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ARTICLE

Pharmacokinetics and pharmacodynamics of cannabis-based medicine in a patient population included in a randomized, placebo-controlled, clinical trial

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Abstract

Information on the pharmacokinetics (PK) and pharmacodynamics (PD) of orally administered cannabis-based medicine (CBM) in capsule formulation in patient populations is sparse. In this exploratory study, we aimed to evaluate the PK and PD in a probable steady state of CBM in neuropathic pain and spasticity in a population of patients with multiple sclerosis (MS). Of 134 patients participating in a randomized, double-blinded, placebo-controlled, trial, 23 patients with MS (17 female) mean age 52 years (range 21–67) were enrolled in this substudy. They received oral capsules containing Δ^9-tetrahydrocannabinol (THC, $n=4$), cannabidiol (CBD, $n=6$), a combination (THC&CBD, $n=4$), or placebo ($n=9$). Maximum doses were 22.5 mg (THC) and 45 mg (CBD) a day divided into three administrations. PD parameters were evaluated for pain and spasticity. Blood samples were analyzed using an ultra-high-performance liquid chromatography–tandem mass spectrometer after protein precipitation and phospholipid removal. PK parameters were estimated using computerized modeling. The variation in daily dose and PK between individuals was considerable in a steady state, yet comparable with previous reports from healthy controls. Based on a simulation of the best model, the estimated PK parameters (mean) for THC (5 mg) were C_{max} 1.21 ng/mL, T_{max} 2.68 h, and half-life 2.75 h, and for CBD (10 mg) were C_{max} 2.67 ng/mL, T_{max} 0.10 h, and half-life 4.95 h, respectively. No effect was found on the PD parameters, but the placebo response was considerable. More immediate adverse events were registered in the active treatment groups compared with the placebo group.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

In recent decades, the demand for cannabis-based medicine (CBM) has increased. The existing description of the pharmacokinetics (PK), as well as the pharmacodynamics, of cannabinoids is primarily based on inhaled whole-plant cannabis in a healthy (male) population.

WHAT QUESTION DID THIS STUDY ADDRESS?

The PK of orally administered CBM in capsule formulation in a real patient population in an expected steady state is explored.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The PK of CBM in a multiple sclerosis patient population shows high variability when orally administered, and bioavailability was restricted. Low concentrations of cannabinoids were measured using an ultra-high-performance liquid chromatography–tandem mass spectrometer after protein precipitation and phospholipid removal. A computerized model made it possible to explore and describe the PK of Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Treatment with CBM was associated with adverse events.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

When administering CBM in oral capsule formulation, one should be aware of the low bioavailability and the great variation in blood concentration between individuals, and therefore an individualized dosing schedule is recommended.

INTRODUCTION

Patients with the demyelinating disease multiple sclerosis (MS) often suffer from neuropathic pain and spasticity.[1] The possibility of using cannabis-based medicine (CBM) for symptom relief in MS has been debated widely in the last couple of decades. The pain modulation of cannabinoids is complex and involves several simultaneous targets, including the modulation of neural conduction of pain signals via cannabinoid receptor type 1 (CB_1), activation of descending inhibitory pain pathways, and, possibly, modulation of chronic inflammatory processes via cannabinoid receptor type 2 (CB_2).[2,3] Cannabinoids have been extensively reviewed.[4,5] The well-known and potent psychoactive phytocannabinoid Δ^9-tetrahydrocannabinol (THC)[6] and its affinity for CB_1 is believed to mediate an anti-spastic therapeutic effect.[7] Clinical studies have shown an effect of THC-containing products on spasticity in MS.[8–10] The non-psychotropic cannabinoid cannabidiol (CBD) and the CB_2 receptor seem to play a less important role.[11] In preclinical studies, CBD has shown interesting anti-inflammatory and neuroprotective properties; however, the evidence of effects in human studies is less well documented.[12–14]

In addition to a sedative effect, performance, cognitive, and psychomotor impairment are well-described pharmacodynamic (PD) effects of THC (reviewed by Lucas et al.[15]). Less is known about the efficacy on neuropathic pain, and studies investigating PK/PD and efficacy in a placebo-controlled setting are few[16] and have been desired.[17]

Oral-formulated THC and CBD have poor bioavailability due to hepatic first-pass metabolism, primarily via hepatic P450 isozymes (CYP3A4, CYP2C9, CYP2C19).[18,19] Hydroxylation of THC results in the active metabolite 11-hydroxy-tetrahydrocannabinol (THC-OH) that further oxidates to 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (THC-COOH), and is finally excreted as THC-COOH-glucuronide.[18,20,21] Due to high lipophilicity, THC is readily distributed to the brain and other highly perfused tissues.[20] Cannabinoids' elimination has been reported to be biphasic, with an initial half-life of about 4 h.[22] Less-perfused fatty tissues accumulate THC and release it slowly. Therefore, excretion may be prolonged for days to weeks. Due to the biphasic pattern and accumulation, the true half-life is difficult to calculate.[21] The PK and PD properties of THC and CBD have been subject to extensive review by, for example, Grotenhermen, Huestis, and Millar et al.[21,23,24] Most studies were based on a few patients, often recreational, healthy (male) users, with either a single dose or heavy use of inhaled cannabis.[25–32] The need for investigation of cannabinoids PK/PD in a patient population has been addressed,[5,15,17] since the metabolism of CBM may be different in patients compared to healthy

controls. The market for CBM is fast-growing. However, since the description of medical-grade cannabinoid products/whole-plant molecules is so sparsely described, it is important to clearly define standardization and PK/PD characteristics in a controlled setting.

The present study aimed to explore the PK/PD of oral CBM in a steady-state condition. Capsules containing either THC, CBD, or a combination of THC&CBD were orally administered in a population of patients with MS in a placebo-controlled design. Blood samples were analyzed by ultra-high-performance liquid chromatography–tandem mass spectrometer (UHPLC–MS/MS) and the PK parameters were evaluated using descriptive statistics and a computer software model.

METHODS

Study design

The study followed the Helsinki Declaration Guidelines and was approved by the Danish Medicine Agency (ID2018071161), The Science Ethics Committee (VEK nr 1-10-72-291-18), and Central Denmark Region's internal notification 1-16-02-582-18. It was conducted at the Department of Neurology, Aarhus University Hospital, Denmark during the period 2019–2021. The study was registered with the EU Clinical Trials Register EudraCT 2018-002315-98. Good Clinical Practice (GCP) guidelines were followed, and the project was monitored by the GCP units. The study followed the CONSORT checklist for randomized controlled trials. The design and randomization of the study have been described previously.[33] The results from the main study evaluating the efficacy of CBM on neuropathic pain and spasticity has been published recently.[34]

Study subjects

The patients included in the present substudy were a subgroup of patients enrolled in the national, randomized, placebo-controlled, clinical trial investigating the effect of CBM on pain and spasticity in MS or spinal cord injury (SCI) (MedicalCannabisMSSCI2018) described by Hansen et al.[33,34] Inclusion criteria for the national trial were a mean pain and/or spasticity intensity >3 on a 0–10 numeric rating scale (NRS), a stable disease, age >18 years, and informed consent available. Exclusion criteria were, among others: renal and liver insufficiency, competitive pain diseases, opioid treatment, previous or current addiction to alcohol/medication/drugs, current recreational cannabis use or use within the last 3 months, medical cannabis prescribed within 3 months, or positive urine screening (Ferle NanoSticka® drug test). Study patients were randomly allocated to one of four treatment lines: THC, CBD, THC&CBD, or placebo. The national study consisted of a baseline (1 week before randomization), followed by a 3-week titration phase, 3 weeks in the steady state, and 1 week of phasing out. All patients allocated to the substudy were diagnosed with MS and admitted for the additional blood samples in a steady state. A steady state is defined as when absorption equals clearance and occurs approximately after 4–5 half-lives. In the present study, we expected a probable steady-state condition in treatment weeks 5–6. A supplementary consent for the substudy was obtained before randomization. For the substudy, patients had to be self-reliant (wheelchairs and walking aids were accepted).

Randomization

For the national trial, randomization was performed centrally at Glostrup Pharmacy (Denmark) which also manufactured, packaged, and labeled the project medicine. Block randomization was used in a 1:1:1:1 allocation ratio. Study medication was oral capsules containing either THC (2.5 mg/capsule), CBD (5 mg/capsule), THC&CBD (2.5 + 5 mg/capsule), or placebo. Maximum daily doses were nine capsules (maximum THC = 22.5 mg and CBD = 45 mg) divided into three daily doses. THC was naturally extracted from the *Cannabis sativa* plant and CBD was synthetically produced. Patients, investigators, and analysts were blinded (after blood sample analysis the blinding ceased).

Intervention

For the present substudy, patients were admitted to the Department of Neurology, Aarhus University Hospital for approximately 25 h when in a steady-state condition (treatment weeks 5–6) They were admitted in the morning and discharged the following day. On admission, they were drug fasting (for the project medicine) from the night before. A peripheral venous catheter (PVC) was placed in the median cubital vein on the non-dominant hand (if possible). To start the flow in the PVC a 2 mL syringe was used followed by a vacuette adapted to the PVC. The blood samples were collected in 4 mL gray-top vacutainer collection tubes containing sodium fluoride and oxalate. To increase the uptake,[35] the project medicine was taken with a meal provided by the hospital (not standardized). There was unlimited access to beverages (non-alcoholic), and no restrictions regarding caffeine. Paracetamol was allowed

as an "escape drug", and the study drug was used as an "add-on" to patients' ongoing treatment.

Study assessments

Pain, spasticity, and adverse events (AEs) were registered for 24 h. Blood samples were taken before the first dose on the day of admission (0 h) and then at 1, 2, 4, 6, 8, 10, 12, 15, 18, 21, and 24 h after the first dose. Dosing times were up to three times a day starting with timepoint 0 h. Whole-blood samples were kept at room temperature until patient discharge, then in a refrigerator (5°C) for up to 2 days before being frozen and stored at −80°C in the Department of Forensic Medicine, Aarhus University until analysis. The whole-blood samples were analyzed for THC, THC-OH, THC-COOH, Δ^9-tetrahydrocannabinolic acid A (THCA-A), CBD, and cannabinol (CBN) after extraction using protein precipitation and phospholipid removal by filtration as described by Sørensen and Hasselstrøm.[36] Subsequently, the samples belonging to the treatment groups were re-analyzed by a modified version of the same method with increased sensitivity (Sørensen and Hasselstrøm). Briefly, 150 µL whole blood was transferred to a 2 mL 96-well plate. Then, 15 µL 300 mM ascorbic acid solution, 150 µL methanol (MeOH), and 150 µL standard isotope-labeled internal standard (SIL-IS) solution were added in succession to each well. The plate was shaken at 1650 rpm for 30 s after each reagent addition and a standing time of 5 min was allowed after the addition of MeOH and SIL-IS. Finally, 450 µL acetonitrile (MeCN) was dispensed into the wells, and mixing was performed by six pipette aspiration/dispense cycles using wide-bore tips. After a standing time of 10 min, the plate was centrifuged at 5000***g*** for 5 min. A 600 µL volume of the supernatant was transferred to an ultrafiltration filter plate fitted with a 30-kDa Omega membrane (Pall Corporation, Ann Arbor, MI, USA) and centrifuged at 2000***g*** for 5 min. The filtrate was mixed with 10 µL formic acid (FA) and transferred to an Ostro plate (Waters, Milford, MA, USA). The plate had been previously washed with 500 µL MeCN and dried for at least 5 min under a full vacuum (40 kPa for 5 min). A volume of 500 µL of the filtrate was transferred to a glass-lined multi-well plate and the filtrate was evaporated to bare dryness under a stream of hot 40°C nitrogen. The residues were redissolved in 100 µL 70% MeCN acidified with 0.05% FA. Finally, the plate was sealed with a pierceable foil. The analysis was performed on an UHPLC–MS–MS system (Excion UHPLC coupled to a QTRAP 6500+; Sciex, Ontario, Canada). The lower limits of quantification were 0.025, 0.1, 0.1, 0.03, 0.01, and 0.03 ng/mL for THC, THC-COOH, THC-OH, CBD, THCA-A, and CBN, respectively. The relative reproducibility standard deviations (i.e., the day-to-day variation of independent analytical results) were in the ranges of 9%–12% and 6%–8% at the individual cannabinoid concentrations of 0.2 and 20 ng/mL, respectively. Patients answered questionnaires at the time for each blood sample concerning pain intensity, spasticity, pain relief, and AEs. Pain intensity and spasticity were recorded on an 11-point NRS (0 = no pain/spasticity to 10 = worst possible pain/spasticity). Pain relief was recorded on a five-point categorical scale (0 = no pain relief to 4 = complete relief). Pain intensity difference (PID) and spasticity intensity difference (SID) compared the baseline value on the day of admission ($t = 0$) with pain and spasticity at given timepoints during the admission (NRS 0–10). A small or negative value for PID or SID represents no effect or worsening symptoms, whereas a positive value represents ease of symptoms. AEs were registered in a questionnaire (NRS 0–10): to what extent do you experience nausea, dizziness, drowsiness, headache, confusion, affected vision and hearing impressions, hunger, affected ability to control movements, and affected concentration? After at least 24-h admission, a global evaluation/categorical measure of the study medicine was performed by both patient and investigator on a five-point verbal rating scale (1 = poor, 2 = fair, 3 = good, 4 = very good, 5 = excellent). All surveys were completed in Danish.

Adverse events and safety

A thorough registration of any potential AEs was conducted during the main study of this project and has been published elsewhere.[33,34] In addition, AEs were registered simultaneously with the blood samples during admission in this substudy.

Data presentation and statistical analysis

No power calculation was made, as the substudy was exploratory. Study data were collected and managed using REDCap® (Research Electronic Data Capture) tool hosted at Aarhus University.[37,38] Whole-blood extraction and analysis were performed at the Department of Forensic Medicines, Aarhus University, Denmark. Patient demographics and blood samples are presented using descriptive statistics. An unpaired *t*-test was used for the evaluation of pain relief and global evaluation between each active treatment group compared with placebo. A one-way analysis of variance (one-way ANOVA) was used to compare outcomes between groups. A p-value <0.05 was considered statistically significant. The concentration of THC, CBD, THC-COOH, and THC-OH were plotted against time. Pearson correlation was used to calculate

the correlation between the metabolites THC or CBD and PID/SID. Analyses were conducted in STATA version 17.0 and GraphPad Prism 9.3.1.

The PK modeling and estimation were performed at the Section for Drug Abuse Research, Department of Forensic Sciences, Division of Laboratory Medicine, Oslo University Hospital, Norway. The individual data with multiple (up to three) administrations without washout were used. The data corresponding to dose = 0 ($n = 2$) in the morning were not used due to presence of the drugs in the blood due to prior unknown dose and administration time. The population PK parameters were estimated using Monolix (version 2021R2; Lixoft, Antony, France) in combination with the R package Rsmlx. For this purpose, the "pkbuild" function of Rsmlx was used to explore the structural PK models included in Monolix's library for oral/extravascular administration and select the most parsimonious model best fitting the data based on the lowest corrected Bayesian Information Criterion (CBIC). This library comprised standard models with first, zero-order, or mixed double absorption, lag, one to three compartments, and linear or Michaelis–Menten elimination kinetics. Goodness-of-fit (GOF; plot and tests of the distribution of population and individual weighted residuals) and potential weaknesses in the model (overparametrization) were checked before selecting the considered best model.[39] Bootstrapping parametric resampling of new 200 datasets, using the Rsmlx function "bootmlx", was applied to the selected best models to reduce the uncertainty of the population parameters.[40,41] The means of the model population parameters resulting from the bootstrapping were used as the final parameters for the selected structural models (Table 2). The original experimental data were later fitted in Monolix by applying these final parameters as initial values and setting the number of iterations to 0 for the stochastic approximation expectation maximization (SAEM) algorithm, and the GOF plots determined (Figure S1). The resulting fitted experimental data were used for calculating the theoretical area under the curve to infinity (AUC_{INF}), maximal concentration (C_{max}), time to C_{max} (T_{max}), and the apparent volume of distribution by non-compartmental analysis with PKanalix (version 2023R1; Lixoft) for each of the doses in the experiment. Half-lives were calculated by dividing 0.693 by the rate of elimination (k_{pop}). The covariate model building (SAMBA method) of Monolix was used to test the possible effect of the available covariates; simultaneous co-administration of CBD or THC, sex, age, and body mass index (BMI). The parameters estimates of the resampled (bootstrapped) 200 datasets were used in Simulx (version 2023R1; Lixoft) to obtain 24-h simulations of single administration for each dose group and drug (Figures S2 and S3). Each simulation group consisted of 20 simulated individuals.

RESULTS

Patients

Due to recruitment difficulties in the randomized trial, only 24 patients were randomized for the substudy. One patient failed admission due to acute minor surgery (not related to the project). Twenty-three (all Caucasian) patients (17 female, 73.9%) mean age 52 years (range 21–67) with MS from the MedicalCannabisMSSCI2018 trial completed the admission. A flowchart showing the allocation is presented in Figure 1.

Fourteen patients were in active treatment with CBM in steady state, and nine were in the placebo group. Patients in the active treatment groups had been on treatment for an average of 36 (range 29–42) days and the daily number of capsules varied from one to nine (one to three daily doses).

Blood samples were evaluated for all patients. No cannabinoids were measured in the placebo group. For the placebo group ($n = 9$) the median age was 57 years (range 21–66 years), the median BMI was 27.3 kg/m^2 (range 19.5–35.1), seven females (77.8%), and capsules a day median 9.0 (range 6–9). The demographics and concomitant medication of all patients on active treatment are presented in Table 1. The maximum dose (3 + 3 + 3 capsules) was only reached by 8/14 patients (57%), which contributed to the apparent variation.

Pharmacokinetics

The summary statistics for the 14 patients are presented in Table S1 (experimental dataset). The concentration curves and time/doses from each patient varied considerably (Figure 2).

Due to the low number of patients and the relatively long intervals between sampling points, in variable multiple doses steady-state design, a computer-generated model for PK parameters was performed. Concentrations of each metabolite from the combined THC&CBD group were added to the THC and CBD groups, respectively, which gave 10 patients in the CBD calculation and 8 patients in the THC calculation.

The best fit for the THC data was achieved by a one-compartment model with zero-order oral absorption, and linear elimination (Table 2). According to the model, the zero-order absorption lasted for about the first 2.67 h after administration, and, from its rate of elimination, a half-life of approximately 2.75 h was estimated. Neither the simultaneous co-administered CBD doses, nor gender, BMI, or age, had a significant effect on THCs' PK parameters, in the original model.

For CBD, the one compartment with linear elimination models and first-order absorption showed a slightly better CBIC, diverging only in 0.11 units, than the same model

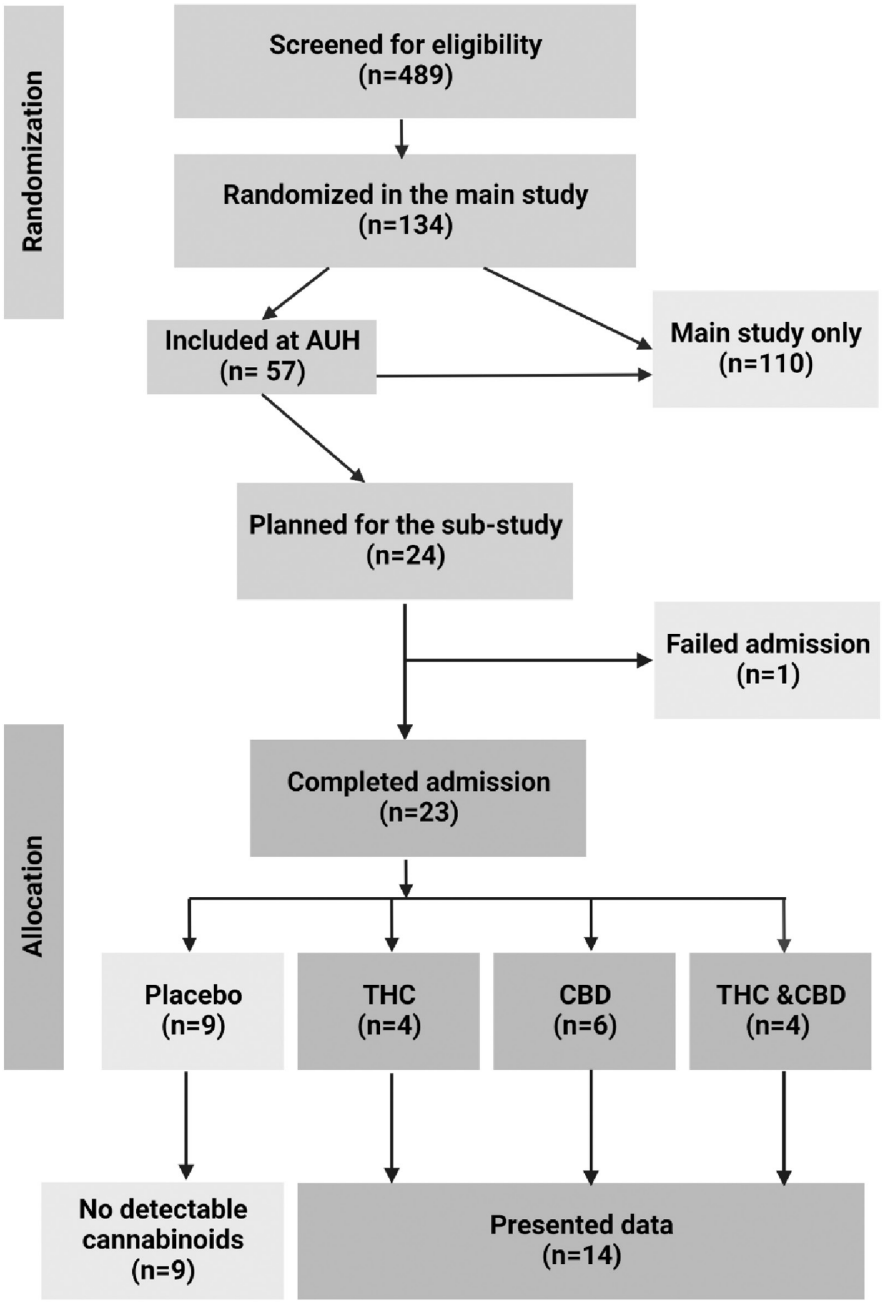

FIGURE 1 Flowchart for the overall trial and the pharmacokinetic substudy. AUH, Aarhus University Hospital; CBD, cannabidiol; THC, Δ^9-tetrahydrocannabinol. Created with Biorender.com.

with zero-order absorption, and therefore was the best model fitting the data. However, its correlation matrix of the population parameter estimates (Fisher Information Matrix) resulted in high max/min eigenvalues, indicating a certain degree of overparameterization, that is, a high correlation between the estimated parameters, consequently resulting in a low confidence in the fitting. Besides, bootstrapping of this model resulted also in a very large, implausible rate of absorption (ka). Consequently, the one-compartment model with zero-order oral absorption and linear elimination was favored and selected (Table 2). The zero-order absorption time of CBD was estimated at 0.07 h, much shorter than for THC. The half-life was estimated at approximately 4.95 h. No effect of co-administration of THC, nor gender, BMI, or age, was found on CBD absorption, distribution, or elimination.

BMI showed a significant effect on the time of the zero-order absorption (Tk0) on the original model. However, the inclusion of this covariate only slightly improved the fitting (BIC from −1034.6 to −1048.6), and the BMI's effect parameter (β_{BMI}) on Tk0 presented a high correlation (about −0.97) with Tk0, considerably increasing the eigenvalues of the correlation matrix of the population parameter estimates (Fisher Information Matrix). These outcomes indicated that BMI did not provide significant information to the model and contributed to its overparameterization. Therefore, this covariate was not included in the model for the subsequent bootstrapping.

TABLE 1 Patient demographics including disease-modifying treatments, anti-spastics, pain medication, and central nervous system stimulants.

Treatment	Patient ID	BMI (kg/m^2)	Capsules morning/midday/evening	Full dose	Concomitant medication use
THC	1	27.5	3+3+3	Yes	Gabapentin, peginterferon beta-1a, paracetamol (p.n.)
THC	15	22.3	2+2+2	No	N/A
THC	17	24.7	2+2+3	No	Modafinil (p.n.), paracetamol (p.n.)
THC	19	21.3	3+3+3	Yes	Baclofen (+ p.n.), duloxetine, fingolimod, gabapentin, tizanidin
CBD	6	24.9	3+3+3	Yes	Citalopram, paracetamol, pregabalin
CBD	7	24.8	3+3+3	Yes	Baclofen, gabapentin
CBD	10	28.1	3+3+3	Yes	Duloxetine, fingolimod, pregabalin
CBD	11	21.1	1+1+2	No	N/A
CBD	13	28.4	0+0+2	No	Fampridine
CBD	16	34.2	3+3+3	Yes	Baclofen, diclofenac 50 (p.n.), paracetamol (p.n.)
THC&CBD	2	27.2	3+3+3	Yes	Baclofen, fingolimod, mirabegron (p.n.), modafinil (p.n), tizanidin
THC&CBD	8	25.9	0+0+1	No	Acetylsalicylic acid/caffeine (p.n.), baclofen, modafinil oxcarbazepine, tolterodin
THC&CBD	12	27.6	1+1+2	No	Fampridine, mirabegron, paracetamol (p.n.)
THC&CBD	22	18.3	3+3+3	Yes	Baclofen, pregabalin, paracetamol (p.n.)

Note: Doses, vitamins, antihypertensive, antidepressants (except those indicated for neuropathic pain), statins, etc. are not listed in the table.

Abbreviations: BMI, body mass index; CBD, cannabidiol; N/A, no concomitant medicine registered; p.n., per necessity; THC, Δ^9-tetrahydrocannabinol.

Based on the fitting of the experimental data to the final model parameters, the T_{max}, C_{max}, AUC to infinite, and the apparent volume of distribution for THC and CBD were calculated (Table 3) for each dose. Both the AUC and C_{max} for both THC and CBD were linearly proportional to the dose, whereas no differences between doses were observed for T_{max} and the apparent volume of distribution.

Pharmacodynamics

The placebo group is included in the presentation of efficacy/PD parameters as a control group.

The PD parameters mean PID and mean SID are presented in Figure S4.

No significant differences were found when comparing the active treatment groups with placebo regarding PID and the sum of PID (SPID). The placebo group had a significantly higher (favorable) SID outcome when compared with both the THC and the CBD group ($p < 0.01$).

Pain relief, patient global evaluation, and investigator global evaluation

No clinically relevant reduction was found in pain relief (PR) (NRS > 2), neither in the active groups nor in the placebo group; however, the placebo response was considerable (Table S2). There was no significant difference between the patient and investigator global evaluation ($p > 0.05$).

Safety and tolerability/adverse events

All AEs reported during the admission were tolerable and mild to moderate. There were no withdrawals due to AEs during the admission. However, the placebo group had a statistically significant (*t*-test placebo vs. all active $p < 0.05$) lower AE profile in all parameters except for nausea, hunger, and headache. When using one-way ANOVA, only nausea did not prove a significant difference between groups ($p = 0.96$). The mean of each reported (predefined) side effect for each group is reported in Figure 3. The fifth graph shows the AEs reported by patients not reaching full dosage ($n = 6$, two from each treatment line, all due to AEs). The most frequent side effect within all the active groups was drowsiness.

DISCUSSION

The present study explored the PK and PD of the two cannabinoids THC and CBD, alone or in combination. THC (natural) and CBD (synthetic) were administered in an oral formulation, in a steady-state, in a real MS patient

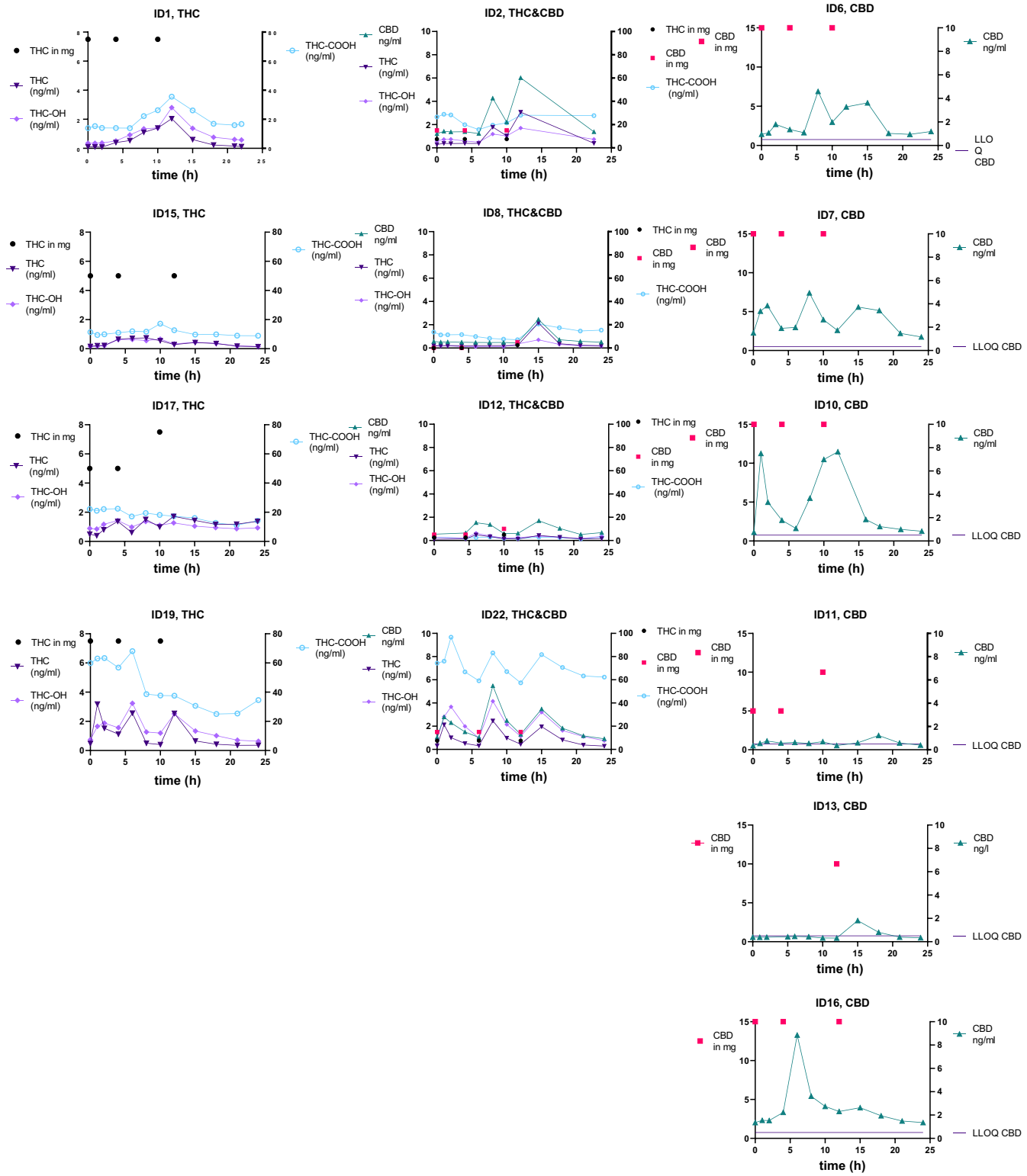

FIGURE 2 Concentration curves of metabolites over time with the administered dose of study medication from the three active treatment groups (THC, THC&CBD, and CBD) during the 24 h in a steady state. Concentration from each patient in the THC group (left), THC&CBD group (center), and CBD group (right). CBD, cannabidiol; LLOQ, lower limit of quantitation; THC, Δ^9-tetrahydrocannabinol; THC-COOH, 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol; THC-OH, 11-hydroxy-tetrahydrocannabinol. Concentration in whole blood (ng/mL). Black circles illustrate time and dose (mg) of THC administration. Red squares illustrate time and dose (mg) of CBD administration. Note the different scales between the groups and the use of two *y*-axes.

TABLE 2 Pharmacokinetic model of Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD).

Parameter	Mean	CI of mean	%CV	Median	25% Percentile	75% Percentile
THC $Tk0_{pop}$	2.67	2.39–2.95	75.6	2.45	1.35	3.85
THC V_{pop}	3545.10	3384.1–3706.1	32.6	3374.49	2800.82	4009.66
THC k_{pop}	0.252	0.24–0.27	37.3	0.23	0.19	0.29
THC ω_{Tk0}	1.71	1.45–1.97	108.6	1.09	0.73	1.74
THC ω_V	0.42	0.39–0.45	54.3	0.43	0.25	0.58
THC ω_k	0.39	0.36–0.43	66.9	0.36	0.147	0.55
THC a	0.0002	0.00019–0.0002	17.0	0.00020	0.00018	0.00022
THC b	0.41	0.40–0.42	17.0	0.40	0.36	0.46
CBD						
CBD $Tk0_{pop}$	0.07	0.03–0.12	401.2	2.64E-06	1.22E-07	8.86E-05
CBD V_{pop}	4559.78	4473–4646.5	13.6	4479.75	4090.42	4905.78
CBD k_{pop}	0.14	0.14–0.14	10.6	0.14	0.13	0.15
CBD ω_{Tk0}	4.01	3.76–4.26	44.6	4.08	2.97	4.93
CBD ω_V	0.15	0.14–0.16	58.2	0.14	0.07	0.22
CBD ω_k	0.095	0.087–0.103	62.7	0.073	0.051	0.130
CBD a	0.00054	0.0005–0.0006	13.8	0.00054	0.00049	0.00056
CBD b	0.43	0.42–0.43	15.3	0.42	0.37	0.47

Note: Means with 95% confidence interval (CI) and coefficient of variation (%CV), and medians with 25%–75% percentiles of the population parameters of the one-compartment model with zero-order oral absorption and linear elimination for Δ-9 tetrahydrocannabinol (THC) and cannabidiol (CBD), as estimated from 200 datasets obtained by resampling (parametric bootstrap). For THC an elimination rate (k) of 0.25 implies a half-life of 2.75 h (half-life = ln2/k). For CBD an elimination rate (k) of 0.14 implies a half-life of 4.95 h. Tk01: time (hours) of the zero-order absorption. V: apparent volume (L) of distribution. k: rate (min^{-1}) of elimination. ω: standard deviation of the random effects of the corresponding parameter. a and b: parameters of the error model.

population. This explorative study succeeded in presenting PK and PD parameters of two cannabinoids, THC and CBD. Even though the cohort was small, it can be considered representative of the background patient group suffering from neuropathic pain and spasticity when it comes to age, disease severity, and sex.

In general, the concentrations of orally administered THC and CBD were low. To accommodate these low concentrations, a reanalysis of the samples with a 16 times higher sensitivity was performed. In addition, software modeling was used to assess the PK parameters of THC and CBD in a multi-dose, steady-state setting. The aim was to derive from the limited experimental data further useful information about the population PK of the administered cannabinoids and their underlying physiological processes. For this purpose, a library of standard PK models was tested, and the most parsimonious structural models selected for each drug based on fitting statistics, as information criteria, and visual guides (GOF graphs). For both drugs, the best fitting model was based on a one-compartment model with concentration-independent zero-order absorption, both of which are quite common in oral administration, and a first-order elimination.

In the present study, we found that T_{max} for THC was about 2.68 h, the absorption time was 2.67 h, and the half-life was 2.75 h. The findings for oral administered THC T_{max} and C_{max} were in accordance with those previously reported by Huestis in the *Handbook of Cannabis*.[20] The half-life here described is shorter than in other studies.[21,24] Elimination of THC can be divided into an initial (approximately 4 h) and a terminal phase (days) with high variabilities.[22] Thus, the short half-life estimated in the present study is most probably due to the short sampling period between doses, corresponding only to the initial elimination phase. The PK parameters from the patient population in this study did not differ substantially from previously reported PK parameters (often healthy volunteers),[21,42] suggesting that the absorption and distribution of THC is not affected by the MS condition.

When evaluating the PK parameters of CBD obtained from the model, we found that it was quickly absorbed (0.07 h) and its half-life was about 5 h. The estimated T_{max} for CBD was faster (0.08–0.11 h) than previously reported (2–4 h),[21] however, and coincident with this finding, the medians of the experimental T_{max} from the summary statistics were much longer (2–5 h; Table S1). The PK of CBD have been previously reviewed by Miller et al.,[24] finding only eight studies investigating CBD alone in humans, and only one reporting the bioavailability. Miller et al.[24] described that the AUC and C_{max} were dose-dependent, and in oral formulation C_{max} was influenced by the fed state. CBD T_{max} occurred between 0 and 5 h, did not seem

TABLE 3 Pharmacokinetic parameters estimated from the model.

Parameter	Dose (mg)	Mean	CI	Geometric mean	%CV	Median	25% Percentile	75% Percentile
THC	2.5	3.23	2.7–3.7	3.17	22.08	2.80	2.80	3.76
AUC_{INF}	5	7.03	6.6–7.5	6.93	18.93	6.98	5.60	8.51
(ng*h/mL)	7.5	10.81	10.5–11.1	10.66	17.57	11.20	8.40	12.19
THC	2.5	0.57	0.50–0.63	0.56	16.36	0.51	0.51	0.64
C_{max}	5	1.21	1.15–1.26	1.20	14.03	1.20	1.02	1.40
(ng/mL)	7.5	1.85	1.81–1.88	1.83	12.96	1.89	1.54	2.03
THC	2.5	2.68	2.68–2.69	2.68	0.25	2.68	2.68	2.69
T_{max}	5	2.68	2.67–2.68	2.68	0.28	2.68	2.67	2.68
(h)	7.5	2.67	2.67–2.68	2.67	0.44	2.68	2.67	2.68
THC	2.5	3173	2753–3594	3126	22.08	3545	2709	3545
$Volume_{dist}$	5	2906	2728–3084	2864	18.93	2842	2331	3545
(L)	7.5	2831	2754–2909	2791	17.57	2658	2443	3545
CBD	5	9.44	8.5–10.4	9.22	24.38	7.74	7.74	11.92
AUC_{INF}	10	19.02	17.0–21.0	18.84	17.21	20.67	16.77	20.86
(ng*h/mL)	15	32.35	31.6–33.1	31.60	23.10	36.43	23.21	37.42
CBD	5	1.33	1.20–1.46	1.30	24.20	1.09	1.09	1.67
C_{max}	10	2.67	2.39–2.95	2.65	16.86	2.90	2.36	2.92
(ng/mL)	15	4.54	4.44–4.65	4.44	22.83	5.11	3.27	5.25
CBD	5	0.08	0.08–0.08	0.08	7.55	0.08	0.08	0.09
T_{max}	10	0.10	0.09–0.11	0.10	20.98	0.11	0.09	0.11
(h)	15	0.09	0.09–0.09	0.09	14.80	0.09	0.08	0.10
CBD	5	3912	3565–4260	3826	24.38	4560	2960	4560
$Volume_{dist}$	10	3781	3341–4222	3744	17.21	3412	3382	4273
(L)	15	3435	3345–3525	3348	23.10	2904	2827	4560

Note: Means with 95% confidence interval (CI), geometric means with coefficient of variation (%CV), and medians with 25%–75% percentiles of the area under the curve to infinity (AUC_{INF}), maximal concentration (C_{max}), time to C_{max} (T_{max}), and the apparent volume of distribution associated with the terminal phase ($Volume_{dist}$ = Dose/λz/AUC_{INF}). These parameters were calculated by non-compartmental analysis of the original experimental data fitted to the estimated parameters from the final model after bootstrapping (Table 2) split for each dose of Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD). The estimations are based on the following number of observations: THC 2.5 mg: 3; THC 5 mg: 6; THC 7.5 mg: 13; CBD 5 mg: 5; CBD 10 mg: 3; CBD 15 mg: 18.

to be dose-dependent, and the authors also address a "lack of information about the role on different formulations and routes of administration on absorption".[24] Thus, the observed difference in T_{max} between the experimental data and the model results are possibly caused by the combination of limited experimental data available in the study during this period and a high variance of this parameter, as observed in the experimental data. In this context, we must point out that the absorption time ($Tk0_{pop}$) for CBD, a crucial parameter influencing T_{max} estimated from the bootstrapping, showed a coefficient of variation of about 400%, the highest by far of all the other estimated parameters for both drugs.

The longer absorption time and the shorter half-life would explain the lower blood concentration and AUC for THC compared to similar doses of CBD (e.g., 5 mg). However, this difference is less than might be expected due to the smaller apparent volume of distribution of THC. Besides, the very large apparent volumes of distribution observed would indicate that both compounds readily distribute to peripheral tissues or, more likely, that only a small proportion of their dose is absorbed, reflecting their very low bioavailability.[23] AUC by administered dose was not calculated in the summary statistics of the experimental data as some patient took different doses throughout the day, and some only took very few capsules.

Regarding efficacy, we found no effect of CBM compared with placebo when evaluating PID and SID in a steady-state condition. This is in accordance with findings from the main study where we found no difference between active treatment and placebo when evaluating patient-reported pain and spasticity on a 0–10 NRS.[34] Advocates of CBM may oppose the use of isolated cannabinoids when debating efficacy and AEs, and whole-plant

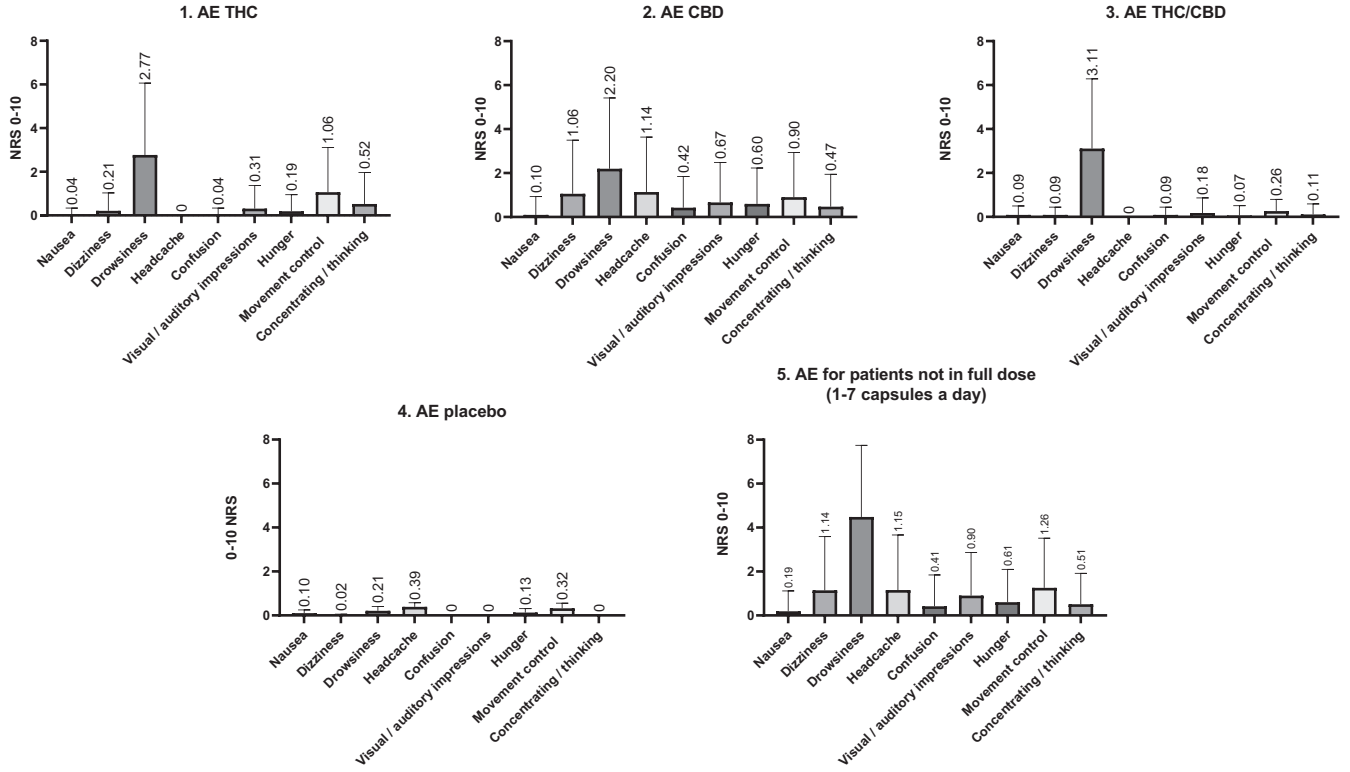

FIGURE 3 Adverse events (mean score on a 0–10 scale with standard deviation) for the placebo group and each of the active treatments. The fifth graph shows the characteristics of the adverse events for patients not reaching full dosage. AE, adverse events; CBD, cannabidiol; NRS, numeric rating scale; THC, Δ^9-tetrahydrocannabinol.

product chemistry is more complex than isolated cannabinoids,[42] but with no differences at the molecular level.[43] There is a lack of medical-grade whole-plant standardized products available for investigation. Hence, the effect, PK, and PD of the isolated cannabinoids can be evaluated but is not comparable with whole-plant products. The doses of THC and CBD used in this trial equal the use in clinical practice, and considerations about doses have been described previously.[33] The placebo response was considerable in this study (also found in the main study published separately), which is also seen in the majority of other (pain) studies.[34,44,45] The placebo effect is potentially high when evaluating CBM, because of the high expectance of effect in the patient population[46,47] and the 75% chance of getting an active substance in the particular trial. The placebo response may be better evaluated if the expectancy of getting active treatment was lower (e.g., 25%–50% chance of getting active treatment)[48] by using a non-treated control group, or a dose–response trial design.

The concurrent evaluation of PK and PD, and a placebo group available as a control, can be considered as strengths of this study.

The study has limitations to consider, foremost the limited data due to the small sample size and low number of patients in each treatment arm and the relatively long interval, minimum 1 h, between samples. Thus, estimating PK parameters directly from the experimental data was subject to high uncertainty due to the great variance in the administered dose and uncertainty in the time of peak concentrations. Previous studies investigating the PK of cannabinoids had even fewer patients included, reflecting the difficulties in conducting studies in a clinical trial setting.[14,24] In an attempt to overcome these limitations, the calculations of T_{max}, C_{max}, area under the curve, and apparent volume of distribution were based on the fit of the experimental data using the model parameters derived from bootstrap resampling. These procedures could help to reduce the uncertainties in the results due to these limitations, as is the case since the experimental data remained reasonably within the simulations obtained from the model (Figures S2 and S3), have explanatory predictive capability, and may be useful in further studies for the development of clinical effective treatments with cannabinoids.

Patients' meals and drinks were not standardized, and therefore absorption could vary both between subjects and between each dose. However, all patients had a meal along with each dose, a setting reflecting dosage recommendations in real life. Furthermore, the small sample size increased the risk of type 2 error and a lack

of power (no power calculation was made for the substudy due to its explorative design). Some whole-blood samples were missing due to technical difficulties in drawing samples. In a few cases it was necessary to rinse the PVC 10 min before sampling to obtain flow. Being in a steady-state may have blurred acute/subacute AEs after drug administration. However, reported AEs were generally more frequent in CBM-treated patients than in the placebo group.

CONCLUSIONS

We present the first study to examine both PK and PD parameters of CBM in a MS patient population. Pharmacokinetic modeling indicated that both cannabinoids are absorbed from the gastrointestinal tract though a zero-order process, whereas blood elimination follows a linear first-order process. Regarding the PD results, the presence of a placebo control group allowed for the assessment of potential improvements in patients not receiving active treatment and we found the placebo response to be considerable in this population. No effect was found comparing cannabinoids to placebo on PD parameters in a steady-state condition. More AEs were observed in the active treatment group. These data indicate that CBM can be safely used in a patient population; however, the placebo response is considerable. Studies with shorter intervals between sampling and with a longer duration are proposed in the future to investigate the terminal half-life of THC and CBD and/or the PK/PD parameters in an acute setting.

AUTHOR CONTRIBUTIONS

J.S.H., F.B., K.B.S., J.B.H., L.K.S., M.K., and E.A.S. wrote the manuscript. E.A.S., K.B.S., J.S.H., N.B.F., P.V.R., H.K., F.S., T.P., R.M.H., and S.G. designed the research. J.S.H. performed the research. J.S.H., J.B.H., L.K.S., and F.B. analyzed the data. J.B.H., L.K.S., and F.B. contributed new reagents/analytical tools.

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CONFLICT OF INTEREST STATEMENT

M.K. has received speaker honoraria from Biogen and holds stocks in Novo, Regeneron, Amgen, Novartis, and Genmab. S.G. has received support for congress participation from Merck. F.S. has served on scientific advisory boards, served as a consultant, received support for congress participation, or received speaker honoraria from Alexion, Biogen, Bristol Myers Squibb, H. Lundbeck A/S, Merck, Novartis, Roche, and Sanofi Genzyme. His laboratory has received research support from Biogen, Merck, Novartis, Roche, and Sanofi Genzyme. R.M.H. has received support for congress participation from Merck and Ipsen. T.P. has received research support for the MS clinic at Aarhus University Hospital from Merck, Alexion, Roche, Biogen, Novartis, and Sanofi. N.B.F. has received consultancy fees from Merck, Almirall, NeuroPN, Vertex, and Novartis Pharma, and has undertaken consultancy work for Aarhus University with remunerated work for Biogen, Merz, and Confo Therapeutics. She has received grants from IMI2PainCare, an EU IMI 2 (Innovative Medicines Initiative) public–private consortium, and the companies involved are Grunenthal, Bayer, Eli Lilly, Esteve, and Teva. P.V.R. has received speaker honoraria from Biogen, Roche, Merck, Alexion, and Novartis; support for congress participation from Biogen, Merck, Roche, and Sanofi; fees for serving on advisory boards from Bristol Myers Squibb, Merck, Roche, Novartis, Biogen, Sanofi, and Alexion. K.B.S. served as a consultant for Takeda, and received travel grants from TEVA, Biogen, Merck, and Novartis. All the other authors declared no competing interests for this work.

DATA AVAILABILITY STATEMENT

The data used in this study can only be made available through an application to Central Denmark Region by contacting the primary investigator julihans@rm.dk.

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