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Cannabidivarin for HIV-associated neuropathic pain – a randomized, blinded, controlled clinical trial

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Abstract

The human immunodeficiency virus (HIV) remains a major burden to the health care system and neuropathic pain is the most common neurological complication of HIV infection. Since current treatment strategies often lack satisfying pain relief, cannabinoids are discussed as a new option. We investigated cannabidivarin as treatment for HIV-associated neuropathic pain. We conducted a randomized, double-blind, placebo-controlled cross-over study. Patients underwent two successive treatment phases (4 weeks each) and were treated with cannabidivarin (400mg/d) or placebo in a randomized order. A 3-week wash-out phase was designed to eliminate potential carry-over effects. Patients were followed up for 3 weeks after the end of the second treatment phase. The primary endpoint was pain intensity on an 11-point numeric rating scale, recorded in a diary. Secondary endpoints were additional pain medication, pain characteristics and quality of life. We included 32 patients. The mean pain intensity under cannabidivarin was 0.62 points higher compared to placebo (p=0.16; 95% CI -0.27 to 1.51). Cannabidivarin did not influence the amount of additional pain medication, pain characteristics or quality of life. The incidence of adverse events was similar during both treatments. No suspected unexpected adverse reactions occurred during either treatment. Cannabidivarin was safe but failed to reduce neuropathic pain in HIV-patients. This may be explained by a lack of cannabinoid receptor activation, as indicated by preclinical experiments. Although a larger patient number might be desirable, we would not expect a change in the conclusions since the present differences are far from statistical significance. Therefore, we would currently not consider CBDV as a clinically meaningful treatment option for neuropathic pain.

Introduction

Approximately 7-8% of the general population suffer from neuropathic pain, defined as ´pain that arises as a direct consequence of lesions or diseases affecting the somatosensory system' [1,2]. Chronic neuropathic pain impairs quality of life and negatively affects the patients' social relationships [3]. Among various diseases that can underlie neuropathic pain, human immunodeficiency virus (HIV) infection belongs to the most prevalent [4]. Despite the development of highly effective antiretroviral therapy, HIV remains a major burden to the health system [5].

HIV-associated neuropathic pain usually occurs together with distal sensory neuropathy with symptoms of burning or dysesthesia in combination with numbness in stocking- or glove-like distribution [6], and may be caused by the inflammatory effects of HIV-infected macrophages and other neurodegenerative mechanisms [6,7]. Furthermore, antiretroviral drugs, mainly dideoxynucleoside reverse transcriptase inhibitors, can cause mitochondrial and nerve damage [7] so that they are no longer recommended [8]. Despite novel, more effective and less neurotoxic antiretroviral drugs, the prevalence of neuropathic pain in HIV-infected patients is still high and causal treatment is not available [6]. Although treatment of chronic neuropathic pain should be based on both pharmacological and interdisciplinary non-pharmacological approaches (e.g. behavioral, physical and/or occupational therapy) [4], pharmacological therapy often predominates. Antidepressants, anticonvulsants and opioid analgesics are medications of choice [9]. However, they often lack efficacy [4] and are limited by side effects such as respiratory depression, addiction and sedative effects [10], resulting in extensive additional costs and reduced quality of life [3,11,12].

Endocannabinoids, e.g. 2-arachidonylglycerol and anandamide, influence the transmission of pain signals by acting on cannabinoid (CB)-receptors 1 and 2 [13]. Some exogenous cannabinoids have shown promising results in the treatment of neuropathic pain but they were limited by complicated dosing of smoked cannabis and side effects like nausea or drowsiness [14–16]. Therefore, improved cannabinoid and opioid analgesics are being developed [9,13,17,18].

In this study, we investigated cannabidivarin (CBDV) a novel phytocannabinoid derived from the *Cannabis sativa* L. plant, in patients with HIV-associated neuropathic pain. Using a double-blind cross-over trial design, we assessed pain, side effects and quality of life, and sought to correlate treatment responses to the patients' genotype.

Methods

Study design

Data were collected from 1st January 2017 to 8th January 2019. We conducted a randomized, placebo-controlled, double-blind cross-over phase II trial in a single-center outpatient setting. All patients received both treatments (CBDV and placebo) in two successive phases. The order of treatments (CBDV-placebo [C-P] or placebo-CBDV [P-C]) was allocated by chance (randomized). Each patient was monitored for 13 weeks. After the screening phase, baseline values on pain scales, questionnaires and medication were recorded during a one-week phase (**Figure 1**). This was followed by a 4-week treatment phase A with either placebo or CBDV. A subsequent 3-week washout phase was included to eliminate potential carry-over effects. The duration of the wash-out phase was based on data showing an accumulation of cannabinoids in fatty tissue resulting in a half-life of about 5 days after long-term oral administration [19]. Thereafter, another 1-week baseline phase ensued, followed by treatment phase B. Patients were then followed up for another 3 weeks. Throughout the study, the patients documented data in diaries (see also study protocol in supplementary materials).

Study participants

Participants were recruited through personal contacts to physicians and patient-advocacy groups in the greater Berlin area, as well as by advertisement in the Berlin public transportation system. Before inclusion, subjects were screened for age (18-65 years), vital signs and pain intensity [≥ 4 on an 11-point numeric rating scale (NRS)]. The diagnosis of HIV-associated sensory neuropathy was confirmed by a clinician (CS, MC or ML) based on patient history, the Douleur Neuropathique 4 interview (DN4i) and the Clinical HIV-associated Neuropathy Tool (CHANT) [20,21]. Exclusion criteria were pregnancy and lactation, major psychiatric conditions, severe diseases of the central nervous system, hepatic, renal or cardiovascular diseases or use of conventional cannabinoids, examined by blood test. Electrocardiograms were recorded on the day of screening and analyzed for abnormalities by an experienced cardiologist (AM). Infection with hepatitis virus B or C and AIDS-defining diseases were debarred by consulting HIV specialists. The use of concomitant analgesics (including antidepressants and anticonvulsants) as needed was permitted throughout the study. Standard laboratory values (full blood count, liver function tests, electrolytes, glucose, urea, cholesterol, creatinine, creatinine kinase, protein and international normalized ratio) were recorded on the day of screening and during the trial.

Outcome measurements

The primary outcome was pain intensity measured thrice a day (8:30 AM, 1:00 PM and 7:00 PM) by an 11-point NRS (0 = no pain, 10 = worst pain imaginable), as documented in the patient diary. For each day, the arithmetic mean of the three NRS scores was determined. According to several previous studies on neuropathic pain [22,23], a decrease of mean NRS values by at least 20% between the last day of baseline measurement and the last day of treatment was defined as a clinically relevant effect (responder). The number of responders and non-responders to each treatment was determined. Secondary endpoints were pain characteristics, quality of life and sleep, measured by questionnaires. We used painDETECT [24], the Brief Pain Inventory (BPI) [25] and the DN4i [21] for evaluation of pain intensity and pain characteristics, the Hospital Anxiety and Depression Scale (HADS) [26] to evaluate anxiety and depression, and the 36-Item Short Form Survey (SF-36) [27], the Patient Global Impression of Change (PGIC) [28] and the Insomnia Severity Index (ISI) for quality of life and sleep [29], respectively. All questionnaires were applied on the last day of each baseline phase and on the last day of each treatment phase, except PGIC, which was only used at the end of each treatment phase. Concomitant medication and side effects were recorded in the patient diary. For the analysis of concomitant pain medication we used the Medication Quantification Scale (MQS) in its 3rd version, which assigns a score (on an unlimited scale) based on the detrimental effects and dose of each pain medication [30]. For analysis of side effects, patients were asked to document any adverse or unusual events. These were discussed with a study physician at each visit. For standardized documentation, we used paper-based tables and classified the events with the Common Terminology Criteria for Adverse Events, Version 4.03.

Randomization, allocation concealment and blinding

Randomization to the sequence of treatments occurred in blocks of 4 by use of paper-based, computer-generated random lists, which were stored in a locked cabinet. Included patients were pseudonymized by generating a serial number (ID). Allocation to the treatment sequence was documented and kept in sealed envelopes. All patients and staff involved in patient contacts and assessment of outcomes were blinded until the end of the study.

Monitoring

Two independent monitors conducted unblinded monitoring of patient safety and adherence to good clinical practice (GCP) principles throughout the trial.

Investigational Medicinal Products (IMP)

The active agent and placebo, both dissolved in sesame oil, were identically appearing and tasting solutions. The IMP was packaged in amber-glass bottles by GW Pharmaceuticals. All bottles were subject-specific and marked with the patient ID. The bottles with active agent contained 50 mg CBDV/ml. Patients were instructed to use 8 ml of the solution orally every morning at 9 AM, corresponding to 400 mg CBDV in the verum treatment phase (for detailed information see **Table S1**). The dose was chosen based on preclinical and clinical phase-1 studies, showing that daily doses between 200 and 800 mg were well tolerated [31].

Inactivation of HIV in blood samples, DNA isolation and genetic analysis

Blood samples were obtained during the last visit from 28 patients who gave consent for genetic analysis. 5 ml of peripheral venous blood was mixed with 15 ml of Red Cell Lysis Solution (Epicentre R) and incubated at room temperature for 10 minutes. After centrifugation, supernatant was discarded, and the pellet was dissolved in 7.5 ml Tissue and Cell Lysis Solution (Epicentre R). The solution was kept at 65°C for one hour for inactivation of HIV and cell lysis. Samples were then stored and transported at -20°C until genotyping by deCODE Genetics (Reykjavik, Iceland). Whole genome sequencing was performed by the Infinium Global Screening array (GSA24, Illumina).

Statistics

Sample size was calculated by nQuery Advisor® 7.0 based on the primary endpoint (NRS scale) and the cross-over study-design. According to previous literature, a pain reduction by 20% upon verum compared to placebo and a common standard deviation (SD) for the period differences of 2.5 seemed to be achievable and would have been clinically meaningful [22,23,32]. We calculated that 21 patients per sequence group were sufficient to show this effect (e.g. a reduction of 20% from 6 points to 4.8 points) with a power of 85% and a two-sided type-I error of 0.05 using a paired t-test for 2x2 crossover designs. To account for an estimated 15% dropouts, we aimed at a total of 50 patients. Because some guidelines define higher pain reductions as clinically relevant [33], we also provide 30% and 50% pain reduction analyses to allow our data to be used in data syntheses.

Statistical analysis was based on the intention-to-treat principle, i.e. every patient who started treatment and had at least one post-baseline measurement of the primary endpoint was included in the full set for the efficacy analysis. Continuous variables are shown as mean, SD and range, while categorical parameters are given as absolute and relative frequency. For the continuous endpoints, first, the

difference between sequence-specific baseline and the value after treatment was calculated. Then, for each individual the difference between the two treatment effects (CBDV - placebo) was determined. A paired t-test taking period effects into account was used for comparing the two treatments. In case of non-normality of data distribution, a non-parametric version was applied instead. 95% confidence intervals (CI) were calculated for the treatment effects. Further, for the primary endpoint, a random subject intercept mixed model was calculated. This model used the change of NRS values from phase baseline to post-treatment as dependent variable, and treatment, phase, and NRS phase baseline value as independent variables. All p values resulting from the analyses have to be considered as non-confirmatory using a cutoff of 0.05. All analyses were done using R (version 3.5.0) [34] (see also statistical analysis plan in supplementary materials).

Study approval

Written informed consent was obtained from all participants prior to inclusion in the study. The trial protocol, patient information and informed consent sheets were approved by the ethics committee of the state regulatory authority Berlin (Landesamt für Gesundheit und Soziales; 15/0255 EK 13) and the German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte; 61-3910-4040377). The CONSORT guidelines and checklist, GCP principles and the Declaration of Helsinki were strictly followed. The study was registered at EudraCT (https://www.clinicaltrialsregister.eu/) under number 2014-005344-17.

Results

Patient population

From January 2015 to September 2018 a total of 194 patients were contacted by email or phone, of which 55 were screened in the study center. Screening was terminated as planned at the end of financial support. 34 patients gave informed consent and were assigned a patient ID. The data of two patients could not be used for final efficacy analysis due to missing data or screening failure but were included in the safety population (for more information see **Figure S1**). Characteristics of the remaining 32 patients included in the efficacy analysis are shown in **Table 1**. All patients met the inclusion criterion of a positive DN4i (≥3) and CHANT. Of the remaining 32 patients, 4 dropped out during the study but were not excluded from analysis. Patients were randomized to receive CBDV in treatment phase A followed by placebo in treatment phase B (C-P), or placebo in phase A followed by CBDV in phase B (P-C).

Primary endpoint

Overall, mean pain intensity (NRS) at the end of CBDV treatment was 0.62 points higher compared to placebo; this difference was not significant (p=0.16; 95% CI -0.27 to 1.51) (**Figure 2, Figure 3, Table S2**). The mixed model provided very similar results (difference 0.63; 95% CI -0.05 to 1.32). The differences between mean NRS at end of the treatment and baseline were not statistically significant for any substance or treatment phase (**Figure 3**). The mean NRS value at the end of follow-up (3 weeks after end of treatment phase B) was 2.74 (SD: 1.47) in the C-P group and 3.67 (SD: 2.62) in the P-C group. During CBDV treatment, 9 patients experienced a mean pain reduction of at least 20 % and were therefore classified as CBDV responders. By the same criteria, 19 patients were classified as placebo responders. Based on a 30% pain reduction, 6 patients were CBDV-responders and 13 patients responded to placebo. A 50% pain reduction was experienced by 1 patient under CBDV and by 9 patients under placebo.

Secondary endpoints

No statistical differences between CBDV and placebo were detectable by any of the questionnaires analyzing pain characteristics, sleep quality, subjective impression of change or quality of life (**Table 2**, **Figure 4**). No significant changes in specific parameters in the painDETECT questionnaire were detectable. Overall, the intake of additional pain medication, measured by the MQS, was not significantly different between CBDV and placebo (median treatment effect of CBDV compared to placebo = 0, p=0.52, 95% CI -0.05 to 2.85; non-parametric rank sum test) (**Figure 5**). After CBDV treatment, the differences in MQS-values between baseline and end of treatment were +1.13 (SD=7.13) in the C-P group and -0.16 (SD=0.61)

in the P-C group. After placebo treatment, these differences were +0.11 (SD=3.79) and -1.87 (SD=5.26) in the C-P group and P-C group, respectively.

Adverse events

31 patients (91.2%) experienced at least one adverse event (AE) during CBDV treatment; 27 patients (79.4%) had at least one AE during placebo. During each treatment (CBDV or placebo), 9 patients (26.5 %) experienced an AE that was considered to be related to study medication (**Table S3**). One serious AE (acute myocardial infarction) was recorded during CBDV treatment but was judged as not related to study medication. This patient (male, 62 years) had the following cardiovascular risk factors: History of arterial hypertension, transient ischemic attack, pulmonary embolism and factor-V-Leiden mutation. The most common AEs were diarrhea and dry mouth (3 cases during each treatment) (**Table S3**). The incidence of AEs was similar in both treatment phases. All AEs were of low or moderate severity; 1 patient withdrew study participation due to an AE (cough) during CBDV treatment. This was considered related to treatment. No clinically relevant or medication-related changes of laboratory values were noted.

Genetic analysis

Samples from 28 patients who gave consent to genetic analysis were genotyped using the Infinium Global Screening array (GSA24, Illumina), and whole genome sequencing was performed on this subset of patients by deCODE Genetics (Reykjavik, Iceland). The small sample size did not allow a meaningful genome-wide association analysis of response. However, these data may have utility in future meta-analysis efforts, and can be queried for the role of individual markers identified in other studies.

Discussion

CBDV failed to reduce neuropathic pain intensity in HIV-patients. Additionally, we could not observe any statistically or clinically significant effects on use of supplementary pain medication, specific pain characteristics or quality of life. CBDV and placebo produced similar rates of adverse events which were of mild to moderate severity.

According to data on CB receptor knock-out mice and pharmacological studies, the mechanisms underlying analgesic effects of cannabinoids are thought to be based on the activation of CB1 and/or CB2 receptors, leading to an inhibition of pain signal transmission and/or anti-inflammatory effects [13,35,36]. This may either be achieved by exogenous cannabinoids or by inhibiting enzymes degrading endocannabinoids (fatty acid amide hydrolase and/or monoacylglycerol lipase). Costa et al. also showed that antinociception can be produced by a cannabinoid re-uptake inhibitor in rats [37]. In addition, effects of phytocannabinoids not primarily activating CB receptors have been described [36].

CBDV is mainly known for its anticonvulsant effects [38]. Limited preclinical data indicated the occurrence of antinociceptive effects without binding to CB receptors [31]. Antinociceptive effects of cannabinoids not activating CB receptors were observed in animal studies [39] but not in humans so far. Different mechanisms of action were hypothesized, such as inhibition of diacylglycerol lipase-α [40], another enzyme influencing endocannabinoids. Some groups observed an activation of transient receptor potentials (TRP) [40] and postulated that this activation could lead to desensitization of sensory neurons [41].

To evaluate clinical effects, we assessed both pain intensity and the amount of supplemental pain medication. A dose reduction of additional pain medication can minimize detrimental side effects and can therefore be useful. CBDV however, did not significantly change pain intensity or the use of additional pain medication as compared to placebo. Potentially promising effects may be assumed in Figure 5 but should be considered visually misleading since real differences on the unlimited MQS were small and not statistically significant. We also examined whether CBDV can influence pain characteristics such as burning sensation, numbness or heat hyperalgesia. Due to the possible involvement of TRPV1 [40], a receptor which is responsible for heat sensation [42], one might assume that CBDV can alleviate burning sensations in neuropathic pain patients. In the painDETECT questionnaire however, CBDV did not influence any specific pain characteristics. To our knowledge, this is the first study investigating the influence of CBDV on such parameters.

Overall, CBDV was ineffective in our trial. This is in line with recent extensive meta-analyses that did not detect clinically relevant analgesic effects of cannabinoids in humans with chronic non-cancer pain [14,43] . The analysis by Stockings et al. included all cannabinoids, all study designs, considered all outcomes

recommended by the IMMPACT group, and it assessed the clinical relevance of these findings [14]. In our study, a notable (but statistically nonsignificant) pain reduction was observed in patients receiving placebo during the first phase (P-C) and a difference between the groups was visible at baseline A (**Figure 2**). However, on the day of screening, the NRS scores were quite similar (**Table 1**). Since patients were randomized and did not receive any test substances before baseline A, this NRS difference was due to chance. Another NRS difference is visible in group P-C between baselines A and B (**Table S2**). To account for baseline variations in the statistical analysis, we included sequence-specific baseline values into a linear mixed model. It is conceivable that patients who were not treated sufficiently for pain before entering our study benefitted psychologically due to the enhanced attention in the setting of a clinical trial. Similar findings were reported in several previous studies and meta-analyses on neuropathic pain in HIV patients [44–46]. This underlines the importance of a multidisciplinary approach including psychotherapy to treat chronic pain.

Chronic pain negatively influences many other facets of the patient´s life according to the biopsychosocial model of pain [3,12,47]. Cannabinoids are known to influence emotional processes. For example, the CB receptor agonist Δ9-tetrahydrocannabinol (THC) may reduce the unpleasantness but not the intensity of pain [48]. We did not ask our patients about previous use of cannabinoids. However, CBDV failed to improve any of these features in the current study. Again, this is in agreement with previous meta-analyses that did not find significant impacts of cannabinoids on physical or emotional functioning in patients with chronic non-cancer pain [14].

CBDV does not bind to CB-receptors [31,38] and therefore should not show typical CB receptor-mediated psychotropic side effects such as euphoria, reduced anxiety or feeling ´high´ [49], consistent with our findings. Since the most common side effects (diarrhea and dry mouth) did not differ between CBDV and placebo, we do not consider these AEs related to CBDV treatment. However, they could be associated with the sesame oil solution. We only observed side effects of low to moderate severity and only one patient withdrew due to such effects. For a more detailed analysis, a larger number of patients may be advantageous.

One SAE (myocardial infarction) occurred during treatment with CBDV but was not considered related to CBDV. There are data supporting increased cardiovascular risk due to cannabinoids, but these data suggest a CB-receptor mediated mechanism [50]. CBDV and its major metabolites lack appreciable affinity and functional activity at the CB1-receptor [38] and neither clinical nor preclinical data point out any increase in cardiovascular risk. Therefore, the available information suggests that an association between CBDV and myocardial ischemia is unlikely.

We were able to obtain blood samples from most patients, but this sample size was not sufficient for a meaningful genome-wide association study regarding treatment responses. However, these data are available upon request and may have utility in future meta-analysis efforts.

The time frame for patient inclusion was limited by the end of financial support. Due to additional, unexpected recruitment difficulties (many patients lost interest since we could not offer a satisfying remuneration), we could only enroll 16 patients per treatment sequence group instead of a planned sample size of 21. Although a larger patient number might have been desirable, we would not expect a marked change in the conclusions since the present results are far from statistical significance. Even the lower border of the 95% CI of the mean differences in NRS score does not promise any clinical relevance.

To conclude, this study showed that CBDV did not elicit more adverse side effects than placebo but failed to alleviate neuropathic pain or associated parameters in HIV patients. We presume that activation of CB receptors is necessary for significant analgesia. This was the first study investigating CBDV for neuropathic pain and further research with larger numbers of patients and possibly other types of neuropathic pain is desirable. However, since our results did not reveal any significant differences, we would not consider CBDV a clinically meaningful treatment option for HIV-associated neuropathic pain.

Study Highlights

What is the current knowledge on the topic?

Pain relief in patients with HIV-associated neuropathic pain is often unsatisfying but cannabinoids have shown promising results in preclinical studies.

What question did this study address?

Can pain relief be achieved by the novel phytocannabinoid cannabidivarin in patients with HIV-associated neuropathic pain?

What does this study add to our knowledge?

Cannabidivarin was safe but failed to improve neuropathic pain or quality of life in HIV patients.

How might this change clinical pharmacology or translational science?

Despite encouraging preclinical data, cannabidivarin is not a promising substance for treatment of patients with HIV-associated neuropathic pain. We presume that clinical pain relief is unlikely to be achieved without activation of cannabinoid receptors.

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Author contributions

L.E., R.R. and C.S. wrote the manuscript; S.S., L.E. and C.S. designed the research; L.E., S.S., M.C., M.L., Ö.C., A.M. and C.S. performed the research and R.R., L.E. and C.S. analyzed the data.

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Figure Legends:

Figure 1: **Study design**: Abbreviations: V = Visit; R = Randomization

Figure 2: **Pain intensity over time**: Descriptive presentation of pain intensities per day (means) by treatment sequence. CBDV-placebo (black, broken line); Placebo-CBDV (grey, continuous line); BL= Baseline NRS = Numeric Rating Scale

Figure 3: **Pain intensity difference by treatment and phase**: Differences (medians) between numeric rating scale (NRS) values on the last day of CBDV (white) and placebo (grey) phases and baseline (BL) values, respectively. Negative values indicate pain reduction; bars indicate minimum and maximum values; dots indicate values outside of 1.5* interquartile range (paired t-test; n = 32)

Figure 4: **Treatment effects on quality of life**: Differences (medians) between CBDV and placebo effects as measured by SF-36. Bars indicate minimum and maximum values; dots indicate values outside of 1.5* interquartile range (paired t-test; n = 32). Abbreviations: SF-36: 36-Item Short Form Survey; BP: Bodily Pain; GH: General Health; MH: Mental Health; PF: Physical Functioning; RE: Role Emotional; RP: Role Physical; SF: Social Functioning; VT: Vitality

Figure 5: **Medication quantification scale (MQS) values over time**: Descriptive presentation of MQS values per day (means) by treatment sequence. CBDV-placebo (black, broken line); Placebo-CBDV (grey, continuous line); BL = Baseline; n = 32

Supplementary Files

1. Table S1
2. Table S2
3. Table S3
4. Figure S1
5. Statistical Analysis Plan
6. Study Protocol

Table 1: Data on day of initial screening

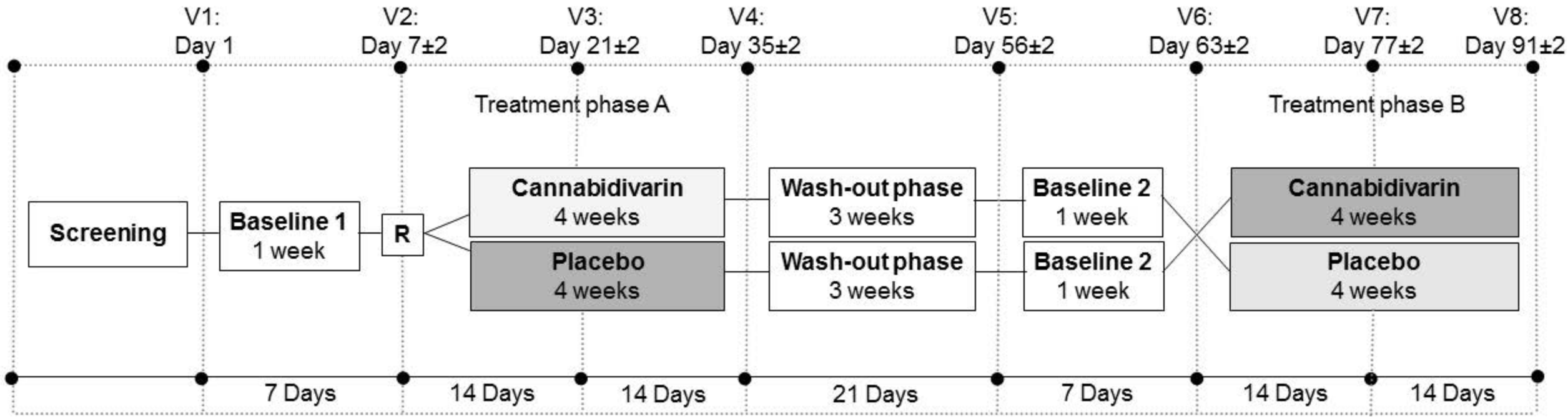
		Treatment sequence CBDV-Placebo	**Treatment sequence Placebo-CBDV**	**Total**
Male (n)		16	15	31
Female (n)		0	1	1
Age (years)	mean (SD)	52.31 (8.06)	48.31 (9.62)	50.31 (8.96)
	range	36 - 65	31 - 65	31 – 65
NRS score (0-10)	mean (SD)	6.12 (1.15)	6.44 (1.59)	6.28 (1.37)
	range	4 - 8	4 - 9	4 – 9
DN4i (0-7)	mean (SD)	5.19 (1.17)	5 (0.89)	5.09 (1.03)
	range	3 – 7	4 – 6	3 – 7
Duration of pain (years)	mean (SD)	16.47 (7.91)	9.94 (8.77)	13.1 (8.87)
	range	2 - 30	1 - 27	1 – 30
Duration of HIV infection (years)	mean (SD)	24.88 (9.17)	17.81 (10.81)	21.4 (10.2)
	range	3 - 33	2 - 32	2 – 33
On cART (n)		16	15	31

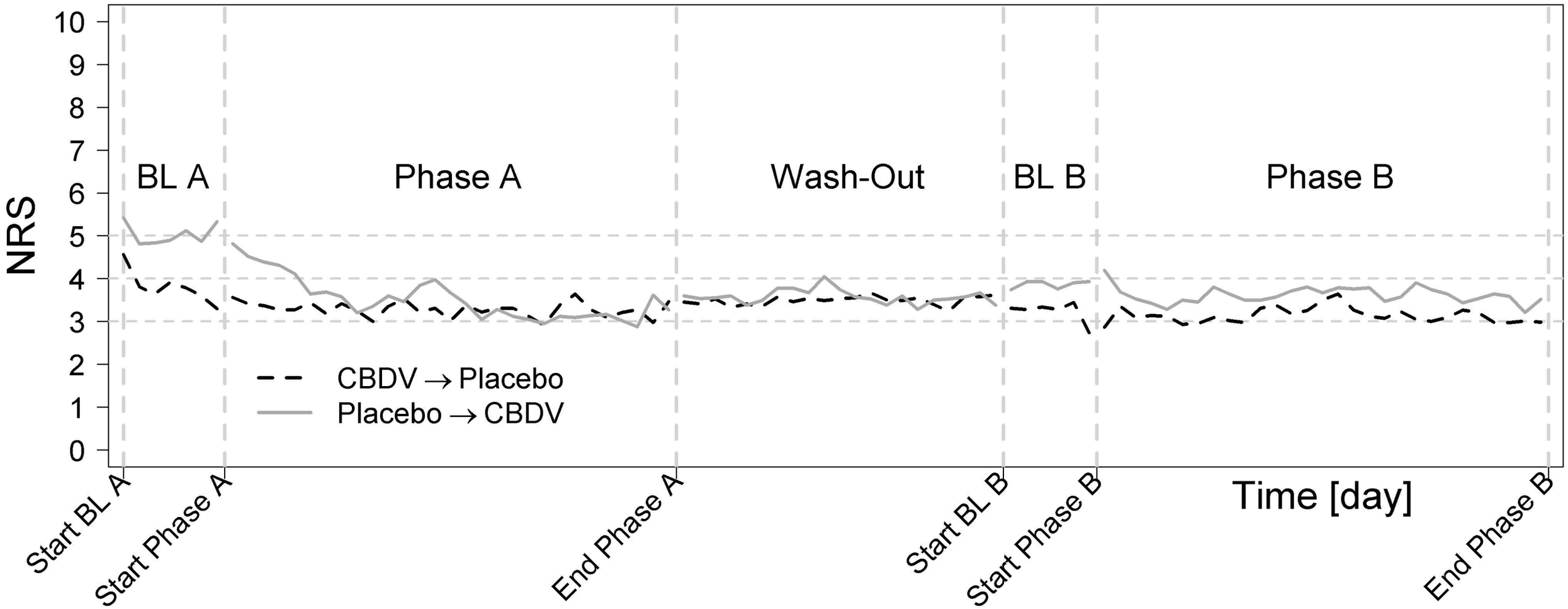
Abbreviations: cART = combined Antiretroviral Therapy; SD = standard deviation

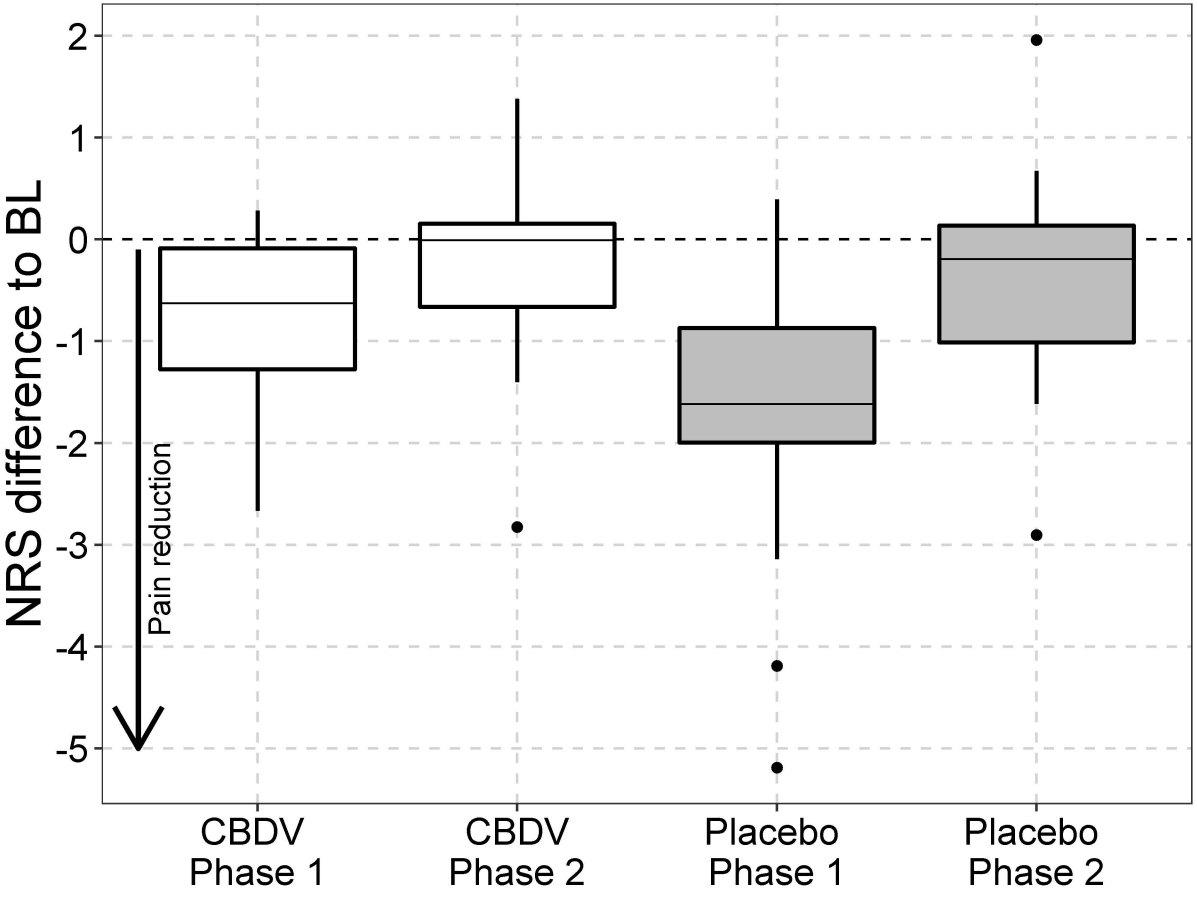
Table 2: **Effects of CBDV versus placebo assessed by questionnaires.**

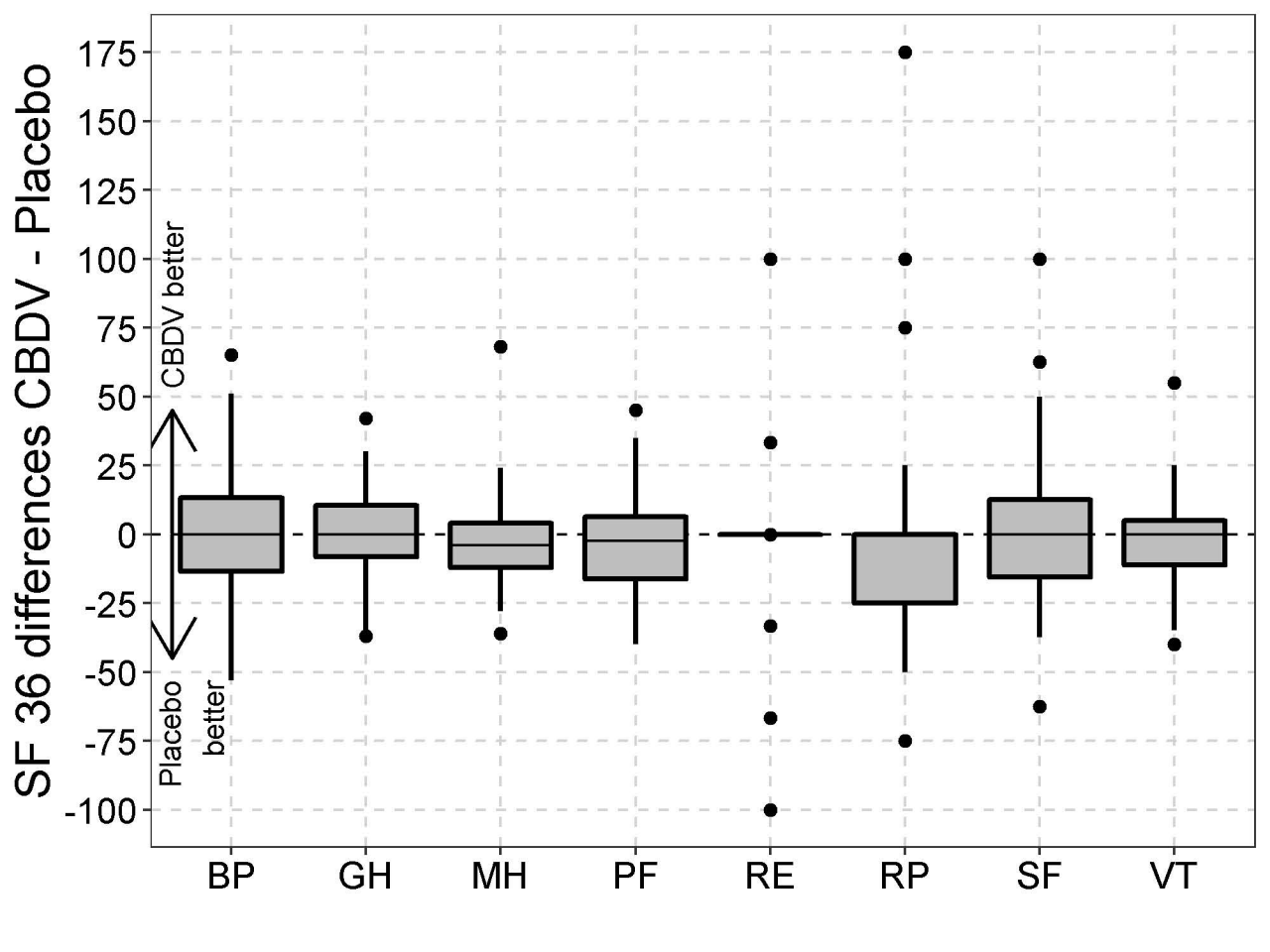
Questionnaire (score range)	**Effect CBDV vs. Placebo**
painDETECT (0 to 38)	**-0.84** (p=0.53, 95%CI -3.59 to 1.91)
DN4i (0 to 7)	**-0.50** (p=0.18, 95%CI -1 to 0.50)
BPI (pain intensity) (0 to 10)	**+0.23** (p=0.76, 95%CI -0.63 to 1.25)
BPI (influence on daily living) (0 to 10)	**-0.35** (p=0.22, 95%CI -1.36 to 0.43)
HADS (anxiety) (0 to 21)	**-0.60** (p=0.51, 95%CI -2.44 to 1.24)
HADS (depression) (0 to 21)	**0** (p=0.91, 95%CI -1.50 to 1.50)
ISI (0 to 28)	**-1.50** (p=0.24, 95%CI -5.50 to 1)
PGIC (0 to 7)	**-0.50** (p=0.26, 95%CI -1.50 to 0.50)

painDETECT and DN4i: higher values indicate presence of neuropathic pain; PGIC: higher values indicate a subjective improvement; all others: lower values indicate lower impairment. Paired t-tests, see Methods


V1:
Day 1
V2:
Day 7±2
V3:
Day 21±2
V4:
Day 35±2
V5:
Day 56±2
V6:
Day 63±2
V7:
Day 77±2
V8:
Day 91±2
Treatment phase A
Treatment phase B
Screening
Baseline 1
1 week
R
Cannabidivarin
4 weeks
Placebo
4 weeks
Wash-out phase
3 weeks
Wash-out phase
3 weeks
Baseline 2
1 week
Baseline 2
1 week
Cannabidivarin
4 weeks
Placebo
4 weeks
7 Days
14 Days
14 Days
21 Days
7 Days
14 Days
14 Days


NRS
10
9
8
7
6
5
4
3
2
1
0
BL A
Phase A
Wash-Out
BL B
Phase B
CBDV → Placebo
Placebo → CBDV
Start BL A
Start Phase A
End Phase A
Start BL B
Start Phase B
End Phase B
Time [day]


NRS difference to BL
2
1
0
-1
-2
-3
-4
-5
Pain reduction
CBDV
Phase 1
CBDV
Phase 2
Placebo
Phase 1
Placebo
Phase 2


SF 36 differences CBDV - Placebo
175
150
125
100
75
50
25
0
-25
-50
-75
-100
CBDV better
Placebo better
BP
GH
MH
PF
RE
RP
SF
VT

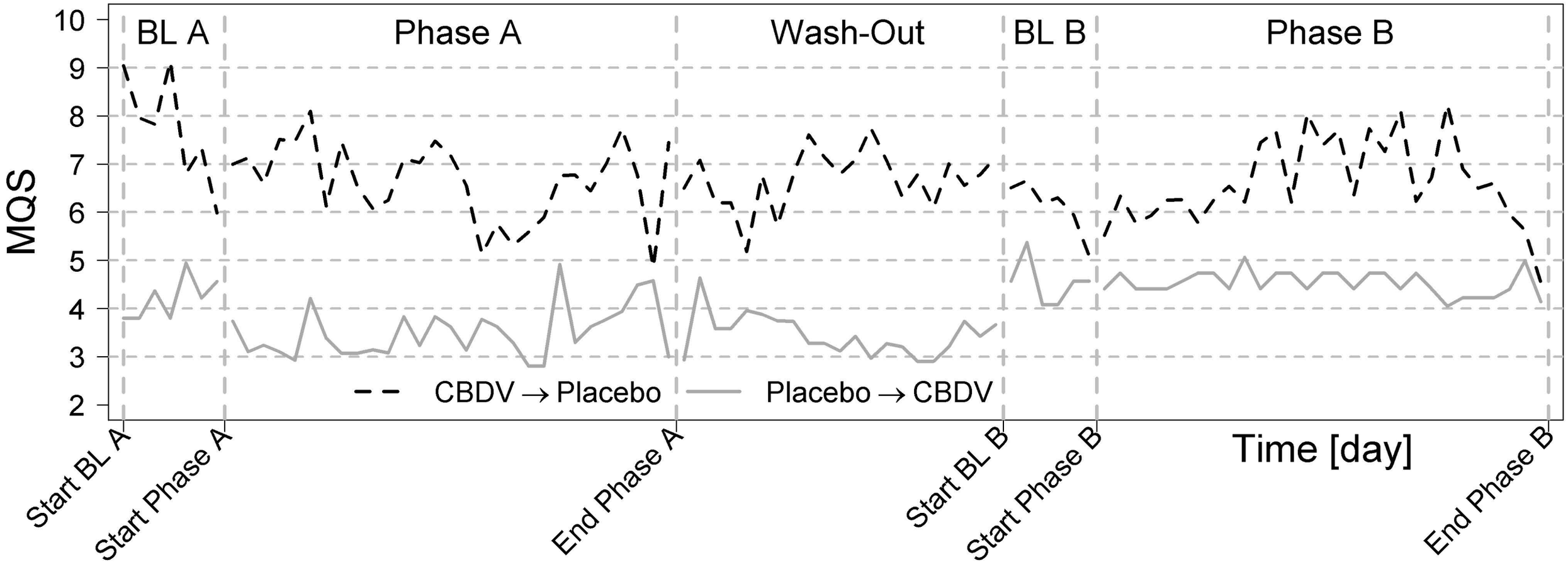

BL A
Phase A
Wash-Out
BL B
Phase B
MQS
10
9
8
7
6
5
4
3
2
CBDV → Placebo
Placebo → CBDV
Start BL A
Start Phase A
End Phase A
Start BL B
Start Phase B
End Phase B
Time [day]

Table S1: Investigational medicinal products

Material	**CBDV Solution (50 mg/mL)**	**Placebo Solution**
CBDV	50.0 mg	-
Anhydrous Ethanol	79.0 mg	79.0 mg
Sucralose	0.5 mg	0.5 mg
Strawberry Flavor	0.2 mg	0.2 mg
Refined Sesame oil	q.s. to 1.0 mL	q.s. to 1.0 mL

Abbreviations: q.s. = quantum satis.

Table S2: NRS values at different time points

		Treatment sequence CBDV-Placebo	**Treatment sequence Placebo-CBDV**	**Total**
NRS last day baseline phase 1	n	16	16	32
	mean (SD)	3.62 (1.62)	5.23 (2.43)	4.43 (2.19)
	range	1.3 - 6.7	2 - 9.3	1.3 - 9.3
NRS last day treatment phase 1	mean (SD)	3.29 (1.74)	3.25 (2.4)	3.27 (2.07)
	range	0.7 - 6.3	0 - 10	0 - 10
NRS difference treatment phase 1	mean (SD)	-0.44 (0.57)	-1.98 (2.03)	-1.24 (1.68)
	range	-1.7 - 0.3	-6 - 1.3	-6 - 1.3
Pain reduction $\underline{\geq}$ 20% treatment phase 1	n	4	13	17
NRS last day baseline phase 2	mean (SD)	3.3 (1.98)	3.88 (2.69)	3.59 (2.34)
	range	0.3 - 7	0.3 - 10	0.3 - 10
NRS last day treatment phase 2	mean (SD)	3.01 (2.14)	3.57 (1.92)	3.29 (2.02)
	range	0 - 8	0.7 - 7.3	0 - 8
NRS difference treatment phase 2	mean (SD)	-0.29 (0.99)	-0.31 (1.82)	-0.3 (1.44)
	range	-1.5 - 1.7	-3.3 - 4.7	-3.3 - 4.7
Pain reduction ≥ 20% treatment phase 2	n	6	5	11

Abbreviations: SD = standard deviation

Table S3: Adverse events related to study medication

	Number of patients (%)	
Adverse event	**CBDV**	**Placebo**
Concentration disturbance	1 (2.9)	1 (2.9)
Constipation	0 (0)	1 (2.9)
Diarrhea	3 (8.8)	1 (2.9)
Dizziness	0 (0)	2 (5.9)
Dry mouth	3 (8.8)	5 (14.7)
Dysesthesia	0 (0)	1 (2.9)
Dyspepsia	0 (0)	1 (2.9)
Fatigue	0 (0)	1 (2.9)
Gastrointestinal irritation	0 (0)	1 (2.9)
Headache	1 (2.9)	3 (8.8)
Hyperhidrosis	0 (0)	2 (5.9)
Hypertrichosis	1 (2.9)	0 (0)
Insomnia	0 (0)	1 (2.9)
Mood disturbance	0 (0)	1 (2.9)
Nausea	0 (0)	2 (5.9)
Numbness in neck	1 (2.9)	0 (0)
Pruritus	1 (2.9)	1 (2.9)
Tachycardia	0 (0)	1 (2.9)
Vision disturbance	0 (0)	1 (2.9)

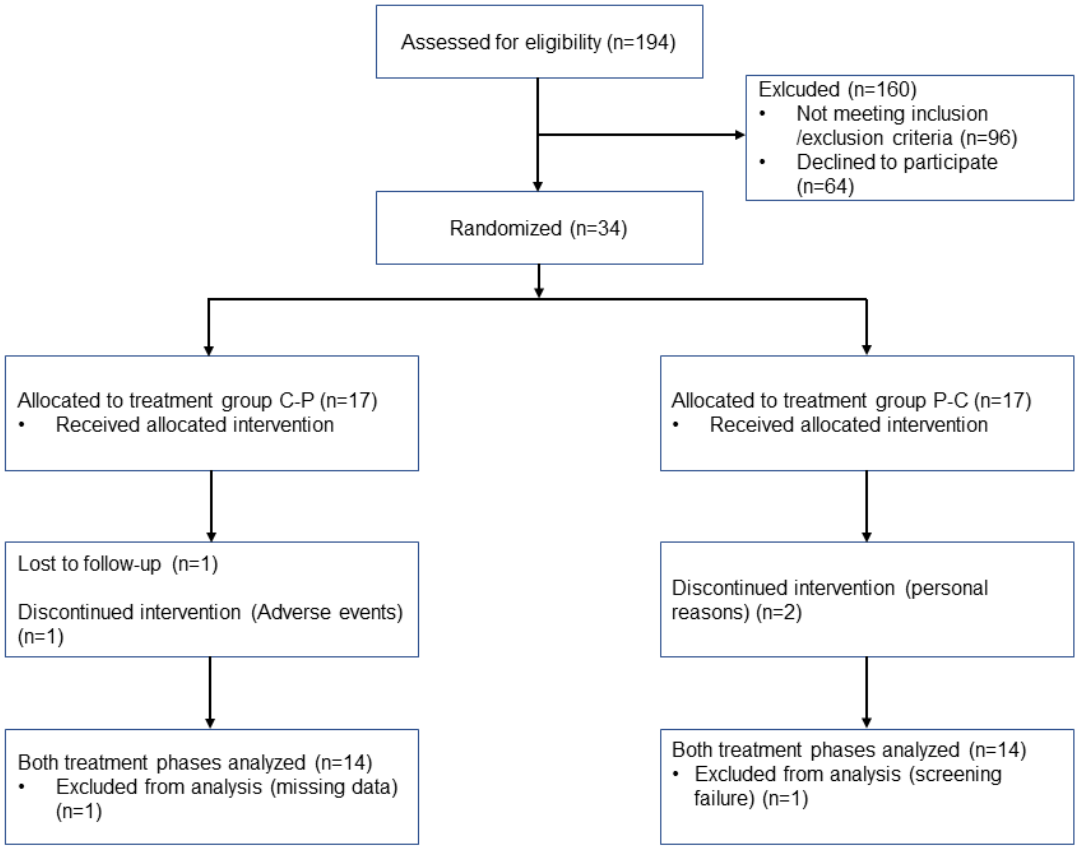


Figure S1: Flow chart of patient inclusion

Oral cannabidivarin (CBDV) solution for treatment of HIV-associated neuropathic pain - a randomized, double-blind, placebo-controlled phase II study

Statistical Analysis Plan

Version 0.3; January 19, 2017

EudraCT-number:	2014-005344-17
Sponsor Trial-Code:	CBDV_2014
Version:	4.0
Date:	19.01.2017

Prof. Dr. med. Christoph Stein,
Coordinating investigator

Place, Date, Signature

Robert Röhle, Statistician

Place, Date, Signature

ORAL CANNABIDIVARIN (CBDV) SOLUTION FOR TREATMENT OF HLV-ASSOCIATED NEUROPATHIC PAIN - A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE II STUDY 1

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1 Study background

1.1 Aim of the study

1.1.1 Primary endpoint

The primary objective of this clinical trial is pain reduction in patients with chronic, painful HIV-associated neuropathy when using CBDV as compared to placebo.

1.1.2 Secondary endpoints

The secondary objectives of this clinical trial include the following questions:

- Does CBDV have any effects on specific pain characteristics?
- Is rescue medication needed?
- Is CBDV sufficiently safe?
- Does CBDV have an effect on physical or mental functions?
- Does patients' expectation have any influence on the effect of CBDV and placebo?
- Does CBDV have any influence on patients' acute subjective responses?
- Does CBDV have an impact on the quality of life and sleep?
- Is there an association between the response to the treatment with CBDV and the genotype of the patients?

1.2 Study design

This investigator-initiated clinical trial is a randomized, double blind, placebo controlled, cross-over study phase II. All participants receive both treatments (CBDV and placebo) in two successive phases. The order of treatments will be allocated by chance (randomized). The trial extends over a period of 13 weeks and is divided into 5 phases. Phases 1 and 4 represent baselines of 1 week each; in phases 2 and 5 study treatments will be administered over a time period of 4 weeks each. Phase 3, a 3-week washout phase, is designed to eliminate a potential carry over effect between both treatment phases. After phase 5 there will be an observation period of 6 weeks to detect any AEs. The schematic procedure is shown in Figure 1.

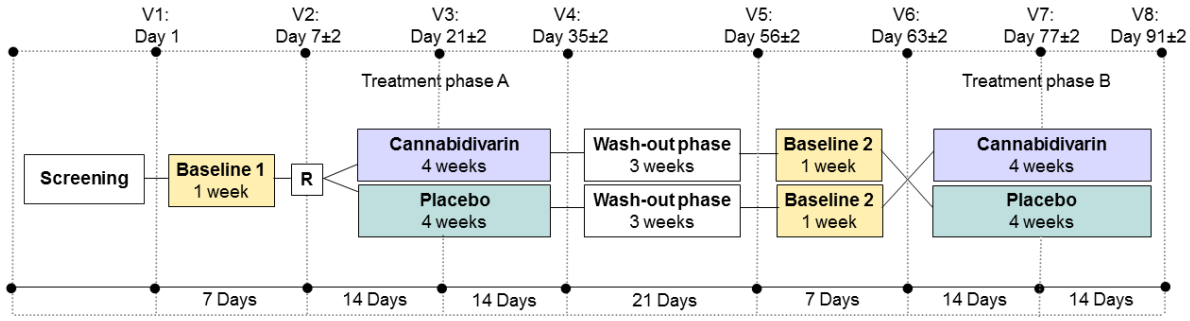

Figure 1: Study design

1.2.1 Treatment / Investigated medicinal product

CBDV is administered as an oral solution (50 mg/ml). The clear, yellowish preparation has a negligible THC content of <0.2%, which is why it does not fall under the narcotics law. A similarly composed solution without active ingredient is used as a placebo. Both solutions are equally administered orally. In the following, the term "study solution" is used when the randomized, blinded substance (CBDV or placebo) is meant.

1.2.2 Blinding

The study is double-blinded. A set of emergency envelopes containing one envelope for each randomisation number is stored in a safe at the trial centre, accessible to all authorised staff. These emergency envelopes contain information on the allocation of the investigational product and should only be opened when it is essential from a medical point of view to know which investigational product the subject is receiving for diagnostic or therapeutic decisions. The date and reason for opening the emergency envelope must be documented by the investigator or an authorized person on the emergency envelope, in the Case Report Form (CRF), and in the subject's medical record.

1.2.3 Case Number Planning

Case number planning was based on the primary endpoint of the 11-point scale (NRS) of pain intensity and a planned crossover design with two parallel groups. The assumption was that the pain intensity under placebo application was on average 6 points. Based on previous publications, it has been shown that the intensity of pain in painful HIV-associated neuropa-

thy can be reduced by approx. 20% by the administration of cannabinoids (Abrams et al., 2007; Ellis et al., 2009). Thus, we assume an average pain intensity of 4.8 points in our verum group. The corresponding standard deviation of 2.5 points was conservatively estimated from the confidence intervals given in the literature (Demant et al., 2014). For this purpose, the standard deviations of 1.1 and 2.58 over CI/2 = 1.96*sqrt(n) were calculated from the half confidence intervals (CI/2) given in the literature as 0.3 and 0.7. The corresponding n in the literature was 52, and finally an SD of 2.5 was chosen because an SD of 1.1 seemed too optimistic. The square of this standard deviation is considered a conservative estimate of the variance of the differences within the subjects. Using a two-seized paired t-test for a 2x2 crossover design, a α=0.05 and a β=0.85 result in a case number of 21 patients per sequence group. After considering about 15% dropouts, the total number of patients to be included in the study is 50. The case number planning was done with the commercial software nQuery Advisor® 7.0.

1.2.4 Inclusion Criteria

Patients meeting all mentioned inclusion criteria can be enrolled into the study:

- Male and female patients with chronic, painful HIV-associated neuropathy (NRS-score ≥4); women who are post-menopausal for more than one year; female patients of child-bearing potential are allowed to participate in this study only if they are permanently sterilized (e,g. tubal occlusion, hysterectomy) or if they provide a negative pregnancy test and are willing to use a highly effective method of contraception (e.g. hormonal contraceptives) during the course of the study and for three months thereafter
- Age: 18-65 years
- Body mass index (BMI): 18-30 kg/m 2
- Fluency in German language
- Signed written informed consent

1.2.5 Exclusion criteria

Patients presenting one of the following criteria will be excluded:

- Individuals related to or dependent on the sponsor, the trial site or the investigator
- Individuals housed in institutions due to official or judicial orders
- Co-incident severe diseases of the central nervous system (e.g. dementia)
- Co-incident major psychiatric conditions
- Acute disorders with functional limitations and/or limitations of neurological assessment
- Limited mental capacity or knowledge of the German language

- Chronic or previous abuse of recreational drugs and/or alcohol
- Pregnancy and lactation as well as planning pregnancy during the course of the study and for three months thereafter
- Men and women of childbearing potential not using adequate contraception during the clinical trial and three months thereafter
- Intolerance to the study medication or to one of the components of the study medication
- Hepatic diseases where
    - the level of ALT or the level of AST exceed three times the upper limit of normal range, and bilirubin exceeds two times the upper limit of normal range or the INR exceeds 1.5 times the upper limit of normal range
    - the levels of ALT or AST exceed three times the upper limit of normal range, in combination with symptoms (fatigue, nausea, vomiting, pain or tenderness in the right upper quadrant, fever, rash and/or eosinophilia)
    - the levels of ALT or AST alone exceed eight times the upper limit of normal range
    - the levels of ALT or AST exceed five times the upper limit of normal range for longer than two weeks
- Chronic renal insufficiency (with significant deviation of the Creatinin-level from the normal range)
- ECG-Parameters outside following reference ranges: PR-interval: 120 ms (lower limit), 220 ms (upper limit); QRS-duration: 0 ms (lower limit), 120 ms (upper limit); QT-interval: 0 ms (lower limit), 500 ms (upper limit); QTcF-Interval (males): 0 ms (lower limit), 430 ms (upper limit), QTcF (females): 0 ms (lower limit), 450 ms (upper limit)
- Clinically significant cardiovascular or metabolic diseases: uncontrolled hypertension (lower
- limit: 90/40 mmHg, upper limit: 140/90 mmHg (18-45 years), 160/90 mmHg (>45 years)); severe heart failure (NYHA > III); abnormal heart rate (lower limit: 40 min -1 (18-45 years), 50 min -1 (>45 years), upper limit: 90 min -1); heart attack within the past 12 months
- Active participation in other clinical trials three months before or within this clinical study

1.2.6 Randomization

The study is double-blinded and randomized. The randomization to the sequence group is carried out in blocks of four via paper-based random lists, which are strictly confidential and stored in a locked cabinet at the study center.

The included patients receive a serial number. Upon unblinding, they are assigned to the sequence group using sealed envelopes.

2 Evaluation collectives

2.1 Definitions

All subjects who have signed the informed consent form and received a randomization number will be counted as inclusion/randomization subjects, even if they have not received an investigational product.

The full analysis set (FAS), based on the Intention-To-Treat (ITT) principle, consists of all randomized subjects who meet all inclusion criteria, who meet no exclusion criteria, who have received at least one dose of an investigational product, and who have had at least one post-baseline determination of the primary endpoint. The FAS is the primary evaluation population. In FAS evaluations, subjects are assigned to the treatment regimen to which they were randomized.

The safety population comprises all subjects who have received at least one dose of an investigational product. In safety population evaluations, subjects are assigned to the treatment regimen to which they were randomized.

2.2 Indications

For all efficacy analyses, the FAS is the primary evaluation population, while the safety population is used for all safety analyses.

3 Study Centers

Recruitment and treatment of the test subjects are carried out in a single test center.

4 Evaluation Variables

4.1 Demographiy and Baseline Characteristics

- Gender
- Age
- Weight and height
- NRS pain value
- Montreal Cognitive Assessment [MoCA] Test
- Antiretroviral drugs
- onset of pain
- Pre-existing conditions (cardiovascular complaints, heart attack, angina pectoris, arrhythmia, respiratory diseases, lung diseases (asthma, COPD), stroke, other neurological

complaints, skin diseases, abdominal complaints, kidney/urinary tract diseases, other diseases)

- Neurological examination (neuropathic pain at rest and during stimulation, motility and muscle tone, reflexes, surface and depth sensitivity))

4.2 Primary Endpoint

The primary endpoint of this clinical trial is the change in pain intensity from baseline to the end of treatment measured on an 11-point scale (NRS) from baseline to CBDV compared to placebo.

For this purpose, the values of the last 7 days of the two baseline phases and the values of the last 7 days of the two treatment phases are averaged separately and the two corresponding differences per period are calculated from the average value of the respective treatment and baseline phases. For patients with less than 7 days of baseline phase, the respective existing values are averaged.

As a second variant, only the values of the last day of the baseline phases or treatment phases are used and the corresponding differences are calculated.

Based on these two variants, the proportion of patients with at least 20% pain reduction in relation to the respective baseline mean value is also determined.

4.3 Secondary Endpoints

4.3.1 Effectiveness

- Additional consumption of pain medication using the Medication Quantification Scale (MQS) according to Harden (Harden et al., 2005) and Gallizi (M. Gallizzi, Gagnon, Harden, Stanos, & Khan, 2008; M. A. Gallizzi, Khazai, Gagnon, Bruehl, & Harden, 2015). Analogous to the calculation of the primary endpoint, the values of the last 7 days or the last day of the baseline phases and treatment phases are averaged and the corresponding difference limits determined.
- Analysis of physical and mental functional parameters (painDETECT, Brief Pain Inventory [BPI] (Radbruch et al., 1999), Hospital Anxiety and Depression Scale [HADS]) for visits 1 (BL 1), 4, 6 (BL 2) and 8
- Analysis of acute subjective well-being after CBDV application (Patient Global Impression of Change Scale [PGIC] (Hurst & Bolton, 2004), Drug effects questionnaire [DEQ-5] (Morean et al., 2013)) for V4 and V8 (PGIC) and in the first week of treatment (DEQ-5)
- DN4i for screening (BL 1), for V4, V6 (BL 2) and V8
- CHANT for screening (BL1), for V4, V6 (BL 2) and V8

- Neurological examination for V3, V4, V6, V7 and V8

Contrary to the information provided in the study protocol, it was not possible to determine patient expectations because the additional effort for the patients was judged to be too great.

4.3.2 Safety/Tolerability

- AEs and SAEs
- Analysis of the side effects of CBDV

4.3.3 Quality of life

- Life (36-Item Short Form Health Survey [SF-36]) and sleep quality (Insomnia-Severity Index [ISI] (Morin, Belleville, Belanger, & Ivers, 2011)) at V2 (BL 1), V4, V6 (BL 2) and V8

5 Handling of missing values and outliers

5.1 Missing Values

For the primary endpoint, no values are replaced, and mean values are used when calculating the pain values for baseline and treatment (see Section 4.2). This is done in contrast to the information in the study protocol, since the available values are averaged in each case.
When determining the MQS values, the following procedure is followed: In the absence of information on the dose category of a drug, the mean value of the other days in the same treatment phase (screening + BL1 + BL2; placebo; CBDV) is used. If two dose categories occur with the same frequency, one of them is selected at random. If no values are available for other days in the same treatment phase, the category "Lower 50% of the therapeutic dose" is used. Missing information on the drug in the existing dose category will not be replaced.
Samples of missing values are also reported after the study to assess the appropriateness of the procedure. If necessary, further procedures are applied to replace the missing values in a sensitivity analysis and the differences in the results are analyzed.
Missing values in the standardized questionnaires will be replaced according to the corresponding specifications. Missing values in the overall or partial scores are not replaced.

5.2 Outliers

As the effectiveness endpoints examined are fixed scores with a predefined range of values, no outliers are examined, as these have already been checked in the data management process.

6 Statistical Analysis

6.1 General Information

Descriptive analyses for continuous parameters include mean, standard deviation, median, interquartile distance, and minimum and maximum, while for categorical variables the absolute and relative frequencies are given with the respective basic totals. All analyses of the study are to be regarded as non-confirmative.

6.2 Demography and Baseline Characteristics

Demographic and baseline characteristics are presented descriptively per sequence group and in total.

6.3 Pre/accompanying medication and diseases

The presence of concomitant diseases is presented descriptively. The antiretroviral drugs for current therapy as well as the current pain medication are listed per patient.

6.4 Exposure to therapy/compliance

Exposure to therapy is descriptively evaluated using the daily dose of the test medication given in the patient diaries. In particular, the proportion of patients with dose reduction or partial or complete discontinuation in the treatment areas are presented descriptively.

6.5 Primary Analyses

The evaluation of the primary endpoint is carried out analogously to the case number planning with a two-sided t-test, taking into account the differences between the periods, whereby a p-value < 0.05 is considered significant. A 95% confidence interval for the difference in therapy outcome is also given. This test is performed for both variants of the calculation of the primary endpoint

In addition to this test for treatment effect variability, a linear mixed model with fixed effects for treatment and period and a random intercept over the patients is used to test the treatment effect together with the period effect.

The proportion of patients with more than 20% improvement in pain intensity is described separately by period and sequence.

6.6 Secondary Analyses

6.6.1 Effectiveness

The consumption of additional pain medication measured with MQS is evaluated analogously to the primary endpoint by means of t-test or mixed linear model.

The scores for the painDETECT (individual categories and overall value), the BPI (mean value questions 3-6 and 9-15), the HADS (anxiety and depression), PGIC, DEQ-5 (individual

result), SF-36 (individual scores) and ISI are evaluated analogously to the primary endpoint using the t-test.
If the normal distribution assumption of the t-test is violated, the variant of the rank sum test after Putt and Chinchilli (Putt & Chinchilli, 2004) is used.
The evaluation of the correlation of a response to therapy (more than 20% pain reduction to BL) and the genotype is performed by DeCode Genetics.

6.6.2 Safety and Tolerability

In contrast to the information given in the study protocol, AEs and SAEs were coded according to CTCAE V 4.0, and are assigned to the treatment with CBDV or placebo. The presentation is based on the number of patients with a specific AE/SAE as well as on the severity and its relation to the study medication
AEs and SAEs are also provided per patient as a listing with identification of the corresponding phase of occurrence.

6.7 Subgroup Analysis

No subgroup analyses are planned.

6.8 Interim Evaluations

No interim evaluations are planned.

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CLINICAL TRIAL PROTOCOL

Oral cannabidivarin (CBDV) solution for treatment of HIV-associated neuropathic pain - a randomized, double-blind, placebo-controlled phase II study

EudraCT-Number	2014-005344-17
Sponsor Trial Code	CBDV_2014
Version	4.0
Date	Jan. 19, 2017

Sponsor	**Coordinating investigator**
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List of abbreviations

AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
AMG	German drug law (Arzneimittelgesetz)
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BfArM	Regulatory authority (Bundesinstitut für Arzneimittel und Medizinprodukte)
BPI	Brief Pain Inventory
CB	Cannabinoid
CBD	Cannabidiol
CBDV	Cannabidivarin
CNS	Central nervous system
CRF	Case Report Form
CYP_{450}	Cytochrom P450
DEQ-5	Drug Effects Questionnaire-5
EC	Ethics committee
ECG	Electrocardiogram
GCP	Good Clinical Practice
GCP-V	GCP-regulation
HAART	Highly active antiretroviral therapy
HADS	Hospital, Anxiety and Depression Scale
HIV	Human Immunodeficiency Virus
HIV-SN	HIV-associated sensory neuropathy
IB	Investigator's Brochure
IC_{50}	50 % inhibitory concentration
ICH	International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISI	*Insomnia Severity Index*
ITT	Intention-To-Treat
KKS	Coordination center for clinical trials (Koordinierungszentrum für Klinische Studien)
MoCA	Montreal Cognitive Assessment
NOAEL	No Observed Adverse Effect Level
NRS	Numerical Rating Scale
PGIC	Patient Global Impression of Change
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SF-36	*36-Item Short Form Health Survey*
SNI	Spared Nerve Injury
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Events
THC	Tetrahydrocannabinol

Synopsis

Title	Oral cannabidivarin (CBDV) solution for treatment of HIV-associated neuropathic pain - a randomized, double-blind, placebo-controlled phase II study
Short title	Cannabidivarin (CBDV) for neuropathic pain in HIV
EudraCT	2014-005344-17
Sponsor Trial Code	CBDV_2014
Indication	Chronic painful HIV-associated neuropathy
Phase	II
Treatments	Study medication: Cannabidivarin (CBDV) Comparative therapy: Placebo (CBDV Vehicle)
Primary objective	Pain reduction when using cannabidivarin (CBDV) as compared to placebo
Secondary objectives	• Does CBDV have any effects on specific pain characteristics? • Is rescue medication needed? • Is CBDV sufficiently safe? • Does CBDV have an effect on physical or mental functions? • Does patients' expectation have any influence on the effect of CBDV and placebo? • Does CBDV have any influence on patients' acute subjective response? • Does CBDV have an influence on the quality of life and sleep? • Is there an association between the response to the treatment with CBDV and the genotype of the patients?
Trial design	Randomized, double blind, placebo-controlled clinical trial with cross-over design

Trial population	Principal inclusion criteria:
	• Male and female patients with chronic, painful HIV-associated neuropathy (NRS-score ≥4); women who are post-menopausal for more than one year can participate in this study; female patients of child-bearing potential are allowed to participate in this study only if they are permanently sterilized (e,g. tubal occlusion, hysterectomy) or if they provide a negative pregnancy test and are willing to use a highly effective method of contraception (e.g. hormonal contraceptives) during the course of the study and for three months thereafter
	• Age: 18-65 years
	• Body mass index (BMI): 18-30 kg/m^2
	• Fluency in German language
	• Signed written Informed Consent
	
	Principal exclusion criteria:
	• Individuals related to or dependent on the sponsor, the trial site or the investigator
	• Individuals housed in institutions due to official or judicial orders
	• Co-incident severe diseases of the central nervous system (e.g. dementia)
	• Co-incident major psychiatric conditions
	• Acute disorders with functional limitations and/or limitations of neurological assessment
	• Limited mental capacity or knowledge of the German language
	• Chronic or previous abuse of recreational drugs and/or alcohol
	• Pregnancy and lactation as well as planning pregnancy during the course of the study and for three months thereafter
	• Men and women of childbearing potential not using adequate contraception during the clinical trial and three months thereafter
	• Intolerance to the study medication or to one of the components of the study medication
	• Hepatic diseases where
	  • the level of ALT or the level of AST exceed three times the upper limit of normal range, **and** bilirubin exceeds two times the upper limit of normal range **or** the INR exceeds 1.5 times the upper limit of normal range
	  • the levels of ALT or AST exceed three times the upper limit of normal range, in combination with symptoms (fatigue, nausea, vomiting, pain or tenderness in the right upper quadrant, fever, rash and/or eosinophilia)

	• the levels of ALT or AST alone exceed eight times the upper limit of normal range • the levels of ALT or AST exceed five times the upper limit of normal range for longer than two weeks • Chronic renal insufficiency (with significant deviation of the Creatinin-level from the normal range) • ECG-Parameters outside following reference ranges: PR-interval: 120 ms (lower limit), 220 ms (upper limit); QRS-duration: 0 ms (lower limit), 120 ms (upper limit); QT-interval: 0 ms (lower limit), 500 ms (upper limit); QTcF-Interval (males): 0 ms (lower limit), 430 ms (upper limit), QTcF (females): 0 ms (lower limit), 450 ms (upper limit) • Clinically significant cardiovascular or metabolic diseases: uncontrolled hypertension (lower limit: 90/40 mmHg, upper limit: 140/90 mmHg (18-45 years), 160/90 mmHg (>45 years)); severe heart failure (NYHA > III); abnormal heart rate (lower limit: 40 min^{-1}(18-45 years), 50 min^{-1} (>45 years), upper limit: 90 min^{-1}); heart attack within the past 12 months • Active participation in other clinical trials three months before or within this clinical study
Trial duration and dates	First subject in: January 2017 Last subject in: December, 2018 Duration of the trial: 3 years (estimates)
Number of subjects	50
Number of sites	1
Primary endpoint	Reduction of pain intensity (,,baseline") determined by on an 11-point numerical rating scale (NRS) after CBDV application as compared to placebo.
Secondary endpoints	• Analysis of specific pain parameters • Analysis of rescue medication • Analysis of side effects • Analysis of parameters of physical and mental functions • Analysis of patients' expectation of the clinical effect • Analysis of patients' acute subjective response • Analysis of quality of life and sleep • Genotyping
Statistical analysis	Sample size estimation is based on the primary end point and cross-over design with two parallel groups. We assume a reduction of pain intensity with CBDV by approximately 20% as compared to placebo. Using a two-sided paired t-test for a 2x2 cross-over design, this results in a sample size of 21 patients per group (with α=0,05 and β=0,85). Considering approximately 15% of drop outs, 50 patients have to be included.

Time schedule

Visit / Action	Screening	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Follow-up
Trial day		1	7 ±2	21 ±2	35 ±2	56 ±2	63 ±2	77 ±2	91 ±2	6 weeks
Patient information and informed consent	×									
Inclusion and exclusion criteria	×									
MoCA	×									
Demographic data		×								
Previous and concomitant diseases		×								
Previous and concomitant treatments		×								
Randomization			×							
Pregnancy test	×						×			
Physical exam		×		×	×		×	×	×	
Neurological exam		×		×	×		×	×	×	
Vital signs		×		×	×		×	×	×	
Lab parameters	×			×	×		×	×	×	
Blood sample for genotyping									x	
painDETECT		×			×		×		×	
HADS		×			×		×		×	
BPI		×			×		×		×	
PGIC					×				×	
SF-36			x		X		x		X	
ISI			x		x		X		x	
AEs				×	×	×	×	×	×	×
Rescue medication		×	×	×	×	×	×	×	×	
End of trial										×

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1. INTRODUCTION

1.1 Scientific background

Approximately 7-8% of the general population suffer from **neuropathic pain**, occurring after damage or disease of somatosensory or autonomic nerves in the peripheral or central nervous system (CNS) [1]. Various diseases might underlie neuropathic pain such as multiple sclerosis, diabetes mellitus or HIV-infection. Independent of the cause, chronic neuropathic pain impairs quality of life and negatively affects the patients' social environment and work situation. Although treatment of chronic neuropathic pain should be based on pharmacological and interdisciplinary non-pharmacological approaches (e.g. behavioral, physical or occupational therapy), pharmacological pain therapy often predominates [2]. Drugs of different classes are used such as anti-depressants (e.g. amitriptyline), anti-epileptics (e.g. gabapentin, pregabalin and carbamazepine) and opioid analgesics. Tramadol and morphine are regarded as first choice. However, the application of those drugs is markedly limited by serious side effects which are mainly mediated in the CNS and can lead to addiction, respiratory depression or tolerance. To further investigate these questions a consortium of 11 European research groups is funded by the EU commission (https://www.upf.edu/cexs/news/neuropain.html). As a partner of this consortium we carry out the present study as an "investigator-initiated trial".

HIV-associated sensory neuropathy (HIV-SN) is a peripheral neuropathy and represents one of the most common neurological complications in context of HIV-infection. Although successful highly active antiretroviral therapies (HAART) have been introduced for the treatment of HIV-infections, the incidence of HIV-SN has increased over the last several years [3]. Symptomatic therapy of HIV-associated neuropathic pain follows guidelines for painful neuropathies. However, some of these standard therapies cannot be used due to interactions with HAART (e.g. carbamazepine [3]) or low efficacy (e.g. pregabalin or amitriptyline [2]). This significantly limits the choice of efficient pain medications. Consequently, efforts are made to find additional therapeutic approaches for HIV-associated neuropathic pain.

In this context the medical use of **cannabis and cannabinoids** is discussed [4]. Using different animal experiments and pain models it was shown that delta-9-tetrahydrocannabinol (THC), the most abundant potentially therapeutic ingredient of the *Cannabis sativa* L. plant, and some synthetic derivatives led to effective analgesia [5, 6]. Randomized controlled clinical trials for the treatment of chronic neuropathic pain of different etiology compared cannabis extracts or their main ingredients THC and Cannabidiol (CBD) in diverse formulations with placebo. In most of the studies superiority of cannabinoids over placebo was shown, mainly manifested as pain reduction and amelioration of pain-associated symptoms [7-14]. Despite these positive effects there are still controversial opinions about the medical utilization of cannabinoids in painful neuropathies. For example, cannabis or cannabinoids were mostly applied in inhalative form (such as cigarettes), which does not comply with accepted pharmaceutical applications and does not allow precise dosing. Furthermore, the question was raised how the medicinal use of cannabis and cannabinoids should be controlled and misuse prevented [15]. Also, psychoactive side effects of cannabinoids (such as impaired cognitive function and psychomotor performance, disturbed perception of time and euphoria [16]) as well as drug-drug interactions do not allow an unlimited application in routine medical care so far. Currently, possible pharmacogenomic foundations for the response to Cannabinoids are discussed [17].

Cannabinoids (i.e. phytocannabinoids, endocannabinoids and synthetic cannabinoids) exert their effects mainly via activation of the endogenous cannabinoid (CB) receptor system. While CB_1 receptors are mostly found in the CNS, CB_2 receptors are predominantly expressed on immune cells and under inflammatory conditions in the CNS and peripheral sensory nerve fibers. Psychotropic effects are mainly mediated via activation of CB_1 receptors.

Cannabidivarin (CBDV) is prepared from *Cannabis sativa* L. plants that have defined chemical profiles (chemotypes). As plants rich in CBDV are rare in nature, little is known about the pharmacology of this compound. CBDV was reported to have anticonvulsant actions [18], analgesic properties, and antipsychotic actions in preclinical *in vivo* models, and demonstrates significant anti-cancer activity *in vitro* (unpublished study reports). CBDV has only low affinity to CB_1 and CB_2

receptors. However, CBDV modulates metabolizing enzymes of the endogenous cannabinoid system (ECS). In addition, CBDV may act on ion channels such as Transient Receptor Potential (TRP) channels (TRPV1, TRPV4, TRPA1 and TRPM8) [19]. In context of preclinical experiments different dosages of CBDV were tested in an *in vivo* animal model for neuropathic pain (Spared Nerve Injury, SNI). Application of CBDV resulted in reduced mechanical and thermal hyperalgesia. In addition, expression of several neural and glial genes involved in programmed cell death (apoptosis) and potentially affected by chronic pain in the CNS and peripheral nervous system has been analyzed. CBDV led to a reduced expression, probably pointing at protective, anti-apoptotic mechanisms (see Investigator's Brochure and unpublished study reports). In summary, those data make CBDV a promising candidate for the treatment of neuropathic pain.

1.2 **Trial rationale**

The study population comprises patients with chronic painful HIV-associated neuropathy. Today, HIV-SN is one of the most common neurological complications of HIV-infection and its incidence increases with increasing age and application of HAART. As no causal treatment options are available, patients are usually treated with common medications for painful neuropathies which often do not lead to sufficient pain reduction. Therefore, this clinical trial specifically aims at pain reduction in the above mentioned study population by application of a novel cannabinoid (as compared to placebo).

So far, there are only few randomized controlled clinical trials analyzing cannabinoids for treatment of HIV-associated neuropathic pain. Although those trials achieved positive effects regarding pain reduction by inhalative cannabinoids [8, 9] there are still controversial discussions about their medical application. The chances of success of the present trial are considered very good as the investigational medicinal product (IMP) revealed significant anti-nociceptive and anti-psychotic efficacy in rat models (SNI, conditioned avoidance responding (CAR) and apomorphine-induced stereotypic behavior). In addition, CBDV is available in preparations for oral application which allow constant application of CBDV in pharmaceutically accepted dosage forms. Pre-clinical *in vivo* experiments revealed reduced thermal and mechanical hyperalgesia by CBDV (unpublished study reports from GW Pharmaceuticals), which might be symptoms of painful HIV-SN. It was shown that cannabis preparations are beneficial for treatment of other diseases or symptoms (e.g. Sativex® for moderate to severe spasms associated with multiple sclerosis or Marinol® for AIDS-associated loss of appetite and weight). This trial will elucidate whether CBDV is capable of reducing pain intensity in painful HIV-SN without the incidence of serious side effects. Those data should corroborate the results already obtained in other clinical trials and lead to the application of cannabinoids in treatment of HIV-associated neuropathic pain. Because of the current discussions mentioned in 1.1 about possible pharmacogenomic foundations for the therapeutic response to Cannabinoids the genotype of the patients is determined (as a pilot-study/secondary endpoint) [17].

1.3 **Treatment and rationale for dose selection**

CBDV will be applied as an oral solution (50 mg/ml; the formulation is provided below). The product is a clear yellow liquid, containing less than 0.2% of THC. This formulation is not listed in Schedules I to III of the German Narcotic Drugs Act. The placebo solution is composed of similar ingredients as the active solution but without CBDV. Both solutions will be applied orally. As the study medication is not licensed yet, there are no approved dosages. Based on the results of 13-week repeated oral dose toxicology studies of CBDV in dogs and rats and a NOAEL (no observed adverse effect level) of 50 mg CBDV/kg/day, a maximum dosage of 800 mg/day was calculated for initial application in humans.

This dosage and lower dosages (25, 75, 200 and 400 mg CBDV) did not elicit any serious side effects in a phase I trial in healthy volunteers. Even repeated application of 800 mg CBDV/day was tolerated well in healthy study participants.

Due to the similarity in chemical structures between CBDV and CBD and good tolerance of CBD in humans (e.g. shown after six-week application of 700 mg CBD/day in patients with Chorea Huntington [20, 21]), it is assumed that CBDV will be tolerated by humans just as well as CBD. Based

on these assumptions as well as existing clinical and preclinical data, a dosage of 400 mg CBDV/day over a period of four weeks was considered reasonable and will be used in this clinical trial (for additional information about the IMP see chapter 4).

Material	CBDV solution (50 mg/ml)	Placebo solution
CBDV	50.0 mg	-
Anhydrous ethanol	79.0 mg	79.0 mg
Sucralose	0.5 mg	0.5 mg
Strawberry flavour	0.2 mg	0.2 mg
Refined sesame oil	q.s. to 1.0 ml	q.s. to 1.0 ml

1.4 Risk-benefit assessment

As there are no completed phase II and III clinical trials with CBDV available until now, it is impossible to document benefits at this time. However, it should be noted that several studies have been conducted with CBD Botanical Drug Substance (BDS) containing approximately 0.9-1.9% CBDV of the CBD content [22, 23]. In those studies no side effects or risks associated with CBDV were reported.

Recently the manufacturer initiated two phase II clinical trials for the treatment of focal seizures with CBDV ("A Double Blind, Randomized, Placebo-controlled, Two-part Study to Investigate the Pharmacokinetics, Followed by Efficacy and Safety of GWP42006 as add-on Therapy in Patients with Inadequately Controlled Focal Seizures"; ClinicalTrials.gov Identifier NCT02369471 und NCT02365610). Primary and secondary outcome measures are pharmacokinetic parameters of CBDV and its metabolites in the presence of other antiepileptic drugs as well as assessment of safety and tolerability of CBDV when applied over a longer time period. Even though a precise risk-benefit assessment of CBDV can only be done after completion of additional clinical and epidemiological studies, a possible therapeutic benefit for the treatment of HIV-associated painful neuropathy may be assumed based on data of preclinical toxicology studies and the first-in-human (FIH) clinical trial.

CBDV was developed by GW Pharmaceuticals for the treatment of epilepsy and is similar to THC and CBD prepared from the *Cannabis Sativa* L. plant. While THC is subject to the German Narcotic Drugs Act due to its euphoric effects, CBDV is not a scheduled narcotic drug. According to current scientific findings CBDV has low affinity to the CB_1 receptor (which mediates psychoactive and euphoric effects) and probably acts as a partial CB_2 receptor agonist. In preclinical *in vivo* experiments CBDV did not exert any psychoactive effects and therefore has a low potential for abuse (Tetrad Assay and Abuse Liability Study).

CBDV was tested in a battery of standard safety assays and showed no evidence of CNS, respiratory or cardiac toxicity. Standardized genotoxicity studies showed no evidence of genotoxicity or major organ toxicity after repeated dosing. However, all tested dosages led to increased levels of liver enzymes and hepatocyte hypertrophy in 13 week repeat dose studies in rats. Similar effects were observed in dogs, whereas lower CBDV dosages did not elicit hepatocyte hypertrophy. The recorded hepatocyte hypertrophy is commonly associated with metabolism of xenobiotic substances or their metabolites and considered of minor relevance. Furthermore, reported weight loss in rats and dogs after repeated CBDV application was attributed to the pharmacodynamic properties of this drug.
As shown in preclinical *in vivo* models, CBDV also exhibits anti-psychotic, analgesic and anti-epileptic actions. CBDV did not impair motor activity in animal experiments (Rotarod test in rats), did not enhance chemically induced nausea, and evoked nausea in dogs only at a dosage of 100 mg CBDV/kg/day. In preclinical *in vivo* studies CBDV clearly demonstrated reduced mechanical and thermal hyperalgesia in a model of neuropathic pain (SNI).

Based on preclinical toxicology studies a maximum oral dosage of 800 mg/day was calculated for initial application in humans. Both after single (25, 75, 200, 400, 800 mg) and multiple dosing (800

mg once daily for five days), absorption of CBDV was fast. The maximum plasma concentration increased proportionally with increasing CBDV dosages of 200 mg to 800 mg. CBDV was well tolerated and the incidence of adverse events (AEs) was low. Compared to low dose groups, the incidence of AEs was marginally higher after dosing with 400 mg and 800 mg CBDV; this was also the case after multiple oral doses over five days. After multiple oral applications, slightly more subjects reported at least one AE in the active group (4 [50.0%] subjects) than the placebo group (1 [33.3%] subject). There were no serious or severe AEs and no subject experienced AEs leading to withdrawal of the IMP. Several subjects in both groups experienced no AEs at all. All AEs were mild and the majority was considered IMP-related. Two subjects in the active group were aged 45 years or younger and neither of these subjects reported any AEs. Among others, four out of six participants (aged 45 years and older) reported cough, somnolence, disorientation, nausea, headache and pain in extremities. An age-related trend in the incidence of AEs was not detectable. There were no clinically significant findings in any laboratory tests, vital signs, ECG recordings or physical examinations at any time of the trial. Using the Cannabis Withdrawal Scale (CWS) the majority of subjects did not experience any clinically significant CBDV-associated withdrawal symptoms 24 hours after application.

CBDV is highly bound to plasma proteins. Thus, only a minor part is available as active drug. It is likely that CBDV (similar to e.g. THC [24]) may be stored for as long as four weeks in human fatty tissue and may then slowly released, at sub-therapeutical levels, into the blood. 7-OH-CBDV probably presents the main metabolite in the human body. Until now, two major metabolites of CBDV (6- und 7-Hydroxy (OH)-CBDV) were identified in plasma of healthy volunteers in a FIH-study (GWEP 1303). Currently, there is no evidence for psychoactive (side) effects of those metabolites (at dosages up to 100 mg/kg), confirmed by *in vivo* Tetrad assays in rodents. Further studies to identify metabolites are ongoing at GW pharmaceuticals.
Comparison of concentration versus time profiles following administration of single and multiple CBDV doses were consistent with enteral application on day one and five of the examination. The profiles of both metabolites were consistent with formation of metabolic products following enteral application.
The time of maximum concentration (T_{max}) of study medication in plasma was 4-5 hours for CBDV and 2.5-2.75 hours for both metabolites. After five-day oral application of CBDV significantly elevated maximum concentrations (C_{max}) and AUC-values (concentration versus time curves) were detected for CBDV, 6- and 7-OH-CBDV. As observed following single ascending oral doses of CBDV (25, 75, 200, 400, 800 mg), exposure to 7-OH-CBDV was markedly higher than exposure to CBDV. In all cases, significantly elevated values led to accumulation ratios of 1.5-1.8 for C_{max} and 1.8-2.8 for $AUC_{(0\text{-}inf)}$. The C_{max} ratio of 7-OH-CBDV to CBDV was 2.9 on both day one and five, which indicates neither saturation nor inhibition or induction of metabolites. Overall, low CBDV concentrations were detected in plasma of healthy volunteers. This suggests that steady state was not achieved by day 5. This observation was indirectly confirmed by consistently increasing CBDV concentrations.
In addition, elimination rates ($T_{1/2el}$) were assessed which were 6.37 hours for CBDV and 6.2 hours for 7-OH-CBDV on day one. As both molecules revealed similar elimination rates ($T_{1/2el}$), it can be assumed that 7-OH-CBDV follows kinetics limited by the formation rate.

Similar to THC and CBD, CBDV is metabolized by various hepatic cytochrome (CYP) P_{450} enzymes. There has been no clinical exposure to CBDV to date, so the incidence of drug-drug interactions in patients is currently unknown. *In vitro* induction and inhibition studies with CBDV in human liver microsomes and hepatocytes revealed no significant induction of CYP1A2, 2C9 or 3A4 but potential inhibition of CYP2C19, 2C6 and 2B9. Drug interactions with HAART may occur through CYP3A4, the most important isoenzyme metabolizing antiretroviral drugs. As CBDV did not seem to have an influence on CYP3A4 enzyme activity and CYP2C19 is not involved in metabolizing antiretroviral substances, clinically significant interactions are unlikely.

Cognitive function of healthy subjects was assessed in a FIH-study (GWEP 1303) using the Fepsy battery. In most cases, there was no difference between pre-dose and post-dose test results. However, in some of the reaction time tests, an increase or decrease following dosing was observed. As this effect was observed in both active and placebo groups, it is unlikely to be a drug effect. Pre-

dose and post-dose blood samples of healthy subjects were profiled using microarrays to identify gene expression differences. Additionally, functional analysis was performed to characterize the observed changes. More transcripts were differentially expressed in placebo subjects. However, this may have been due to the lower number of subjects in the placebo group. Transcripts differentially expressed after dosing with CBDV were primarily involved in ribosomal activity and protein translation. In placebo samples, the primary function associated with the differentially expressed transcripts was signal transduction.

So far, efficacy and safety of CBDV was only examined in preclinical studies. Clinical trials that successfully applied cannabinoid substances such as THC or CBD in patients with painful HIV-associated neuropathy support those preclinical data, even though cannabinoids were mainly administered in inhalative application forms (such as cigarettes) [8, 9]. Smoking is a very fast and efficient method of drug absorption, although different inhalation techniques markedly influence the level of drug exposure and lead to large interindividual differences and therapeutic effects. Such factors can be minimized by application of an oral solution, as planned in the present clinical trial. Overall, after reviewing the existing data the risk-benefit ratio can be considered acceptable.

2. TRIAL OBJECTIVES

2.1 Primary objective

The primary objective of this clinical trial is pain reduction in patients with chronic, painful HIV-associated neuropathy when using CBDV as compared to placebo.

2.2 Secondary objectives

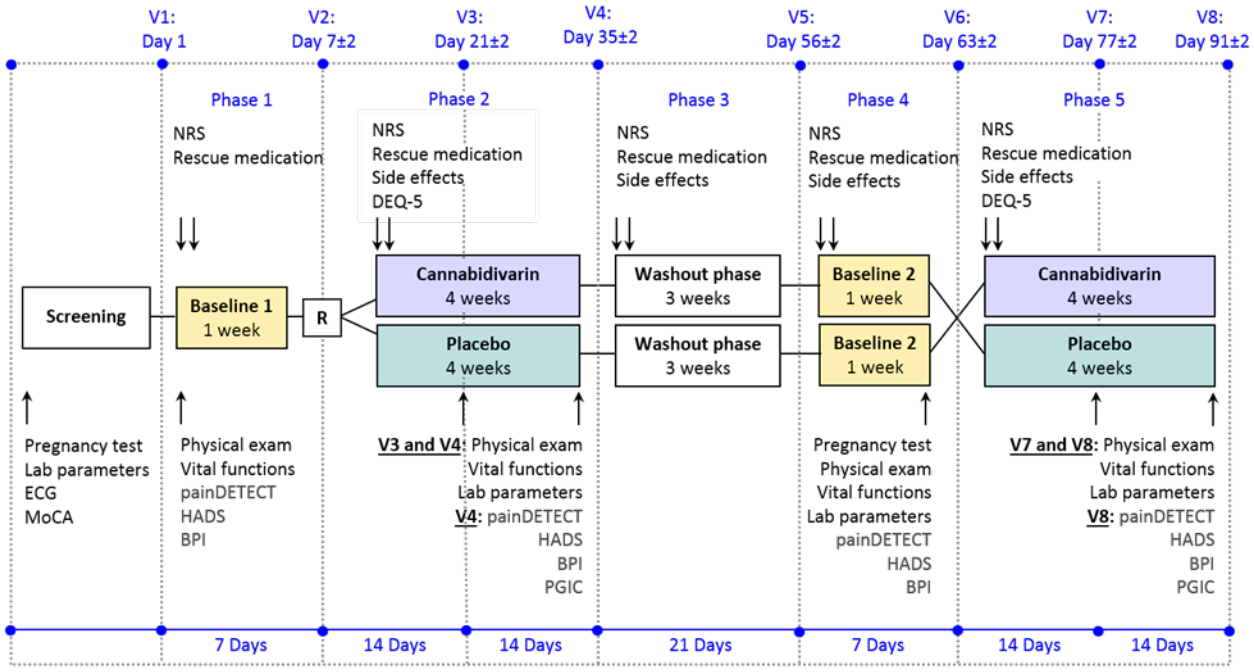
The secondary objectives of this clinical trial include the following questions:

- Does CBDV have any effects on specific pain characteristics?
- Is rescue medication needed?
- Is CBDV sufficiently safe?
- Does CBDV have an effect on physical or mental functions?
- Does patients' expectation have any influence on the effect of CBDV and placebo?
- Does CBDV have any influence on patients' acute subjective responses?
- Does CBDV have an impact on the quality of life and sleep?

Is there an association between the response to the treatment with CBDV and the genotype of the patients?

3. TRIAL DESIGN

This investigator-initiated clinical trial is a randomized, double blind, placebo controlled, cross-over study phase II. All participants receive both treatments (CBDV and placebo) in two successive phases. The order of treatments will be allocated by chance (randomized).
The trial extends over a period of 13 weeks and is divided into 5 phases. Phases 1 and 4 represent baselines of 1 week each; in phases 2 and 5 study treatments will be administered over a time period of 4 weeks each. Phase 3, a 3-week washout phase, is designed to eliminate a potential carry over effect between both treatment phases. After phase 5 there will be an observation period of 6 weeks to detect any AEs.



Study design overview
BPI: Brief Pain Inventory, DEQ-5: Drug Effects Questionnaire, ECG: Electrocardiogram, ISI: Insomnia Severity Index, HADS: Hospital Anxiety and Depression Scale, MoCA: Montreal Cognitive Assessment, NRS: Numerical Rating Scale, PGIC: Patient Global Impression of Change Scale, SF-36: 36-Item Short Form Health Survey, R: Randomization, V: Visit, ↑: one-time measurement, ↓↓: daily measurement.

3.1 Trial duration and time schedule

The duration of this trial is expected to be 3 years. The subject recruitment is planned to start in January 2017 and end in December 2018. The actual overall trial duration or subject recruitment period may differ from these time periods.

3.2 Number of subjects and trial centers

It is planned to enroll 50 subjects, i.e. 25 subjects per treatment group. Recruitment and treatment of subjects shall be performed in 1 trial center.

3.3 Primary endpoint

Primary endpoint of this clinical trial is pain intensity (at ,,baseline"), measured by an 11-point numerical rating scale (NRS) after CBDV application as compared to placebo.

3.4 **Secondary endpoints**

Secondary endpoints of this clinical trial are the following:

- Analysis of specific pain parameters
- Analysis of rescue medication
- Analysis of side effects
- Analysis of parameters of physical and mental functions
- Analysis of patients' expectations regarding the clinical effect
- Analysis of patients' acute subjective responses
- Analysis of quality of life and sleep
- Genotyping

3.5 **Measures taken to minimize/avoid bias**

3.5.1 Randomization

This trial will be conducted in a double-blind and randomized fashion. Randomization to a sequence of treatments will occur in blocks of four using paper-based random lists which will be stored in a lockable cabinet.

Included subjects will receive a serial number. Allocation to the sequence group will be documented inside sealed envelopes. Integrity or breaking the seal, respectively, will be checked and documented after conclusion of the trial by the Koordinierungszentrum für Klinische Studien (KKS) of the Charité.

3.5.2 Unblinding

A set of emergency envelopes, consisting of one envelope per random number, is placed in a safe in the test center and accessible to all entitled employees.

Emergency envelopes contain information about the allocation of study medications and are only to be opened if it is absolutely necessary to know for diagnostic or therapeutic decisions, which participant received which type of medication.

Date and reason for opening of emergency envelopes have to be documented by the investigator or an authorized person on the emergency envelope and in the patient’s CRF and medical file.

Even at the end of the clinical trial, emergency envelopes are not to be opened by the investigator.

3.6 **Selection and withdrawal of subjects**

3.6.1 Recruitment

No subject will be allowed to enroll in this trial more than once. The majority of study participants have already been recruited in context of an observation study at the Charité by personal contact of the investigator with attending physicians in diverse institutes, clinics and practices. Patient support groups (such as “Schwulenberatung” and “Berliner Aids-Hilfe”) have been contacted as well. Additional strategies for patient recruitment comprise publication of this study in public transportation. The cooperation of medical practitioners with a large patient base is crucial for this study. As these practitioners have to make an effort to recruit patients for the study (provision of employees for the search of patients in the patient files or expenditure of their own time to do so, contacting these patients beyond their appointments), the imparting practitioner will be offered a fee of 100 € if the recruited patient is included in the study. As a compensation for extra effort (filling in questionnaires, documentation) the patients will be offered a fee of 200 €, if the study is completed successfully.

3.6.2 Inclusion criteria

- Male and female patients with chronic, painful HIV-associated neuropathy (NRS-score ≥4); women who are post-menopausal for more than one year; female patients of child-bearing

potential are allowed to participate in this study only if they are permanently sterilized (e,g. tubal occlusion, hysterectomy) or if they provide a negative pregnancy test and are willing to use a highly effective method of contraception (e.g. hormonal contraceptives) during the course of the study and for three months thereafter
- Age: 18-65 years
- Body mass index (BMI): 18-30 kg/m^2
- Fluency in German language
- Signed written informed consent

3.6.3 Exclusion criteria

Patients presenting one of the following criteria will be excluded:
- Individuals related to or dependent on the sponsor, the trial site or the investigator
- Individuals housed in institutions due to official or judicial orders
- Co-incident severe diseases of the central nervous system (e.g. dementia)
- Co-incident major psychiatric conditions
- Acute disorders with functional limitations and/or limitations of neurological assessment
- Limited mental capacity or knowledge of the German language
- Chronic or previous abuse of recreational drugs and/or alcohol
- Pregnancy and lactation as well as planning pregnancy during the course of the study and for three months thereafter
- Men and women of childbearing potential not using adequate contraception during the clinical trial and three months thereafter
- Intolerance to the study medication or to one of the components of the study medication
- Hepatic diseases where
    - the level of ALT or the level of AST exceed three times the upper limit of normal range, **and** bilirubin exceeds two times the upper limit of normal range **or** the INR exceeds 1.5 times the upper limit of normal range
    - the levels of ALT or AST exceed three times the upper limit of normal range, in combination with symptoms (fatigue, nausea, vomiting, pain or tenderness in the right upper quadrant, fever, rash and/or eosinophilia)
    - the levels of ALT or AST alone exceed eight times the upper limit of normal range
    - the levels of ALT or AST exceed five times the upper limit of normal range for longer than two weeks
- Chronic renal insufficiency (with significant deviation of the Creatinin-level from the normal range)
- ECG-Parameters outside following reference ranges: PR-interval: 120 ms (lower limit), 220 ms (upper limit); QRS-duration: 0 ms (lower limit), 120 ms (upper limit); QT-interval: 0 ms (lower limit), 500 ms (upper limit); QTcF-Interval (males): 0 ms (lower limit), 430 ms (upper limit), QTcF (females): 0 ms (lower limit), 450 ms (upper limit)
- Clinically significant cardiovascular or metabolic diseases: uncontrolled hypertension (lower limit: 90/40 mmHg, upper limit: 140/90 mmHg (18-45 years), 160/90 mmHg (>45 years)); severe heart failure (NYHA > III); abnormal heart rate (lower limit: 40 min^{-1}(18-45 years), 50 min^{-1} (>45 years), upper limit: 90 min^{-1}); heart attack within the past 12 months
- Active participation in other clinical trials three months before or within this clinical study

3.6.4 Withdrawal criteria

Subjects can withdraw their consent without giving any reasons at any time during the trial. This will not result in any disadvantages for them. However the investigator should try to arrange a final visit in order to record relevant data.

Subjects may be withdrawn from the trial for the following reasons:

- At their own request
- If continuation of the trial would be detrimental to the subject's well-being in the opinion of the investigator (e.g. because of non-tolerable AEs)
- Occurrence of pregnancy
- Non-compliance of participant regarding intake of investigational product and/or keeping visit times and/or due to any other reasons jeopardizing data recording
- Medical reasons, such as unexpected AEs or SAEs, abnormal blood pressure values (see chapter 3.6.3), ECG parameters outside specified values (see chapter 3.6.3) or lab parameters outside specified standard values (see chapter 6.2.5)

The sponsor or investigator decides about withdrawal of subjects from the trial in case of occurrence of criteria mentioned above. The reason for withdrawal must be recorded in the CRF and in the subject's medical records.

In case of withdrawal of a subject at their own request, the reason should be asked for and documented. The subject should be followed up for six weeks after the last application of the study treatment for documentation of the intensity of the pain (NRS-Score), required emergency medication and occurrence of any AEs; those AEs should be documented.

All serious AEs of withdrawn subjects should be followed up until resolution or stabilization of health condition of the subject, but no longer than six weeks after subject's discontinuation from the trial.

Withdrawn subjects will not be replaced.

3.6.5 Premature closure of trial site

For the following reasons the trial may be discontinued:

- Novel scientific findings which do not justify continuation of the trial
- Cumulative occurrence of hitherto unknown AEs regarding their nature, severity and duration, or the unexpected increase in incidence of known AEs, such as abnormal blood pressure values (see chapter 3.6.3), ECG parameters outside specified values (see chapter 3.6.3) or lab parameters outside specified standard values (see chapter 6.2.5)
- Medical or ethical reasons negatively affecting the trial
- Difficulties in the recruitment of subjects

The ethics committee (EC) and the regulatory authority must be notified within 15 days. Additionally, all trial materials must be returned.

4. TRIAL TREATMENTS

4.1 Investigational treatments

The IMP is a clear, yellowish liquid provided by the pharmaceutical manufacturer GW Pharmaceuticals (England) for oral application.

4.1.1 Dosage schedule

The study medication (CBDV or placebo) will be administered over a four week period. While one treatment arm receives CBDV in the first treatment phase, the other one receives placebo. In the second phase treatment groups will be switched and receive the complementary substance (placebo or CBDV). Study medication will be administered daily by means of a syringe at 9 am in a single dosage of 400 mg (=8 ml of liquid).
After conclusion of this trial subjects will only receive medications prescribed by their attending physician.

4.1.2 Therapeutic effects

As no efficacy studies with CBDV have been conducted in humans, there are no data available about CBDV's therapeutic efficacy in pain syndromes at the moment. However, using diverse *in vitro* and *in vivo* animal models (acute and chronic epilepsy and SNI model), CBDV revealed anti-epileptic and analgesic effects. Amongst others, those data are listed in the clinical trial protocol (see above) and the investigator's brochure.

4.1.3 Known adverse events

Adverse events
Unacceptable adverse reactions may develop at any time. With other cannabinoid substances, AEs are usually mild and resolve in a few days. Assuming CBDV exhibits similar effects in humans as the already mentioned cannabinoids, the clinician (in case of unblinding, see above) should consider reducing or interrupting CBDV treatment depending on their seriousness and intensity. For example, a dose reduction might entail a reduction of the original dose (400 mg; 8 ml oral solution) by 100 mg per week to 300 mg (= 6 ml oral solution) and if necessary to 200 mg (= 4 ml oral solution). To date there is one completed clinical trial phase I testing CBDV. During this trial CBDV was generally well tolerated following oral or intravenous, single ascending or multiple oral applications and the overall incidence of treatment-emergent AEs (TEAEs) were low. There were no serious or severe TEAEs and no subject experienced a TEAE that led to withdrawal of the IMP. The most frequently reported TEAEs were headache and somnolence. The incidence of TEAEs was marginally higher after oral dosing with 400 mg and 800 mg than in the 25, 75 and 200 mg dose groups. The incidence of TEAEs was similar following single intravenous doses of CBDV or placebo. The incidence of TEAEs was slightly higher following once daily dosing of 800 mg CBDV for 5 days than placebo. There were no clinically significant findings in any laboratory tests, vital signs (such as ECG recording or pulse) or physical examination findings in any part of the study. Following once daily oral doses of CBDV the majority of subjects scored zero on the cannabis withdrawal scale (CWS) indicating no withdrawal symptoms. At this developmental stage it is assumed that the safety profile of CBDV corresponds to the one of CBD because of similarity in chemical structure.

Contraindications
Because of similar chemical structures, contraindications of CBDV are expected to be similar to those of CBD at this stage of development. CBDV is contraindicated in persons with known or suspected intolerance to cannabis or cannabinoids. CBDV must not be applied during pregnancy or lactation period.

Drug-drug interactions and other interactions
CBDV is metabolized via the cytochrome P450 (CYP_{450}) enzyme system and was tested in specific CYP_{450} induction and inhibition studies. CBDV is a potent inhibitor of CYP2C19 (IC_{50}<1 µM) and a relatively potent inhibitor of CYP1A2, 2B6, 2C9 (IC_{50s} all<10 µM). While CBDV is a relatively weak inhibitor of CYP2D6, 2C8 und 3A4 (IC_{50s} between 10-30 µM), it does not inhibit CYP2E1 (<50% inhibition measured, so no IC_{50} available). In contrast, CBDV does not induce CYP1A2, 2C9 or 3A4 in human hepatocytes at concentrations up to 1 µM. There has been no clinical exposure to CBDV to date, so the incidence of drug-drug interactions in humans with CBDV is currently unknown.

4.1.4 Overdose instructions

Overdoses and symptoms of poisoning after CBDV application are unlikely. CBDV is a cannabinoid devoid of THC without any probable psychoactive effects. Nevertheless, study subjects should be clinically observed by the investigator during the first application of CBDV. Because of similar chemical structures of CBDV and CBD and good tolerance of CBD in humans (doses up to 1500 mg per day [21]), it can be assumed that CBDV will be tolerated in humans just as well as CBD. However, if unwanted effects occur, symptoms have to be treated with supportive measures. Therefore, a medical emergency team and intensive care unit are available anytime (24 hours a day, seven days per week) at the trial site (Charité CBF).

4.1.5 Treatment assignment

The IMP will only be given to study participants who are included into this trial. If participants withdraw from the trial, the identification code (e.g. random number) will be kept and not applied to new participants.

4.1.6 Treatment after the end of the trial

After conclusion of this trial study subjects will continue previous treatments prescribed by the attending physician.

4.1.7 Packaging and labelling

According to the random list, the IMP will be labeled and packed by GW Pharmaceuticals and shipped to the trial site in original containers (100 ml amber glass bottles with child-proof safety cap). The amber glass bottles will be labeled according to § 5 GCP-V. Labels include the following information:

- Sponsor’s name and address
- Name and dosage of the medicinal product
- Lot number (“Ch.-B.”) or code number of the clinical trial
- Dosage form
- Content (Volume)
- Type of application
- Dosage instruction with the single application
- Shelf life (with the note ”use by”)
- Identification code of the study subject
- Note: “For clinical trial use only”
- Storage information
- Note: “Keep out of sight and reach of children”

4.1.8 Drug storage, accountability and elimination

The investigator will confirm and document the receipt of all shipments. All IMPs will be stored in a locked area (e.g. lockable cabinet) at the trial site to which only authorized study personnel has access.

According to the manufacturer's instructions the study medication will be stored below 30°C. Under these conditions the liquid is stable for 18 months. Temperature will be controlled and documented in a temperature log.

The investigator will keep records of release and take-back of IMPs to and from study subjects.

The clinical monitor will check regularly all existing study medications to verify drug accountability of used IMPs.

At the end of the clinical trial all untouched and empty bottles will be sent to the pharmacy of the Charité to be destroyed.

The investigator ensures preparation of a final drug accountability report which will be kept in the investigator site file.

4.1.9 Procedures for monitoring subject compliance

The initial dose of study substance will be applied to the subjects at the trial site by the study personnel. Thereafter, patients will receive the complete amount needed for the next four weeks of the treatment period.

Each time study subjects are scheduled for a visit, they have to bring empty and untouched bottles of study substance. Compliance will be assessed by inspection of glass bottles. The investigator will determine whether the residual volume in the bottle matches with the volume taken by the study subject during the treatment phase.

Details will be documented in the drug accountability form in the investigator site file.

Furthermore, the investigator will review all notes documented in the patient's diary (i.e. pain scores, additional use of pain medication and side effects).

4.2 **Permitted medication**

All medications administered up to entering this study can be continued during this trial. All prescribed pain medications are allowed as rescue medication for unlimited use and will be documented. These medications comprise anti-epileptic drugs (e.g. gabapentin, pregabalin), anti-depressants (e.g. amitriptyline), opioids (e.g. tramadol, morphine, oxycodone), and non-steroidal anti-inflammatory drugs (e.g. aspirin, naproxen, paracetamol, ibuprofen).

5. TRIAL SCHEDULE

This trial is divided into five phases (see chapter 3). Patients will be invited to the trial center for several visits. Subsequent to the last phase, patients will be followed-up for six weeks.

Screening visit
Applying in- and exclusion criteria, potential study subjects will be informed about content and purpose of the trial at the screening visit. To definitively exclude chronic drug abuse (especially cannabis use), pregnancy, Hepatitis-infection, hepatic diseases with elevated levels of ALT, AST and bilirubin as well as chronic renal insufficiency, blood will be taken already in the screening phase for analysis of lab parameters listed in 6.2.5.To exclude dementia, interested subjects will undergo a test for cognitive functions (Montreal Cognitive Assessment (MoCA); see chapter 6.2.1 and appendix „Prüfplan_Fragebögen"). In addition, specific ECG-parameters (see exclusion criteria) will be assessed in the screening phase already.

Visit 1 (day 1): First baseline visit
Patients will arrive at the trial center (CBF) after giving informed consent.
Patients will be asked for demographic data, previous and concomitant diseases as well as previous and concomitant treatments. Besides analysis of vital signs (such as blood pressure, pulse and cardiac function) a physical and neurological examination will be performed and patients' neuropathic pain components will be evaluated by means of the painDETECT questionnaire. Using additional questionnaires (see chapter 6 and appendix „Prüfplan_Fragebögen") patients will be asked for anxiety and depression, as well as impairment of physical functions by pain. Patients will be instructed how to report pain intensity and use of medication/study substances in the patient diary (see appendix „Prüfplan_Patiententagebuch") during the trial (Baseline 1).

Visit 2 (Day 7±2): Randomization
The investigator will review NRS scores and use of medication during the last week documented in the patient diary. The patient is asked to fill in questionnaires regarding the quality of life and sleep (see chapter 6). Thereafter, patients will receive the initial dose of the randomized study substance and the first two bottles of the IMP. They will be informed about handling and storage of the study substance as well as documentation of AEs. Patients will be told how to report their acute subjective responses after application of study substance by means of the DEQ-5 questionnaire (see chapter 6 and appendix „Prüfplan_Fragebögen").

Visit 3 (Day 21±2): Half of first treatment period
Two weeks after the start of the first treatment period, subjects will be asked for NRS scores, rescue medication (see 4.2) and possible side effects as well as their acute subjective responses. The investigator will perform a physical and neurological examination, check vital signs and review laboratory parameters (see 6.2.5). Patients will receive the third/last bottle of the IMP.

Visit 4 (Day 35±2): End of first treatment period/Start of washout-phase
By review of the patient diary the investigator will check NRS scores, rescue medication, side effects and acute subjective responses since the last visit. Vital signs will be checked and patients will be examined, including assessment of neuropathic pain parameters and control of laboratory parameters (see 6.2.5). Questionnaires (see chapter 6 and appendix „Prüfplan_Fragebögen") will be used to assess anxiety and depression, as well as impairment of physical functions by pain. Patients should judge to which extent the treatment changed the disease or symptoms in their opinion. Hereafter the patient is asked to fill in questionnaires regarding the quality of life and sleep. They will be reminded to continue reporting of daily pain intensity, daily use of medication and AEs in the following wash-out period.

Visit 5 (Day 56±2): End of washout-phase/Start of second baseline
At the end of the wash-out period patients will be contacted by phone and asked for pain intensity, rescue medication and AE that occurred during the last three weeks. Patients will be reminded to continue documenting those parameters in the following baseline period.

Visit 6 (Day 63±2): End of second baseline/Start of second treatment period
The subject and investigator will review all parameters documented in the patient diary. To definitively exclude pregnancy, a pregnancy test will be performed in the blood of women of childbearing potential. Besides analysis of vital signs a physical and neurological examination will be performed and patients' neuropathic pain components will be assessed by means of the painDETECT questionnaire. Using additional questionnaires (see chapter 6 and appendix „Prüf-plan_Fragebögen") patients will be asked for anxiety and depression, as well as impairment of physical functions by pain. Additionally the patient is asked to fill in questionnaires regarding the quality of life and sleep. For analysis of clinical, hematological and toxicological laboratory parameters (see 6.2.5) blood will be drawn once. Patients will receive the initial dose of study substance for the second treatment phase and the first two bottles of IMP. They will be informed about handling and storage of the study substance as well as additional documentation of pain intensity, pain medication and AEs. Patients will be told how to report their acute subjective responses after application of study substance by means of the DEQ-5 questionnaire (see chapter 6 and appendix „Prüfplan_Fragebögen").

Visit 7 (Day 77±2): Half of second treatment period
Two weeks after start of the second treatment period, study subjects will be asked for NRS scores, rescue medication and possible side effects as well as their acute subjective responses. The investigator will perform a physical and neurological examination, check vital signs and review laboratory parameters (see 6.2.5). Patients will receive the third/last bottle of the IMP.

Visit 8 (Day 91±2): End of second treatment period
At the end of the second treatment phase the study subject and investigator will review all data documented in the diary over the past four weeks. Vital signs as well as physical and neurological functions will be checked and laboratory parameters will be analyzed (see 6.2.5). An additional blood sample will be taken for the pharmacogenetic analysis performed by the EU consortium partner deCODE Genetics (https://www.upf.edu/cexs/news/neuropain.html). Neuropathic pain parameters, anxiety and depression as well as impairment of physical functions by pain and quality of life and sleep will be assessed by means of questionnaires (see chapter 6 and appendix „Prüf-plan_Fragebögen"). Furthermore, patients should judge to which extent the treatment changed their disease or symptoms.

Follow-up: Six weeks after end of trial
Patients will be asked to continue documenting the NRS-Score, medication and AEs in the patient diary for six weeks and to report them to the investigator by phone or during a last visit at the trial site.

6. TRIAL METHODS

6.1 Assessment of efficacy

All data will be collected by paper-based screening tools and questionnaires, and will be stored together with CRFs. Within one week after the last visit data will be transferred to electronic media (e.g. Excel tables).

Primary endpoint of this study is the assessment of pain intensity. An 11-point numerical rating scale (NRS) will be used (0 means “no pain” and 10 “worst pain imaginable”). Patients will be asked to rate their average pain during the last two hours by choosing a number on the NRS. The values will be assessed three times per day: 30 minutes before application of the study medication at 8.30 am; four hours after application at 1 pm and ten hours after application at 7 pm. Patients will document the scores in their diary (see appendix „Prüfplan_Patiententagebuch“).

Secondary endpoints will be assessed using following screening tools and questionnaires.

1.) Rescue medication

Patients are allowed to take additional pain-relieving medications, such as antiepileptic or analgesic substances that have been prescribed up to entering the study (see chapter 4.2). Rescue application of pain killers is commonly used as an endpoint in clinical pain trials. Daily, patients have to document amount, dosage and duration of application in their diary. At the end of this trial, individual doses of each medication will be documented and analyzed quantitatively using the medication quantification scale (MQS) according to Harden [25]. Using this scale, all pain killers can be converted to a single score and compared quantitatively [26].

MQS III

MEDICATION QUANTIFICATION SCALE

Drug	Dosage Mg/day	Detriment Weight (Table 1)	(X)	Dosage Level (Table 2)	(=)	MQS Score
Morphine Sulfate (IR)	5 mg PRN	3.4	X	1	=	3.4
Trimadol HCl	50 mg QID	2.3	X	2	=	6.9
Nortriptyline HCl	50 mg qHS	2.3	X	3	=	4.6
Aspirin	15 tabs/day (325 mg)	3.4	X	4	=	13.6
					TOTAL SCORE	28.5

2.) Side effects

Side effects will be recorded by the patient daily in the diary. Patients will assess duration and intensity of those side effects. At the end of the trial prevalence of side effects will be calculated and analyzed statistically.

	Mild (e.g. temporary)	Moderate (e.g. disturbing)	Severe (e.g. life-threatening)
Nausea			
Vomiting			
Dry mouth			
Itching			
Dizziness			
Sweating			
Head ache			
Somnolence			
Confusion			
Concentration deficits			

3.) painDETECT
The painDETECT is a screening tool for neuropathic pain. It will be completed by the patient and evaluates specifically to what extent neuropathic pain components are present. The painDETECT asks for pain intensity, disease pattern, localization (if applicable radiation of pain) and pain quality. The answers correspond to scores, which will be multiplied and added at the end. The result can be read off a scale. The painDETECT will be applied in addition to the neurological examination at the beginning of the clinical trial (visit 1), at the end of both treatment phases (visit 4 and 8) and at the end of the second baseline (visit 6) (painDETECT *Screening* tool see appendix „Prüf-plan_Fragebögen“).

4.) Brief Pain Inventory (BPI)
The BPI measures patients’ physical functionality. The BPI is composed of 15 elements which ask for patients’ sleep impairment, mood, social relationships and joy of life [27]. The questions will be answered by the patient on a paper-based questionnaire. Questions 3-6 describe pain intensity. Questions 9-15 assess patients’ average impairment. The BPI will be applied at the same time points as the painDETECT (visit 1, 4, 6, and 8; BPI questionnaire see appendix „Prüfplan_Fragebögen“).

5.) Hospital, Anxiety and Depression Scale (HADS)
The patient is asked to complete 14 questions and give subjective information about his condition. After completion of the questionnaire, subscale values for anxiety and depression will be calculated separately by addition of the scores (0-3). In total, a score of 21 per subscale can be achieved. A score of 0-7 is considered as clinically normal, a score of 8-10 is considered borderline and a score greater than 11 as clinically apparent. The HADS, painDETECT and BPI questionnaires will be applied simultaneously (HADS questionnaire see appendix „Prüfplan_Fragebögen“).

6.) Patient Global Impression of Change Scale (PGIC)
The PGIC-questionnaire [28] measures general improvement of the disease or symptoms, and patients’ satisfaction. Patients evaluate to what extent restriction of activity, symptoms, emotions and quality of life have improved, using a scale from 1-7. A significant, favorable change is a score of 5-7; no significant change is a 1-4 response. The PGIC-questionnaire is to be completed at the end of each treatment period (PGIC-questionnaire see appendix „Prüfplan_Fragebögen“).

7.) Drug effects questionnaire (DEQ-5)
The DEQ-5 [29] is widely used in studies of acute subjective response to a variety of substances, such as alcohol or narcotics. It mainly measures the strength of drug effects and the demand for such effects. Patients are asked to rate their subjective response on a visual analog scale exclusively in the first week of both treatment phases, daily, four hours after application of the study substance (at 1 pm) (DEQ-5 questionnaire see appendix „Prüfplan_Fragebögen“).

8.) 36-Item Short Form Health Survey (SF-36)

The SF-36 documents the quality of life of the patients regarding health. The test is divided into two main categories (physical and mental health) and has different subcategories. The first main category is about the physical and functional capability. It measures the self-sufficiency, locomotion and daily activity, as well as pain, vitality (exhaustion etc.) and subjective health perception. In the second main category social functionality and emotional role function are measured to assess mental well-being and change of health status. To generate a continuous measurement of these items the SF-36 is filled out at the visits 2, 4, 6 and 8. This way the quality of life is assessed before handing out the active compound and the placebo and after the four weeks of intake.

9.) Insomnia Severity Index (ISI)

The Insomnia Severity Index (ISI)-questionnaire is a short test to assess the quality of sleep [30]. The patient is asked about problems to fall asleep, sleeping through the night and wake up early in the morning. Additionally the test assesses the contentment/discontent of the patient with the sleeping routine, the impairment during the day, the burden resulting because of the sleeping problems as well as social components. This test, too, will be handed out at the visits 2, 4, 6 and 8.

6.2 **Other assessments**

6.2.1 Assessment of cognitive functions

The Montreal Cognitive Assessment (MoCA) test was developed as a screening tool for mild cognitive deficits. It considers various cognitive domains, such as attention and concentration, executive functions, memory, language, visuo-constructive skills, conceptual thinking, calculating and orientation.
HIV infection can lead to HIV-associated neurocognitive disorders (HAND) [31]. One has to distinguish between asymptomatic neurocognitive impairments, mild neurocognitive deficits and HIV-associated dementia. In order to ensure comprehensive and substantiated documentation of the parameters by the participant, it is necessary to differentiate patients with HIV-associated dementia from those with asymptomatic or mild cognitive deficits and exclude the former from this trial.
The highest possible of the MoCA test is a score of 30. A score greater than 26 is considered normal; a score below 26 is regarded as mild cognitive deficit. A score less than 20 might be a sign of dementia. In this case the patient should be referred to a memory consultation session or a specialist (MoCA questionnaire see appendix „Prüfplan_Fragebögen“).

6.2.2 Previous and concurrent diseases

Illnesses already known at the time of informed consent are to be documented in the CRF as medical history. Disorders detected during the trial are to be documented in the CRF as AEs.

6.2.3 Previous and concurrent medical therapies

All medical treatments with the exception of the investigational medical products received by the participant at the beginning and / or during the clinical trial are to be documented in the CRF as concomitant medication.

6.2.4 Vital signs

Vital signs will be analyzed at the beginning of the clinical trial (visit 1), at the midpoint (visit 3 and 7) and at the end (visit 4 and 8) of both treatment phases as well as at the end of the second baseline (visit 6) and will be documented in the subject’s CRF.

6.2.5 Laboratory parameters

The following clinical, hematological, virological and toxicological laboratory parameters will be analyzed (information including accepted normal values):

Laboratory parameters	Normal values		
Clinical chemistry	**Common**	**Females**	**Males**
Alanine Aminotransferase (ALT)		10 - 35 U/L	10 - 50 U/L
Albumin	34 - 50 g/L		
Alkaline Phosphatase (AP)		35 - 104 U/L	40 - 129 U/L
Aspartate Aminotransferase (AST)		0 - 31 U/L	0 - 37 U/L
Bicarbonate	22,0 - 29,0 mmol/L		
Bilirubin (total)	0 - 20 µmol/L		
Calcium	2,15 - 2,55 mmol/L		
γ-Glutamyl-Transferase (γ-GT)		6 - 42 U/L	10 - 71 U/L
Chloride	98 - 107 mmol/L		
Glucose	3,50 - 7,90 mmol/L		
Urea	1,70 - 8,30 mmol/L		
HDL-Cholesterol		45-65 mg/dL	35-55 mg/dL
Potassium	3,50 - 5,10 mmol/L		
Creatinine		49 - 92 µmol/L	66 - 112 µmol/L
Creatinine Kinase (CK)		26 - 140 U/L	38 - 204 U/L
Sodium	135 - 145 mmol/L		
Phosphate	0,87 - 1,45 mmol/L		
Protein (total)	63 - 83 g/L		
Prothrombin (PT/INR)	70-130%/0,90-1,25		
Hematology	**Common**	**Females**	**Males**
Haemoglobin		115 - 155 g/L	130 - 170 g/L
Haematocrit		33 - 45%	37 - 50%
Erythrocytes		3,95 - 5,15 /pL	4,4 - 5,8 /pL
Leukocytes	3 - 10 /nL		
Neutrophils	2,0 - 7,5 /nL		
Lymphocytes	1,20 - 3,65 /nL		
Eosinophils	0,0 - 0,4 /nL		
Basophiles	0,0 - 0,1 /nL		
Monocytes	0,2 - 1,0 /nL		
Thrombocytes	150 - 400 /nL		
Mean corpuscular haemoglobin (MCH)	26 - 33,5 pg		
Mean cell volume (MCV)	80 - 99 fL		
MCH concentration (MCHC)	300 - 350 g/L		
Toxicology			
THC*	negative		
Virology			
Hepatitis B Surface Antigen (HBsAg)*	negative		
Hepatitis C Antibody (HCV AB)*	negative		

* Those parameters will be analyzed qualitatively; requirement for inclusion into this study is a negative test result.

As the parameters can vary due to sex and age these references values should only be seen as a guideline. The parameters of each individual patient are separately compared to the specified references of Labor Berlin.

7. SAFETY

This chapter comprises definitions of occurring AEs, procedures for their documentation and reporting as well as assessment of intensity and causal relationships in context of the IMP.

7.1 Adverse events (AEs)

7.1.1 Definition

According to GCP, an adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be

- any symptom (including an abnormal laboratory finding) identified after application of the investigational product, even if this event already existed earlier
- an increase in frequency or intensity of existing symptoms
- a disease temporally associated with the use of a medicinal product
- worsening of a previous medical condition/disease

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned (elective) surgical measures permitted by the clinical trial protocol and the condition(s) leading to these measures are not AEs, if the condition leading to the measure was present before inclusion in the trial. In the latter case the condition should be reported as medical history.

7.1.2 Documentation

- All AEs reported by the subject or detected by the investigator will be documented on the appropriate pages of the case report form (CRF), independent of the intensity of the event.
- AEs will be evaluated by the investigator regarding their intensity and a possible causal relationship with the IMP. Documentation comprises nature of event, start, duration, intensity and causality
- If the AE is serious, the investigator must complete, in addition to the “Adverse Event Page” in the CRF, a “Serious Adverse Event Form” at the time the serious adverse event is detected.
- Every attempt should be made to describe the adverse event in terms of a diagnosis.
- The Sponsor is obliged to document thoroughly all AEs communicated by the investigator. On request, these data will be transferred to the responsible regulatory authority. Personalized data will be anonymized prior to data transfer by means of an identification code of the respective subject.

7.1.3 Period of observation

The period for collection of AEs extends from the first intake of study medication up to 6 weeks after the last application.
If the investigator detects a SAE in a trial subject before or after the end of the period of observation, and considers the event (at least possibly) related to the trial treatment or study medication, he should document and report the SAE as described in 7.2.2 and 7.2.3.

7.1.4 Follow up

All subjects who have AEs, whether considered associated with the use of the investigational product or not, must be monitored to determine the outcome.

The clinical course of the AE will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the

investigator considers it medically justifiable to terminate follow-up, but no longer than 6 weeks after the end of the trial.

Should the AE result in death, a full pathologist's report should be supplied, if possible.

7.1.5 Onset and cessation of adverse events

Onset date	Date and time when new signs and/or symptoms or worsening of pre-existing condition first occur.
End date	Date and time when the symptoms resolve, or the event is considered stable by the investigator.

AEs that are ongoing at the time of death are considered not resolved or resolving.

7.2 Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (SAR)

7.2.1 Definition

A serious adverse event (SAE) or a serious adverse drug reaction (SAR) is any untoward medical occurrence that at any dose

- results in death,
- is life-threatening,
- requires subject hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity or
- is a congenital anomaly/birth defect

Notes

- Death is an outcome of an event. The event that resulted in death should be recorded and reported as SAE.
- Life-threatening means that the subject was at immediate risk of death at the time of the SAE; it does not refer to a SAE that hypothetically might have caused death if it were more severe.
- If the admission is pre-planned or not associated with an AE or results in a hospital stay less than 12 hours, the criterion "hospitalization" is not fulfilled.
- Persistent or significant disability or incapacity means that there is a substantial disruption of a person's ability to carry out normal life functions. The irreversible injury of an organ function (e.g. cardiac arrhythmia, diabetes) fulfils this criterion.

If an event occurs fulfilling those definitions unblinding will be done by the investigator (and in all other cases by the Sponsor), if a change of treatment depends on this.

7.2.2 Documentation

- All SAEs will be documented independent of the investigator's opinion whether or not a causal relationship exists with CBDV.
- Documentation comprises nature of event, start, duration, intensity and causality.
- Associated signs, symptoms and laboratory test abnormalities should be summarized into one single diagnosis, if possible.
- In cases of suspected causal relationship to the study drug this refers to a serious adverse drug reaction (SAR).

7.2.3 Reporting of SAEs by investigator

Using the "Serious Adverse Event Form" SAEs must be immediately (at latest within 24 hours of the investigator's awareness) reported to:

Prof. Dr. med. Christoph Stein
Hindenburgdamm 30, 12203 Berlin
Phone: 030 / 450-551522
Fax: 030 / 450-551939

The initial SAE Report should be as complete as possible including:

- subject's identification,
- name of site and investigator,
- the SAE
- information about the trial medication and
- an assessment of the causal relationship between the event and the trial medication

The SAE report must be reviewed and signed by the investigator. The investigator should provide additional information on the clinical course and the outcome of each SAE as soon as possible (Follow up report). Personalized data have to be anonymized prior to data transfer by means of an identification code of the respective subject.

The coordinating investigator will perform the management of all occurring SAEs and ensure compliance with legally required notifications (according to AMG and GCP-V).

During the trial the Sponsor will provide the regulatory authority (BfArM) and the responsible ethics committee once a year a safety report including a list of all SAEs occurring during the trial.

7.2.4 Onset and cessation of SAEs

Onset date	Date and time when at least one of the above listed criteria for seriousness occurs.
End date	Date and time, the seriousness criteria are no longer applicable.

The end date of the SAE must not be later than the end date of the corresponding AE.

SAEs that are ongoing at the time of death are considered not resolved or resolving.

7.3 **Adverse Drug Reaction (AR)**

- The term adverse drug reaction (AR) applies to clinical trials with novel substances prior to drug approval or their new application areas, especially if the therapeutic dosage is not determined yet.
- In order to make the statement, that an adverse event is a side effect by means of an adverse drug reaction it has to be known whether the affected person received CBDV or not. If the subject received placebo, it is not a side effect.
- For the time being, AEs will be documented in context of this clinical trial. The term side effect/adverse drug reaction can only be used after unblinding.

7.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

7.4.1 Definition

A SUSAR is every SAE with an at least possible relationship to the IMP which is unexpected.

7.4.2 Reporting of SUSARs

SUSARs must be immediately (at latest within 24 hours of the investigator's awareness) reported to the Sponsor:

Prof. Dr. med. Christoph Stein
Hindenburgdamm 30, 12203 Berlin
Phone: 030 / 450-551522
Fax: 030 / 450-551939

- A SUSAR will be reported to the regulatory authorities and to the ethics committee as soon as possible but not later than 15 calendar days, and 7 calendar days if it was fatal or life-threatening. In the latter case follow-up information is to be reported within further 8 days. All investigators will be informed within the same timeframes. The marketing authorization holder of the IMP should be informed too.
- Any safety issues requiring a re-evaluation of the benefit-risk relationship of the IMP will also be reported to the regulatory authorities and the ethics committee as soon as possible but not later than 15 calendar days.
- A SUSAR can be reported to the regulatory authority (BfArM) in writing via the form "Bericht über unerwünschte Arzneimittelwirkungen (auch Verdachtsfälle)". However, the regulatory authority prefers online reporting via their homepage with the following link: https://humanweb.pei.de/index_form.php?PHPSESSID=rredaodjeg81nim2ve3l2egiobohiaet
- Personal data have to be anonymized prior to data transfer by means of an identification code of the respective subject.
- During the clinical trial the sponsor will submit any suspected case to the ethics committee once a year.

7.5 Classification of adverse events (AEs and SAEs)

7.5.1 Assessment of intensity

Mild	The AE is a temporary event which is tolerated well by the subjects.
Moderate	The AE results in discomfort for the subjects and impairs their normal activity.
Severe	The AE results in substantial impairment of normal activities of the subjects.

7.5.2 Assessment of causal relationships

The following definitions will be used for the assessment of a relationship of an AE to the administration of the study drug:

Certain	A reaction • which occurs in a plausible time relationship to drug administration or • where drug concentration has been assessed in body tissue and fluids • which follows a known or expected response pattern to the suspected study drug • which disappears upon withdrawal of the drug (de-challenge) or upon reduced dosing and re-appears upon re-challenge

Probable	A reaction • which occurs in a plausible time relationship to drug administration or • which follows a known or expected response pattern to the suspected study drug and • which disappears upon withdrawal of the drug (de-challenge) or upon reduced dosing and • which cannot be explained by known features of the patient's clinical condition
Possible	A reaction • which occurs in a plausible time relationship to drug administration or • which follows a known or expected response pattern to the suspected study drug • but which could also be explained by other factors
Not related	A reaction for which sufficient information is available to assume that there is no relationship to the study drug and/or another cause is probable (e.g. concomitant medication, disease, accident).
Not assessable	An assessment of causality is not possible.

7.5.3 "Expected/Unexpected"

Unexpected are all AEs or adverse reactions, which do not correspond to the existing information about the IMP regarding nature and intensity.

7.6 **Reporting of pregnancy**

Any pregnancy diagnosed in a female subject during treatment with the investigational product must be reported immediately to the Sponsor:

Prof. Dr. med. Christoph Stein
Hindenburgdamm 30, 12203 Berlin
Phone: 030 / 450-551522
Fax: 030 / 450-551939

Pregnancy occurring during the clinical trial, although not considered a SAE, must be reported within 24 hours. The outcome of a pregnancy should be followed up carefully and abnormal outcome of mother or child should be reported if any.

7.7 **Documentation of abuse, misuse, overdose and medication error**

All special events such as study medication abuse, misuse, overdose and medication errors have to be documented in the subject's CRF and source documents. If they lead to an AE, this has to be documented and reported as an AE/SAE.

8. STATISTICS

Details of the statistical analysis of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP) that will be generated by the KKS of the Charité *and finalized before closing the data base and prior to breaking the blind.* The SAP is based on the protocol including all amendments. The document may modify the plans outlined in this protocol; however any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment. Any deviation from the original SAP must be described and justified in the final report. The statistical analysis will be conducted by means of SAS®.

8.1 **Sample size**

Sample size calculation is based on the primary end point of an 11-point NRS for measuring pain intensity and the cross-over design with two parallel groups. We assume an average pain intensity of 6 under the application of placebo. Recent publications revealed a possible reduction of pain intensity related to painful HIV-associated neuropathy by approximately 20% under application of cannabinoids [8, 9]. Therefore, we assume an average pain intensity of 4.8 in our active group. The associated expected standard deviation with 2.5 was estimated conservatively from confidence intervals published in literature [32]. To this end, standard deviations with 1.1 and 2.58 were calculated via CI/2 = 1,96*sqrt(n) from half confidence intervals (CI/2) specified in literature with 0.3 and 0.7. The related n in literature was 52. Finally, a SD of 2.5 was chosen, as a SD of 1.1 seemed too optimistic. The square of this standard deviation is considered a conservative estimation for the variance of differences within the subjects. Using a two-sided paired t-test for a 2x2 cross-over design results in a sample size of 21 patients per group (with α=0.05 and β=0.85). Considering approximately 15% of drop outs, 50 patients will be included in this clinical trial. Sample size estimation was performed with commercially available software nQuery Advisor® 7.0.

8.2 **Analyzed populations**

All subjects who signed informed consent and those assigned a randomization number are considered as enrolled, respective randomized subjects, even if they have not received any trial treatment.

All randomized subjects *who received at least one dose of trial treatment and with at least one available post-baseline assessment of the primary analysis variable,* will be included in the Intention-to-treat (ITT) population. This population is the primary analysis population. Within ITT population analyses subjects will be assigned to the treatment to which they were randomized.

The safety population comprises all subjects who received at least one dose of trial treatment. In analyses of the safety population subjects will be assigned to the treatment which they actually received.

8.3 **Efficacy analyses**

The primary population for the analyses of efficacy is the ITT population.

8.3.1 Definition and analyses of primary endpoint

Analogous to sample size estimation, analysis of the primary endpoint will be performed with a two-sided t-test, with $p<0.05$ considered significant. In addition to this test for differences of treatment effects a linear mixed model will be used to test the treatment effect together with the period and carryover effect. In case that the level of significance is lower than α=0.05, the test for differences of treatment effects cannot be considered confirmatory.
Missing values will be replaced with baseline values prior to application of CBDV or placebo.

8.3.2 Analysis of secondary endpoints

All analyses of secondary endpoints will be considered purely exploratory, and will be performed by means of common statistical parameters, such as average values, median values, standard deviations etc. Additionally, confidence intervals will be calculated for all relevant parameters.

- Analysis of specific pain parameters
- Analysis of rescue medication
- Analysis of side effects
- Analysis of parameters of physical and mental functions
- Analysis of patients' expectation regarding the clinical effect
- Analysis of patients' acute subjective responses
- Analysis of quality of life and sleep
- Genotyping

Details for analyses of secondary endpoints will be defined in the SAP. Prior to the end of this trial, the SAP will be prepared by the coordinating investigator and the biometrician.

8.3.3 Interim analyses

No interim analyses are planned.

8.4 **Analyses of adverse events**

All summaries and listings of safety data will be performed for the safety population.

AEs will be coded according to MedDRA (*Medical Dictionary for Regulatory Activities*) terminology. Detailed information collected for each AE will include: A description of the event, duration, whether the AE was serious, intensity, relationship to trial drug, action taken and clinical outcome.

Summary tables will present the number of subjects observed with AEs by MedDRA System Organ Class and Preferred Term and corresponding percentages. Additional subcategories will be based on event intensity and relationship to trial drug. A subject listing of all AEs will be prepared.

9. QUALITY CONTROL AND QUALITY ASSURANCE

9.1 Requirements for investigator

The investigator should be able to demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period. The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period. The investigator must nominate an adequately qualified deputy.

9.2 Direct access to source data/documents

The investigator must permit trial-related monitoring as well as inspections by the appropriate regulatory authorities, and provide direct access to source data/documents. The subjects will be informed that representatives of the sponsor or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

9.3 Investigator site file and archiving

The investigator will be provided with an investigator site file (ISF) at the start of the trial. The investigator will archive all trial data and relevant correspondence in the ISF. According to applicable legal regulations and to the ICH-GCP guidelines the ISF, all source data and all essential documents will be kept filed for 10 years after termination of the trial.

9.4 Monitoring

Monitoring will be done by personal visits from Susen Burock (Medical Coordinator, Charité Comprehensive Cancer Center, Campus Charité Mitte).

- The monitor shall ensure that the investigators and members of the investigating staff understand all requirements of the protocol and their regulatory responsibilities.
- The monitor will ensure that the investigator will maintain a list of members of the investigating staff to whom he has delegated significant trial-related duties (“delegation log”).
- The site will be visited by the monitor at regular intervals to ensure compliance with the trial protocol, GCP and legal aspects.
- The presence of correct informed consents will be checked for every subject. The monitor will review the entries into the CRFs for completeness and correctness and verify the entries on the basis of the source documents.
- Details will be specified in the monitoring manual for this trial.
- By frequent communications (letters, telephone, fax), the monitor will ensure that the trial is conducted according to the protocol and regulatory requirements.
- The investigator must allow the monitor to look at all relevant documents and must provide support at all times to the monitor.

9.5 Inspection by authorities

Regulatory authorities may request access to all source documents, CRF, and other trial documentation in case of an inspection. Direct access to these documents must be guaranteed by the investigator who must provide support at all times for these activities. Source data documents can be copied during inspection provided the identity of the subject has been made unrecognizable.

10. DATA MANAGEMENT

10.1 Data collection and CRFs

All patient data will be recorded in anonymized form. Each subject will be uniquely labeled by a patient number. Investigators will keep a confidential list, where patient numbers are linked to the subject's full name. This confidential list will be filed in the respective ISF and protected against unauthorized access. Only members of the study team have access to this list. The monitor and the inspector are only allowed to have insight into the list.

Data collection is based on paper-based case report forms (CRFs). A CRF will be provided for each subject. All trial data will be documented in the subject's medical record and in the CRF.

The investigator or a designated member of the investigating team is responsible for ensuring that all sections of the CRF are correctly completed. If the investigator authorizes other persons of the investigating team, names, initials, functions and signatures of these designated members have to be entered into the "delegation log".

Each completed CRF page provided with a signature field must be dated and signed. The original CRFs stay in the trial center (CBF). The investigator, or a designated member of the investigating team, should complete the CRF pages as soon as possible after the information is collected, preferably on the same day that a trial subject is seen for an examination, treatment, or any other trial procedure. An explanation should be given for any missing data.

Any errors should have a single line drawn through them so that the original entry remains legible and the correct data should be entered beside it with an explanation and the investigator's signature and date.

10.2 Data handling

Checks for plausibility, consistency and completeness of the data will be performed during data entry. Based on these checks, queries will be produced. Any missing data or inconsistencies will be reported back to the respective site and clarified by the responsible investigator.

All controlled and confirmed or corrected data will be released for data entry. All changes during data entry will be documented, signed by the investigator and stored together with the CRFs.

After completion of data entry the access rights will be withdrawn and the database will be declared closed. The pilot-study regarding genotyping is conducted on anonymized blood samples through the EU consortium partner deCODE Genetics (https://www.upf.edu/cexs/news/neuropain.html).

11. ETHICAL AND LEGAL ASPECTS

11.1 Good clinical practice (GCP)

The procedures set out in this trial protocol will be performed according to the worldwide recognized principles of good clinical practice (GCP; as defined in the ICH-E-6 Guideline, January 1997), and in compliance with the ethical principles described in the current version of the Declaration of Helsinki.

Furthermore, the requirements of the current versions of German Drug Law (Arzneimittelgesetz, AMG), the GCP regulation (GCP-Verordnung, GCP-V), and the Federal Data Protection Law (Bundesdatenschutzgesetz, BDSG) - under consideration of the pertinent Data Protection Law of the particular Federal State (Landesdatenschutzgesetz, LDSG) - will be adhered to.

11.2 Patient information and informed consent

Before being admitted to the trial, the subject must consent to participate after being fully informed by the investigator or a designated member of investigating team about the nature, importance and individual consequences of the trial (including the anonymized genotyping) and their right to terminate the participation at any time.

The patient should also have the opportunity to consult the investigator, or a physician member of the investigating team, about the details of the clinical study.

After reading the informed consent document, the subject must give consent on the day of the screening visit in writing. The subject's consent must be confirmed by the personally dated signature of the subject and by the personally dated signature of the person conducting the informed consent discussions.

A copy of the signed informed consent document must be given to the subject. The original signed consent document will be retained by the investigator.

If the subject has a primary physician, the investigator should inform them about the subject’s participation in the trial, provided the subject agrees hereto.

11.3 Confidentiality/Generation of Patient-ID

The name of the subjects and other confidential information are subject to medical professional secrecy and the regulations of the German law on data protection (Federal and Federal State Data Protection Laws; Bundes- und Landesdatenschutzgesetz). The name of the subjects and other confidential information will not be supplied to the sponsor.

During the trial, subjects will be identified solely by means of an individual identification code (e.g. subject number, randomization number). The investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

Trial findings stored on a computer will be stored in accordance with local data protection law and will be handled in strictest confidence. For protection of these data, organizational procedures are implemented to prevent distribution of data to unauthorized persons. The appropriate regulations of data legislation will be fulfilled in its entirety.

The subjects will declare in the written consent to release the investigator from the medical professional secrecy to allow identification of subject’s name for monitoring purposes by monitors, inspections by health authorities, and other authorized persons.

11.4 Responsibilities of investigator

In accordance with § 67, Section 1 AMG and § 12, Section 1 GCP-V this clinical trial will be notified by the investigator to the local regulatory authority responsible for investigator (LAGeSo) as well as to the higher federal authority (BfArM).

Furthermore, the local regulatory authority will be notified within 90 days after completion of the trial by the investigator.

If the trial has been discontinued or terminated prematurely by the sponsor, the notification has to state the underlying ground and be carried out within 15 days (§ 12, Section 2 GCP-V).

The responsibilities of the investigator with regard to documentation and reporting (according to § 12, Section 4-7 GCP-V) are described in chapter 7.

The investigator nominates adequately qualified members of the investigating team and must instruct and supervise them in order to ensure that they are adequately informed about relevant information regarding the trial, especially the trial protocol and Investigators Brochure.

Furthermore, the investigator has to nominate a deputy with comparable qualification to his/hers.

The investigator will maintain a list of the members of the investigating team and other persons to whom significant trial-related duties have been delegated (“delegation log”).

11.5 Approval of trial protocol and amendments

11.5.1 Submissions

Before the start of the trial, the sponsor submits a written application to the higher federal authority responsible for Investigational Medicine Products for granting the authorization of the trial as well as a written application to the independent, interdisciplinary ethics committee responsible under federal state law for a favorable opinion.

Before entering the first subject into trial and supplying IMP to the investigators all ethical and legal requirements for starting the clinical trial have to be fulfilled. The regulatory authority has to be notified.

11.5.2 Amendments of protocol

Subsequent changes to protocol during an ongoing trial have to be implemented via amendments. The sponsor is responsible for obtaining both the authorization of the trial by the higher federal authority and the favorable opinion by the responsible ethics committee, provided this is mandatory by § 10, Section 1 GCP-V.

11.5.3 Notification about new sites and replacement of investigator/deputy

The inclusion of new trial sites and replacement of Investigator/Deputy during an ongoing trial are liable to a favorable opinion by the independent, interdisciplinary ethics committee responsible for the investigator.

The notification will be undertaken by a member of the protocol writing committee (see chapter 12).

The affected investigator/deputy is allowed to start the clinical trial only if the favorable opinion by the independent, interdisciplinary ethics committee is available.

11.6 Other information to ethics committees and regulatory authorities

The sponsor is responsible for the ongoing evaluation of the safety of the IMP and the participants of the trial; the corresponding notifications in accordance with § 11 and § 13 GCP-V are described in chapter 7 (“Safety”).

In accordance with § 67, Section 1 AMG and § 13, Section 8 GCP-V, the remaining notifications of the sponsor will be executed by an authorized member of the protocol writing committee (see chapter 12).

11.7 Documentation of correspondence

Relevant correspondence with competent authorities and ethics committees will be properly archived by the sponsor.

11.8 Insurance

According to § 40 AMG, the sponsor has to subscribe to an insurance policy covering its legal liability for injuries caused to participating persons and arising out of this research (maximum limit: € 500.000,- per participating person).

The insurance was taken out at:

HDI-Gerling, Industrie Versicherung AG
Am Schönenkamp 45
40599 Düsseldorf
Phone: 0211/7482 - 0
Fax: 0211/7482 - 460
Insurance policy number: 57 010326 03017

- Any impairment of health which might occur in consequence of trial participation must be notified to the insurance company immediately.
- The subject concerned itself is responsible for notification of the insurance company (if applicable, after consulting the investigator).
- The insured person will consent to and comply with all appropriate measures serving for clarification of the cause and the extent of damage as well as the reduction of damage.
- During the conduct of the trial, the subject must not undergo other clinical treatment except for cases of emergency. The subject is bound to inform the investigator immediately about any emergency treatment.
- The terms and conditions of the insurance are to be delivered to the subject.

11.9 Agreements

11.9.1 Financing

This trial is part of a collaborative European research project („Neuropathic pain: biomarkers and druggable targets within the endogenous analgesia system“) and is funded by the European Commission (FP7-602891-2).

11.9.2 Report

After conclusion of the trial, the sponsor ensures that a report shall be written according to the conditions stipulated in protocol by a member of the protocol writing committee. Pursuant to § 42b AMG („Veröffentlichung der Ergebnisse klinischer Prüfungen“) the investigators consent to the disclosure of their names in the report.

11.9.3 Publications

On completion of data analysis it is planned to prepare publication in appropriate biomedical journals. All collaborators will be listed as authors or contributors according to their contributions as defined in international guidelines (www.ICMJE.org). Prior to release, publications of any type (in

professional journals or as presentation at congresses) always have to be submitted to the coordinating investigator.

12. DECLARATION OF INVESTIGATOR

I have read the above trial protocol and I confirm that it contains all information to accordingly conduct the clinical trial. I pledge to conduct the clinical trial according to the protocol.

I will enroll the first subject only after all ethical and regulatory requirements are fulfilled.

I pledge to obtain written consent for trial participation from all subjects.

I know the requirements for accurate notification of serious AEs and I pledge to document and notify such events as described in the protocol.

I pledge to retain all trial-related documents and source data as described.

I will conduct the trial in compliance with the protocol, GCP and the applicable regulatory requirements.

Investigator

Name	Prof. Dr. med. Christoph Stein
Address	Hindenburgdamm 30
Phone	030 / 450-551522
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E-mail	Christoph.stein@charite.de

_____ _____

Date Signature

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