects can be obtained using mixed models, even when the missing values are not completely random and additional methods for handling missing data, such as multiple imputation, are generally not required (7).

Our main analyses estimate between group differences for the continuous outcomes after 24 weeks of treatment for primary and key secondary outcomes. Repeated measurements at week 0, 4, 12, 20, 24 and the (12-week) follow-up at 36 weeks from baseline, will be analyzed based on linear mixed-effects models. All between-groups differences will be adjusted for baseline level to reduce random variation. The primary statistical model consists of fixed effect factors for design variables and random effects for patients. Fixed effects factors define the expected values of the observations, and random effects define the variance and covariances of the observations: Group, Stratification variable 1 (sex), Stratification variable 2 (age group), and Stratification

variable 3 (severe pain intensity). Observations are made at 6 timepoints for the primary outcome measure (at baseline, 4, 12, 20, 24 and 36 weeks from baseline). Basically, there are two fixed-effect factors: group, time, and the interaction between as well as the three stratifying factors. Random effects result from variation between and within participants. While observations on different participants will be assumed to be independent, we anticipate that measures on the same patient at different times are correlated, with measures taken closely together in time being more highly correlated than measures taken more apart in time (8).

Secondarily an analysis of number of responders (dichotomous outcomes) in the two groups will be carried out. A responder was defined as a participant who reports a more than one FIQ-R unit, 30%, and 50% improvement in pain after 24 weeks of treatment with either CBD or placebo. For these dichotomous outcomes, we will calculate the Risk Ratio (RR) with 95 % CI comparing the two groups. For subsequent ease of interpretation, the RR values might be converted into Risk Differences (RD) and Number Needed to Treat (RD).

Missing Data

Repeated measure using mixed-effects models is based on the ITT population handle missing data indirectly, statistically modeled using repeated-measures linear mixed models (see below). These models will be valid if data are Missing at Random (MAR): *"Any systematic difference between the missing values and the observed values can be explained by differences in the observed data"* (7). Contrasts between groups will be estimated on least squares means derived from the mixed linear models (i.e., primary contrast at 24 weeks form baseline). The main analyses for the dichotomous outcomes will be based on a simple, single-step non-responder imputation in the case of any missing binary outcomes after 24 weeks.

Sensitivity analyses will be performed subsequently to confirm the robustness of the findings, including the following:

- Non-responder imputation: use of a simple single imputation technique where the baseline observation is caried forward. This approach is potentially informative if even if data are Missing Not At Random (MNAR) (9, 10)

- ‘Per Protocol’ population: defined as participants who have been compliant with the schedule of activities and has ingested the project medication throughout the study at the highest tolerated level.

Robustness is a concept that refers to the sensitivity of the overall conclusions to various limitations of the data, assumptions, and analytic approaches to data analysis. Robustness implies that the treatment effect and primary conclusion of the CANNFIB trial is not substantially affected when analyses are carried out, based on alternative assumption or analytic approaches (11).

Harms

Data on adverse events (AE) are collected at all visits up to 36 weeks from baseline. The participants are interviewed about any adverse events occurring during the trial. We will provide information about the severity of the adverse event, and the action taken with regards to the AE i.e., whether any concomitant medication was taken, dose reduction or whether the study drug was paused, discontinued or if other actions was taken. The study physicians assess whether the AE is expected and possible relation to the study drug, based on the Summary of Product Characterizing for CBD as a reference document. The Common Terminology Criteria for Adverse Events (CTCAE version 5.0 will be used as the reference document for graduation the severity of the AE and whether the AE is a Serious Adverse Event (SAE). Harms observed in 5% or more in the study population are reported in this study. Based on the ITT population, the following safety data will be summarized in the final analysis report:

- All adverse events are summarized with a breakdown of severity categories (mild, moderate, severe, and serios), for both treatment arms
- The number and percentages of participants who withdraw from the intervention because of adverse events are reported for both treatment arms.

Statistical software

All analyses will be performed using the statistical software SAS version 9.4 (SAS Institute, Cary, NC, USA).

Figures and Tables Outline

Figure 1. Trial Profile: Patient Flow Throughout the Final Trial

Table 1. Baseline Characteristics for the Intention-To-Treat Population

Table 2. Primary and Key Secondary outcomes at 24 weeks from Baseline in the ITT Population

Figure 2a. The average trajectory in each group for the Pain Intensity (Average pain during the last 7 days) over time from baseline (week 0) to endpoint (week 24) and follow-up (week 36)

Figure 2b. Scatterplot of the individual values of after vs baseline in pain intensity in the intervention group and placebo group from before (at baseline) and after the intervention (at week 24).

Figure 3. Forest plot displaying change from baseline at week 24 in Primary and Key Secondary outcomes using the Standardized mean difference with 95% confidence interval.

Table 3. Harms: Adverse Events in Total and observed in at least 5% of the ITT population.

Appendix Table 2a. Primary and Key Secondary Outcomes at 24 weeks from Baseline, based on the ITT population where missing data is replaced used a single-step non-responder imputation technique for continuous outcomes.

Appendix Table 2b. Primary and Key Secondary Outcomes at 24 weeks from Baseline, based on the Per Protocol population (Repeated Measures Mixed Effects Models)

Figure 1 Trial Profile: Patient flow throughout the trial

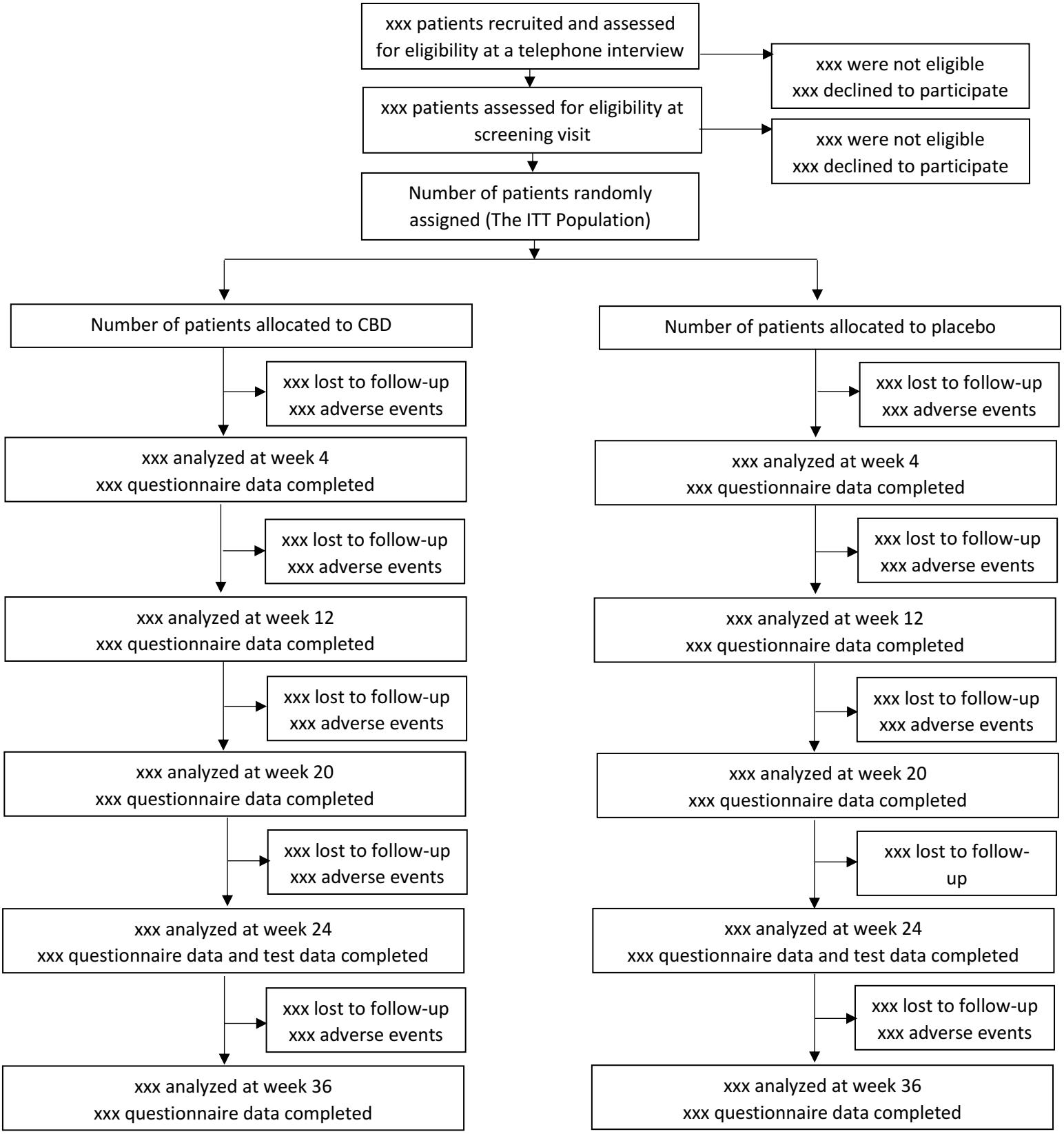

Table 1. Baseline Characteristics for the Intention-To-Treat Population

Variables	CBD	Placebo	Total
Age, years			
Body Mass Index kg/m^2			
Duration of chronic pain in months			
Tender point count, number			
Pain medication:			
– Weak analgesics (Paracetamol/NSAIDs), n (%)			
– Secondary analgesics (Antidepressants/Anticonvulsants), n (%)			
Expecting a positive effect of the study drug, n (%)			
Marital status:			
– Married / cohabiting, n (%)			
Education:			
- Secondary school (9^{th} or 10^{th} grade), n (%)			
- High school, n (%)			
- Bachelor's / Master's degree, n (%)			
Occupation:			
- Working full time, number (%)			
- Working part time with social benefit (Flex job), n (%)			
- Other social transfer income, n (%)			
- Disability pension, n (%)			
- On sick leave, n (%)			
- Pending social welfare application, n (%)			
Primary and Key Secondary Outcomes			
Pain intensity, average last seven days, FIQ NRS 0-10			
Sleep quality, PSQI 0-3			
Sleep duration, PSQI 0-3			
Observed sleep duration SENS, number of minutes			
Observed sleeping patterns, SENS number of awakenings			
Performance-based activities of daily living, AMPS ADL motor ability, Logits			
Performance-based activities of daily living, AMPS ADL process ability, Logits			
Self-reported activities of daily living, ADLQ, Logits			
Quality of life, EQ5D global VAS 0-100			
Energy, FIQ NRS 0-10			

Table 2. Change in Primary and Key secondary endpoints at 24 Weeks from Baseline based on the ITT population (Repeated Measures Mixed Effects Models)

	Change from baseline after 24 weeks of treatment (95% CI)		Difference between groups (95% CI)	P-value
Primary Outcome:	**CBD**	**Placebo**		
Pain intensity, average last seven days, FIQ NRS 0-10				
Key Secondary Outcomes:				
Sleep quality, PSQI 0-3				
Sleep duration, PSQI 0-3				
Observed sleep duration SENS, number of minutes				
Observed sleeping patterns, SENS number of awakenings				
Performance-based activities of daily living, AMPS ADL motor ability, Logits				
Performance-based activities of daily living, AMPS ADL process ability, Logits				
Self-reported activities of daily living, ADLQ, Logits				
Quality of life, EQ5D global VAS 0-100				
Energy, FIQ NRS 0-10				
Responder indices:				
> 1 unit improvement in FIQ-R pain, n (%)				
≥ 30 % improvement in FIQ-R pain, n (%)				
≥ 50 % improvement in FIQ-R pain, n (%)				

Figure 2a. The trajectory for the Pain Intensity (Average pain during the last 7 days) over time from baseline (week 0) to endpoint (week 24) and follow-up (week 36)

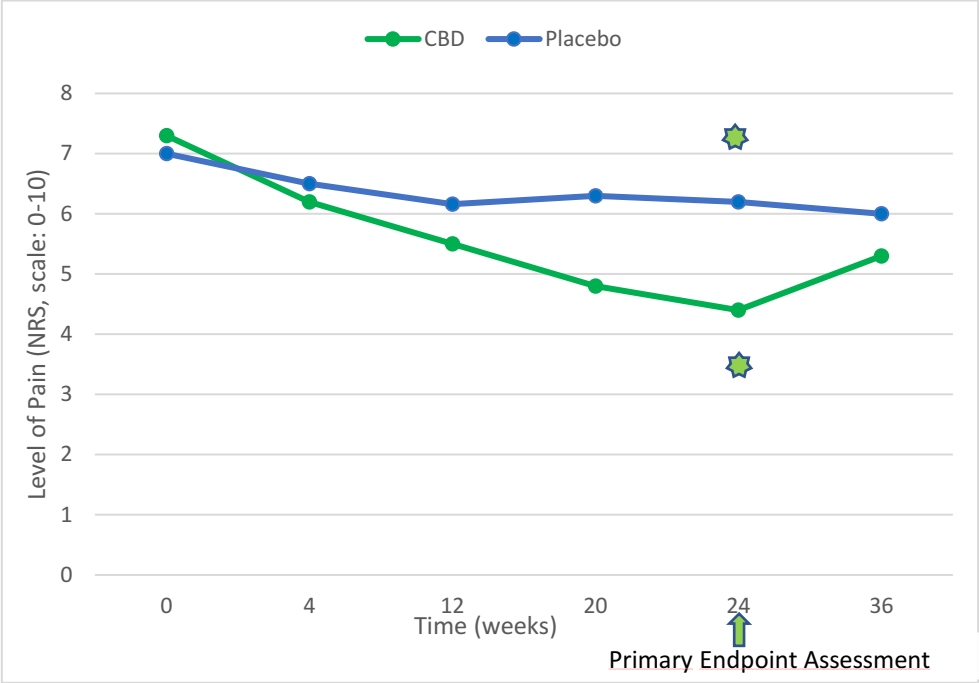

Figure 2a. Scatterplot of the individual values of level of pain intensity in the intervention group and placebo group from before (at baseline) and after the intervention (at week 24).

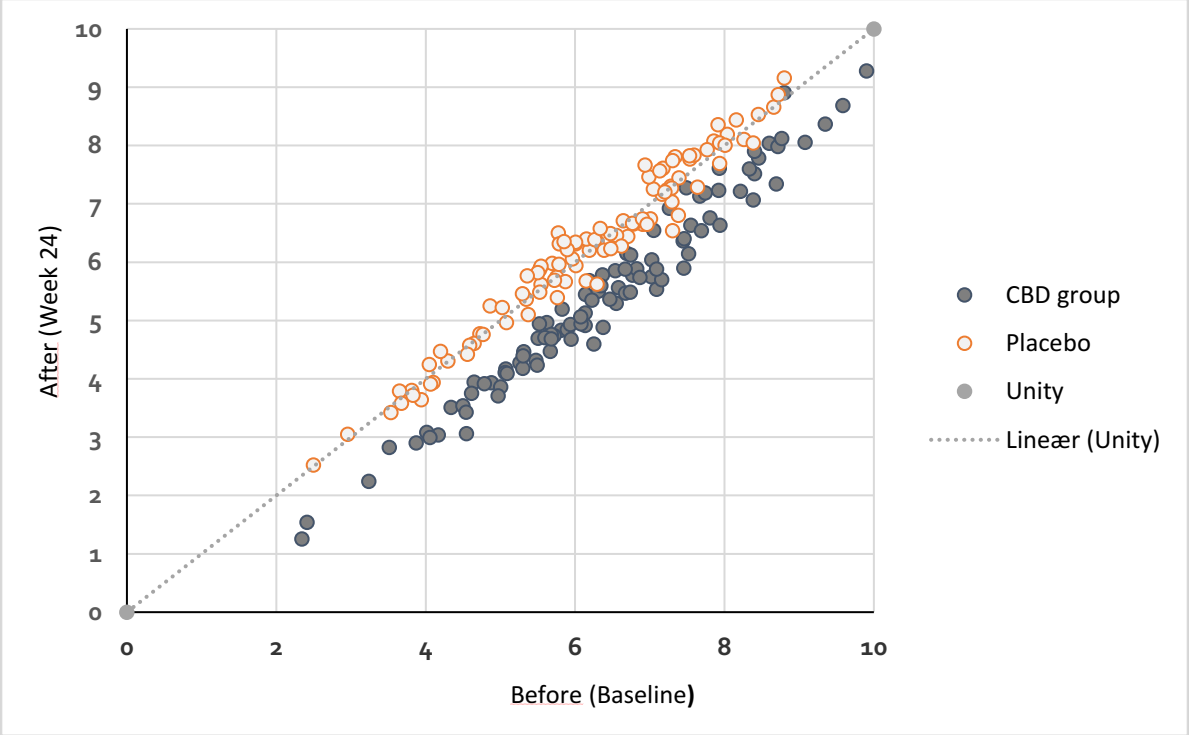

Figure 3. Forest plot of standardized mean differences from baseline to week 24 in Primary and Key Secondary outcomes.

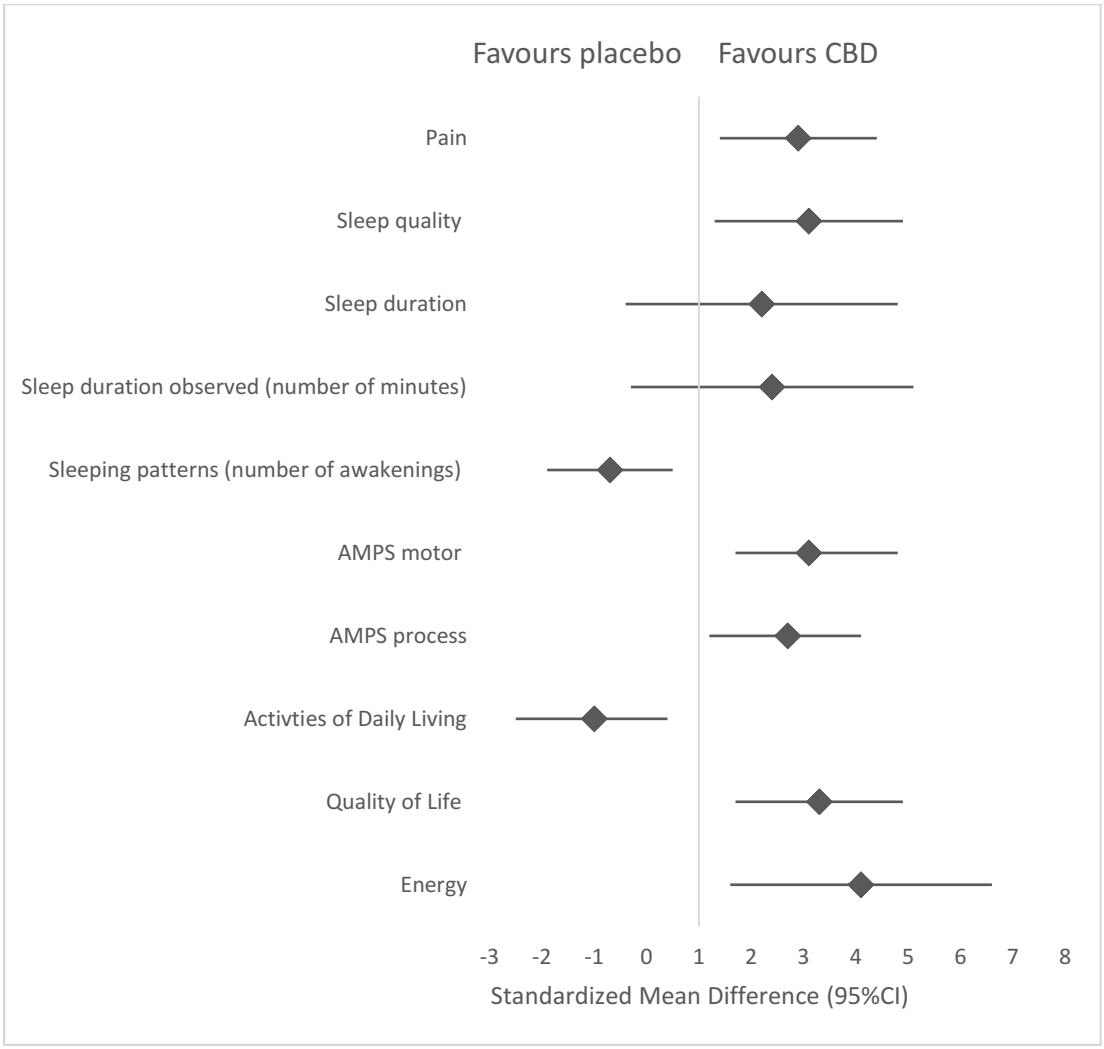

Table 3. Harms: Adverse Events in Total and observed in at least 5% ITT population up to 36 weeks from baseline

Exposure time, patient weeks	**Total**	**CBD**	**Placebo**
AE n patients (%) AE n events (rate per patient week) AE mild, n patients (%) AE moderate, n patients (%) AE severe, n patients (%) Withdrawals due to AE, n (%) SAE, n (%) Deaths, n patients (%)			
Observed AEs in at least 5 % of the ITT population			
Central nervous System • Dizziness (n) • Headaches/migraines (n) • Sensory disturbances (n) Psychological/cognitive • Depressed mood (n) • Anxiety/distress (n) Cardiac system • Palpitations (n) • Hot flashes (n) Gastrointestinal system • Nausea/vomiting (n) • Diarrhea (n) • Constipation (n) • Stomach pain (n) • Increased appetite (n) • Decreased appetite (n) Skin and mucus membranes • Dryness of mouth/throat (n) • Hair loss (n) • Itchy skin(n) • Rash (n) Infections • Covid-19 infection (n) • Common cold (n) • Influenza (n) • Gastroenteritis (n) Musculoskeletal system • Worsening in pain (n) General events • Worsening in fatigue (n) • Worsening in sleep disturbances (n)			

Appendix Sensitivity analyses

Appendix Table 2a. Change in Primary and Key Secondary Outcomes at 24 weeks from Baseline, based on the ITT population, where missing data is replaced using a single-step non-responder imputation technique for continuous outcomes

	CBD	Placebo	Difference (95% CI)	P-value
Primary Outcome:				
Pain intensity, FIQ NRS 0-10				
Key Secondary Outcomes:				
Sleep quality, PSQI 0-3				
Sleep duration, PSQI 0-3				
Observed sleep duration (SENS)				
Observed sleep patterns (SENS)				
Activities of daily living				
- Performance-based ADL AMPS motor, logits				
- Performance-based ADL AMPS process, logits				
- ADL-Q, logits				
Quality of life: EQ5D global 0-100				
Level of energy, FIQ NRS 0-10				

Appendix Table 2b. Change in Primary and Key Secondary Outcomes at 24 weeks from Baseline, based on the Per Protocol population (Repeated Measures Mixed Effects Models)

Primary Outcome:	CBD	Placebo	Difference (95% CI)	P-value
Pain intensity, FIQ NRS 0-10				
Key Secondary Outcomes:				
Sleep quality, PSQI 0-3				
Sleep duration, PSQI 0-3				
Observed sleep duration (SENS)				
Observed sleep patterns (SENS)				
Activities of daily living				
- Performance-based ADL AMPS motor, logits				
- Performance-based ADL AMPS process, logits				
- ADL-Q, logits				
Quality of life: EQ5D global 0-100				
Level of energy, FIQ NRS 0-10				

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