Title page

Nabilone for non-motor symptoms in Parkinson's disease: A Randomized Placebo-controlled, double-blind, parallel-group, enriched enrolment randomized withdrawal Study

(NMS-Nab Study)

Name of test drug/investigational product: Nabilone

Indication: Parkinson´s disease

Name of the sponsor: Medical University of Innsbruck

Development phase of study: IIa

Protocol identification (code or number): 1.4

First patient first visit: 17th October 2017

Study completion date (last patient last visit): 15th July 2019

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The study was performed in compliance with Good Clinical Practices (GCP)

Date of the report: 12th July 2020

Synopsis

(according to ICH Topic E3 Structur and Content of Clinical Study reports – Annex I)

<table>
<tr><td colspan="2">Name of Sponsor:
Medical University of Innsbruck
Represented by:
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Anichstraße 35
6020 Innsbruck
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E-Mail: mui-sponsor@i-med.ac.at</td></tr>
<tr><td colspan="2">Name of Product:
Nabilone (Manufactured by AOP Orphan Pharmaceuticals AG, Vienna, Austria. Distributed by Kwizda)</td></tr>
<tr><td colspan="2">Name of active ingredient:
Nabilone</td></tr>
<tr><td colspan="2">Title of Study: Nabilone for non-motor symptoms in Parkinson’s disease: A Randomized Placebo-controlled, double-blind, parallel-group, enriched enrolment randomized withdrawal Study
(NMS-Nab Study)</td></tr>
<tr><td colspan="2">Study centre:
Medical University of Innsbruck (monocenter study) Department of Neurology Anichstraße 35 6020 Innsbruck Austria
Investigators:
Principal Investigator: Klaus Seppi
Full list in the Appendix</td></tr>
<tr><td colspan="2">Publication: In Submission
Peball M, Werkmann M, Ellmerer P, Stolz R, Valent D, Knaus HG, et al. Nabilone for non-motor symptoms of Parkinson's disease: a randomized placebo-controlled, double-blind, parallel-group, enriched enrolment randomized withdrawal study (The NMS-Nab Study). J Neural Transm (Vienna). 2019 Aug;126(8):1061-72. PubMed PMID: 31129719. PMCID: PMC6647387.</td></tr>
<tr><td>Studied period (years)
first patient in: 17th October 2017
last patient out: 15th July 2019 (for primary endpoint analysis)</td><td>Phase: IIa</td></tr>
<tr><td colspan="2">Objectives
<u>Primary Efficacy Objective</u>
The primary efficacy objective of this study is to demonstrate the efficacy of nabilone for non-motor symptoms (NMS) of patients with Parkinson´s disease (PD), based on the change from randomisation to the Termination visit in the MDS-UPDRS Part I.
<u>Key Secondary Efficacy Objectives</u>
The key secondary efficacy objectives of this study are to evaluate the effect of nabilone on NMS of PD and on different domains of NMS by means of the change from randomisation to Week 4/Termination visit in the following assessments:
• Movement Disorders Society – Unified Parkinson´s Disease Rating Scale (MDSUPDRS (i.e. Part II, III + IV)) (including non-motor symptoms and motor symptoms)
• Non Motor Symptoms Scale (NMSS)
• mood/anxiety domain of MDS-UPDRS Part I (items 1.3 and 1.4)
• different other domains of NMSS and MDS-UPDRS part I
• Hospital anxiety and depression scale (HADS)
• Parkinson´s Disease Questionnaire – 39 (PDQ-39)
• Montreal Cognitive Assessment (MoCA)
• Epworth Sleepiness Scale (ESS)
• Fatigue Severity Scale (FSS)
• Visual Analog Scale (VAS) of Pain
• King's Parkinson's disease pain scale (KPPS)
• Questionnaire for Impulsive-Compulsive Disorders in Parkinson’s Disease–Rating Scale (QUIP-RS)
Moreover, Clinical Global Impression – Global Improvement (CGI-I) scale at Termination Visit is a key secondary efficacy objective.</td></tr>
</table>

Safety Objectives

The safety objectives of this study are to evaluate the safety and tolerability of nabilone in patients with PD with reference to the following:

1. Tolerability:
   - Number of subjects (%) who discontinue the study
   - Number of subjects (%) who discontinue the study due to adverse Events (AEs)
2. Safety Measures:
   - AEs, Serious Adverse Events (SAEs)
   - Clinical and laboratory assessments
   - Vital signs including performance of active orthostatism (measurement of heart rate and blood pressure after 10 minutes of quiet rest in the supine position and at 1, 2, 3, 5, and 10 minutes of active standing)
   - Electrocardiogram (ECG)
   - Patient´s Compliance
   - Prior and Concomitant Medication Use
   - Hallucination item (1.2) of MDS-UPDRS
   - Orthostatic hypotension (OH) item (1.12) of MDS-UPDRS
   - Day-time sleepiness item (1.8) of MDS-UPDRS
   - Columbia Suicide Severity Rating scale (C-SSRS)

Exploratory Objective

The exploratory objective of this study was an Eye-tracking evaluation in PD patients taking nabilone or placebo at the Screening and the Termination visit:

- Change of the reaction time, attention span, and ability to concentrate

Methodology:

Study design and participants

This was a single-centre phase II, randomised, placebo-controlled, double-blind, parallel-group study, using an enriched enrolment randomised withdrawal (EERW) design to assess the efficacy and safety of nabilone for treating NMS in patients with PD. The study was performed at the Movement Disorder Clinic of the Department of Neurology of the Medical University Innsbruck (MUI), Austria. It was approved by the local ethics committee and the Austrian national regulatory authorities. All individuals gave written informed consent before participation. All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Randomisation and masking

Treatment responders were randomly assigned (1:1) to either nabilone in their individual optimal dose or placebo (corn starch) of matching colour and shape and supplied in identical packaging. Randomisation was performed with a computer-generated randomisation schedule provided by the Department of Medical Statistics of the MUI. Respective medication boxes with either verum or placebo were labelled consecutively (1-48) according to the randomisation list to ensure concealment. Neither a member of the study team nor the participants or their care givers were informed about treatment assignment. The study team was supported by the Clinical Trial Center (CTC) of the MUI which monitored the study and surveyed the randomisation process.

Procedures

Phase 1 of the trial was open-label and nabilone, manufactured by AOP Orphan Pharmaceuticals AG (Vienna, Austria), was given orally daily starting with a dose of 0.25 milligrams (mg, one capsule) in the evening after the baseline visit. It was titrated in 0.25 mg-increments every one to four days after consultation with the study team during regular telephone calls. Dose adjustments were performed until patients met the responder criterion defined as a patient-based rating of their NMS as “much improved” (CGI-I Rating Scale: 2) or “very much improved” (CGI-I Rating Scale: 1) on the 7-point CGI-I. Patients failing to meet this responsder criterion at the maximum daily dose of 2 mg or patients with intolerable side effects believed to be related to the study drug were discontinued. Responders went into phase 2 of the trial where they were randomised to their optimal dose of nabilone as established during phase 1 or matching placebo. This four-week, double blind, withdrawal phase ended with a Termination visit from which on the investigational medicinal product (IMP) was tapered. A safety follow-up visit was performed after two weeks of discontinuation from study drug. The study comprised of five on-site study visits and regular telephone calls during titration phases and the first week of the double-blind randomised withdrawal phase (Figure of trial schedule).

Assessments included the other parts and single items of the MDS-UPDRS, the NMSS, the HADS, the PDQ-39, the MoCA, the ESS, the FSS, the VAS of Pain, the KPPS, and the QUIP-RS. Safety parameters were monitored throughout the study via telephone calls and at on-site visits. Blinded assessment of safety was performed during trial conduction via the safety data monitoring board (HGK, KS, MP).

Number of patients (planned and analysed):
Planned**:** 38 patients (19 patients per group), Inclusion target with a drop- out rate of 25 %: 48 patients.
Analysed: 38 patients (19 per group)

Diagnosis and main criteria for inclusion:
The diagnosis of PD was based on UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria and non-motor symptom severity was assessed by the non-motor section (Part I) of the MDS-UPDRS. To be eligible for participation, male and female PD patients had to be older than thirty years of age and have a score of ≥ 4 points on the MDS-UPDRS Part I with ≥ 2 points in either the item for anxiety (1.4) or pain (1.9). The disease had to be stable with steady medication for at least thirty days prior to screening. All participants had to agree to abstain from recreational use of cannabinoids during study participation.
(see Appendix for full list of inclusion and exclusion criteria).

Test product, dose and mode of administration, batch number:
Synthetic cannabinoid nabilone, other components: Polyvinylpyrollidone (Povidone) pregelatinized starch, yellow iron oxide (E 172), titanium dioxide (E 171), gelatin
Manufactured by AOP Orphan Pharmaceuticals AG, Vienna, Austria, in 0.25 mg dosage strength
Mode of administration: oral
Administration form: capsules
Dose: 0.25 – 2 mg per day
Bottles of 28 capsules each
Packaging, labelling and distribution by the company Kwizda.

Phase 1 of the study was an open-label dose titration phase. Eligible patients received 0.25 mg nabilone orally starting in the evening after the screening visit. Nabilone was titrated in 0.25 mg-increments every one to four days (max. 2 mg per day). During the double-blind phase of the trial, patients in the nabilone group received their optimal dose defined in phase 1 (open-label titration) of the study.

Duration of treatment:
see above

Reference therapy, dose and mode of administration, batch number:
Placebo capsules to be used in the double-blind treatment phase are visually and physically indistinguishable from the active drug product and contain no active ingredient. They consist of corn starch.
Manufactured by AOP Orphan Pharmaceuticals AG, Vienna, Austria
Mode of administration: oral
Administration form: capsules
Bottles of 28 capsules each
Packaging, labelling and distribution of the placebo capsules by the company Kwizda.

During the double-blind phase of the trial, patients randomised to placebo received the same number of capsules as during the open-label titration phase, however without active ingredient.

Reference substance:
Placebo (corn starch)

Unblinding:
No patient was allowed to be unblinded before the end of the trial, except for "emergencies". Premature treatment unblinding would have been performed via emergency envelopes by a member of the study team after consultation with the principal investigator in case of an "emergency". An "emergency" can be any event that is serious and related to the treatment in the investigator´s discretion or an event for which knowledge of the treatment group is crucial (i.e. pregnancy).

Criteria for evaluation:
Efficacy Endpoints
Primary Efficacy Endpoint:
The primary efficacy endpoint was the change of the MDS-UPDRS Part I between randomisation and week 4.
Key Secondary Efficacy Endpoints:
The change in the other assessments listed above between randomisation and week 4 were the key secondary efficacy criteria, as well as the CGI-I at Termination Visit.
Safety Endpoints

The safety and tolerability of nabilone were evaluated in this study using the measures described in "Objectives".

Exploratory Endpoints

The change of the reaction time, attention span, and ability to concentrate between screening and the Termination Visit as measured by the Eye-tracking examination were an exploratory endpoint. Because of potential of habituation of the Eye-tracking measurements, we only assessed these measures at Screening and Termination Visit.

Statistical Methods:

A total of 38 patients will have 80% power to detect a probability of 0.231 that an observation in the treatment group is less than an observation in the placebo group using a Wilcoxon rank-sum test with a 0.050 two-sided significance level assuming a true difference of 2.5 points between nabilone and placebo in the primary outcome measure and a standard deviation of the change of 2.4 points.

The NMS-Nab Study is as a mono-centric Phase II, randomized, placebo-controlled, double-blind, parallel-group, EERW study. The primary efficacy criterion was the change in Movement Disorders Society – Unified Parkinson´s Disease Rating Scale Part I score between randomisation and week 4. Since an interpolation of data was not performed in case of a drop-out, the primary analysis is a per-protocol analysis. No interim analysis was planned or conducted. Secondary efficacy criteria were measured as the change in the other clinical scales and questionnaires between randomisation and week 4, except for the CGI-I measures, which are singularly evaluated at week 4. For the study's primary efficacy and secondary efficacy objectives, mean changes from randomisation to the 4-week follow-up in the nabilone and placebo groups were analysed separately within the two groups by Wilcoxon matched-pairs test. Between-group comparison was performed by Mann-Whitney U test. As a sensitivity analysis, we fitted a repeated measures mixed model with MDS-UPDRS Part I sum score as dependent variable and a factorial interaction between group assignment and time as independent variable. For all analyses, statistical significance was set at the 2-sided 5% level. SPSS 22.0 for windows (SPSS Inc., IBM Corporation and other(s) 1989, 2013, Chicago, IL) was used to tabulate and analyse data.

Summary – Conclusions:

Between October 17, 2017, and July 15, 2019 (last patient last visit), 48 participants were screened. There was one screening failure due to the use of prohibited concomitant medication. During open-label titration (phase 1) nine patients were either non-responder as defined per protocol (n=5, 10.42%) or discontinued (n=4, 8.33%, 1 drop-out, 3 due to AEs, Flow chart in Appendix). Thirty-eight patients entered phase 2 and were randomised 1:1 to the placebo or nabilone arm (n=19 each). No patient discontinued phase 2 and all patients were included in the final analysis (Flow chart). Demographic and clinical characteristics were balanced between treatment groups. In the open-label phase, both the MDS-UPDRS Part I and the NMSS decreased significantly in all patients. Median daily dose of nabilone was 1 mg at the beginning of the double-blind study phase (range 0.25 – 1.75 mg). Mean change of the MDS-UPDRS part I score during the randomised double-blind phase was 2.63 points (95%CI 1.53 to 3.74, p=0.002, effect size 1.15) in the placebo versus 1.00 points (95%CI -0.16 to 2.16, p=0.280, effect size 0.42) in the nabilone group (difference: 1.63, 95%CI 0.09 to 3.18, p=0.030, effect size 0.66). The change of the MDS-UPDRS part I score was not significant in the nabilone group which is reflected by the small effect size. The placebo group deteriorated significantly with a large effect size. Additionally, there was a significant between-group difference for the MDS-UPDRS I, which was medium to the disadvantage of the placebo arm.

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List of abbreviations (alphabetical order)

AE	Adverse event
C-SSRS	Columbia Suicide Severity Rating scale
CB	Cannabinoid
CGI-I	Clinical Global Impression of Improvement
CTC	Clinical Trial Center
ECG	electrocardiogram
ECS	Endocannabinoid system
EERW	enriched enrolment randomised withdrawal
ESS	Epworth Sleepiness Scale
EU	European Union
ET	Early Termination Visit
FSS	Fatigue Severity Scale
GABA	gamma-Aminobutyric acid
GCP	Good Clinical Practice
HADS	Hospital anxiety and depression scale
HEENT	head, eyes, ears, nose and throat
H&Y	Hoehn and Yahr
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational medicinal product
IMPD	Investigational medicinal product dossier
ISF	Investigator Site File
IRB/IEC	Institutional review board/independent ethics committee
KPPS	King's Parkinson's disease pain scale
LPLV	Last patient last visit
MDS-UPDRS	Movement Disorders Society – Unified Parkinson´s Disease Rating Scale
Mg	milligrams
MoCA	Montreal Cognitive Assessment
MUI	Medical University of Innsbruck
NMS	Non-motor symptoms
NMSS	Non Motor Symptoms Scale
OH	Orthostatic hypotension
OL	open-label
PD	Parkinson´s Diseases
PDQ-39	Parkinson´s Disease Questionnaire – 39
QoL	Quality of life
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale
RBD	rapid-eye-movement sleep behaviour disorder
RCT	Randomized controlled trial
REM	Rapid eye movement
SAE	Serious adverse event
SCR	Screening visit
SmPC	summary of product characteristics
SUSARs	Suspected unexpected serious adverse reactions
THC	tetrahydrocannabinol
TMF	Trial Master File
V	Visit
SFU	Safety Follow-Up visit
VAS of Pain	Visual Analog Scale of Pain

Ethics approval and consent to participate

Permission for the conduct of the trial was received from the ethics committee (IEC) of the Medical University of Innsbruck (MUI) on June 26th, 2017 (reference number: 1008/2017) and the Austrian regulatory authorities approved the study on the 15th of September 2017. Two amendments to include an eye-tracking analysis as an exploratory endpoint in the study and to conform to the EU Data Protection Law 2018 have been approved by the IEC of the MUI and the regulatory authorities. Informed consent was obtained from all individual participants included in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (IEC MUI, reference number 1008/2017 and the national regulatory authorities) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Patient recruitment was started in October 2017 and ended in July 2019. The first patient was included in December 2017. The study was registered on ClinicalTrials.gov.

The results of this study have been/will be published by study team members according to the principles of publication policy. There are no arrangements on publication issues with subsiding parties.

Investigators and Study Administrative Structure

Administrative structure, data coordinating centre, study centre and recruitment

The NMS-Nab Study was performed at one clinical site, the MUI (Austria, urban and rural setting) which is the sponsor of this trial. Trained members of the study team assessed the outcome measurements using validated questionnaires and clinical routine parameters. The study team undertook the administrative and regulatory function for this trial and had/has access to the final trial dataset. For all work involving data collection or management of subjects, the study centre adhered to the law as laid down in the European Regulation (EU) 2016/679 as well as to the national data protection law. The study team was supported by the Clinical Trial Center of the MUI which performed monitoring and surveyed the randomization process. The safety data management was performed by Hans-Günther Knaus of the Department for Medical Genetics, Molecular and Clinical Pharmacology of the MUI. Data management and statistics is/was conducted by qualified members of the study team of the neurological study centre Innsbruck with statistical advice and supervision from the Department of Medical Statistics, Informatics and Health Economics of the MUI.
Patients were seen in the outpatient department on-site or at the neurologic wards. For interested patients, a member of the qualified research team explained the study purpose, goals, and requirements in an understandable manner and an IEC-approved informed consent form was handed to the patients considering participation. These patients were followed-up by a member of the study team. See Appendix for list of study team members and other involved facilities.

1. Introduction

Parkinson´s Disease (PD) was considered a pure extrapyramidal movement disorder for many decades and research focused on motor symptoms only. However, neuropathological changes in PD are widespread and cause a wide spectrum of bothersome non-motor symptoms (NMS) (1). These include autonomic nervous system dysfunction (orthostatic hypotension, urinary problems, and obstipation), olfactory loss, disorders of mood and cognition as well as sleep problems such

as insomnia, daytime sleepiness, or rapid-eye-movement sleep behaviour disorder (RBD). Many of these may antedate the typical motor symptoms by years or even decades, but the burden of NMS generally increases during the course of the disease. NMS are a major determinant of quality of life (QoL), progressive disability, and dependence in PD patients (1) but there is a paucity of controlled clinical trial data concerning their treatment (2). Available treatment options are limited and outcomes often unsatisfactory. The potential therapeutic effect of cannabinoids on motor and NMS in PD patients is a prominent topic among patients and commonly raised by patients in the consulting room, but there is virtually no sound evidence supporting their use in PD since available trials in PD were either small-sized or uncontrolled (3). The endocannabinoid system (ECS) plays a significant role in many physiological body functions (4, 5), although the exact details of the neural circuitry through which the ECS modulates these functions remain uncertain. In this study, we aimed to investigate the effect of the synthetic cannabinoid nabilone for the treatment of NMS in PD in a controlled fashion. The synthetic drug nabilone is an analogue of tetrahydrocannabinol (THC), the psychoactive component of cannabis, with identical pharmacological properties (5, 6). It acts as a partial agonist on both cannabinoid 1 (CB1) and CB2 receptors in humans, thus mimicking the effects of THC but with the advantage of more predictable side effects and less euphoria. Given the data and possible modes of action of the ECS, we hypothesized that nabilone will improve NMS in patients with PD and will have a favourable safety profile. The primary endpoint of the study was the change from randomisation to week four visit in the Movement Disorders Society – Unified Parkinson´s Disease Rating Scale (MDS-UPDRS) Part I (non-motor Experiences of daily living) score. The outcome of this trial may contribute to a better understanding of the value of cannabinoids for treating NMS in PD patients.

2. Study objectives

Primary Efficacy Objective

The primary efficacy objective of this study is to demonstrate the efficacy of nabilone for NMS of patients with PD, based on the change from randomisation to Week 4/Termination visit in the MDS-UPDRS Part I.

Key Secondary Efficacy Objectives

The key secondary efficacy objectives of this study are to evaluate the effect of nabilone on motor symptoms of PD and on different domains of NMS by means of the change from randomisation to Week 4/Termination visit in the following assessments:

- MDS-UPDRS (i.e. Part II, III + IV) (including NMS and motor symptoms)
- Non Motor Symptoms Scale (NMSS)
- mood/anxiety domain of MDS-UPDRS Part I (items 1.3 and 1.4)
- different other domains of NMSS and MDS-UPDRS part I
- Hospital anxiety and depression scale (HADS)
- Parkinson´s Disease Questionnaire – 39 (PDQ-39)
- Montreal Cognitive Assessment (MoCA)
- Epworth Sleepiness Scale (ESS)
- Fatigue Severity Scale (FSS)
- Visual Analog Scale (VAS) of Pain
- King's Parkinson's disease pain scale (KPPS)
- Questionnaire for Impulsive-Compulsive Disorders in Parkinson’s Disease–Rating Scale (QUIP-RS)

Moreover, Clinical Global Impression – Global Improvement (CGI-I) scale at Termination Visit is a key secondary efficacy objective.

Safety Objectives

The safety objectives of this study are to evaluate the safety and tolerability of nabilone in patients with PD with reference to the following:

1. Tolerability:
   - Number of subjects (%) who discontinue the study
   - Number of subjects (%) who discontinue the study due to adverse events (AE)

2. Safety Measures:
   - AEs, Serious Adverse Events (SAEs)
   - Clinical and laboratory assessments
   - Vital signs including performance of active orthostatism (measurement of heart rate and blood pressure after 10 minutes of quiet rest in the supine position and at 1, 2, 3, 5, and 10 minutes of active standing)
   - electrocardiogram (ECG)
   - Patient´s Compliance
   - Prior and Concomitant Medication Use
   - Hallucination item (1.2) of MDS-UPDRS
   - Orthostatic hypotension (OH) item (1.12) of MDS-UPDRS
   - Day-time sleepiness item (1.8) of MDS-UPDRS

Columbia Suicide Severity Rating scale (C-SSRS)

Exploratory Objective

The exploratory objective of this study is an Eye-tracking evaluation in PD patients taking nabilone or placebo at the Screening and the Termination visit:

- Change of the reaction time, attention span, and ability to concentrate between Screening and Termination Visit as measured by the Eyetracking examination.

3. Investigational Plan

Study drug

Nabilone is an analogue of THC, the psychoactive component of cannabis. Nabilone acts as a partial agonist on both CB1 and CB2 receptor in humans and therefore mimics the effect of THC but with more predictable side effects and less euphoria. A high density of CB1 receptors are found on presynaptic nerve terminals of glutamatergic and gammaaminobutyric acid (GABA)-ergic synapses as well as neurons with μ-opioid receptors in the cortex and limbic areas of the brain, which are responsible for processing of emotion and nociception. Endogenous and exogenous cannabinoids like nabilone might influence sleep and alleviate pain and mood disorders via modulation of monoaminergic, GABA-ergic, glutamatergic neurons and opioid signaling in nociception and mood processing. All of these are common non-motor symptoms (NMS) in patients with Parkinson's Disease (PD) (Protocol NMS-Nab Study, v.1.4, dated 08JUN2018 and Protocol NMS-Nab2 Study, v.1.2, dated 28NOV2018).

AOP Orphan Pharmaceuticals AG is developing Nabilone for use as an antiemetic for chemotherapy-induced nausea and vomiting not responding to conventional antiemetic treatment. Nabilone is marketed as Canemes in 1 mg capsule form in two countries. After oral administration of nabilone, it

is rapidly absorbed via the gastrointestinal tract. The major excretory pathway is the biliary system. The half-life of nabilone amounts to 2 hours, with a half-life of its metabolites of around 35 hours (See Summary of Product Characteristics, 1–31358, dated 06JUL2012, in the source documents for more details).

Study design and participants

This was a single-centre phase II, randomised, placebo-controlled, double-blind, parallel-group study, using an enriched enrolment randomised withdrawal (EERW) design to assess the efficacy and safety of nabilone for treating NMS in patients with PD. Details of the study protocol have been previously published (3).

Randomisation and masking, Unblinding

Treatment responders were randomly assigned (1:1) to either nabilone in their individual optimal dose or placebo (corn starch) of matching colour and shape and supplied in identical packaging. Randomisation was performed with a computer-generated randomisation schedule provided by the Department of Medical Statistics of the MUI. Respective medication boxes with either verum or placebo were labelled consecutively (1-48) according to the randomisation list to ensure concealment. Neither a member of the study team nor the participants or their care givers were informed about treatment assignment. The study team was supported by the Clinical Trial Center (CTC) of the MUI which monitored the study and surveyed the randomisation process.

No patient was allowed to be unblinded before the end of the trial, except for “emergencies”. Premature treatment unblinding would have been performed via emergency envelopes by a member of the study team after consultation with the principal investigator in case of an “emergency”. An “emergency” can be any event that is serious and related to the treatment in the investigator´s discretion or an event for which knowledge of the treatment group is crucial (i.e. pregnancy).

Procedures

Phase 1 of the trial was open-label (OL) and nabilone, manufactured by AOP Orphan Pharmaceuticals AG (Vienna, Austria), was given orally daily starting with a dose of 0.25 milligrams (mg, one capsule) in the evening after the baseline visit. It was titrated in 0.25 mg-increments every one to four days after consultation with the study team during regular telephone calls. Dose adjustments were performed until patients met the responder criterion defined as a patient-based rating of their NMS as “much improved” (CGI-I Rating Scale: 2) or “very much improved” (CGI-I Rating Scale: 1) on the 7-point CGI-I Scale. Patients failing to meet this response criterion at the maximum daily dose of 2 mg or patients with intolerable side effects believed to be related to the study drug were discontinued.

Responders went into phase 2 of the trial where they were randomised to their optimal dose of nabilone as established during phase 1 or matching placebo. This four-week, double blind, withdrawal phase ended with a termination visit from which on the investigational medicinal product (IMP) was tapered. A safety follow-up visit was performed after two weeks of discontinuation from study drug. The study comprised of five on-site study visits and regular telephone calls during titration phases and the first week of the double-blind randomised withdrawal phase (Figure 1). Assessments included the MDS-UPDRS, the NMSS, the HADS, the PDQ-39, the MoCA, the ESS, FSS, VAS of pain, the KPPS, the C-SSRS, the QUIP-RS, and the CGI-I. Safety parameters were monitored throughout the study via telephone calls and at on-site visits. Blinded assessment of safety was performed during trial conduction via the data safety monitoring board (HGK, KS, MP).
The board was meeting on 22th of October 2018 to discuss safety issues and concluded to continue the study as planned due to acceptable risk/benefit evaluation. The report of the meeting is attached to this report.

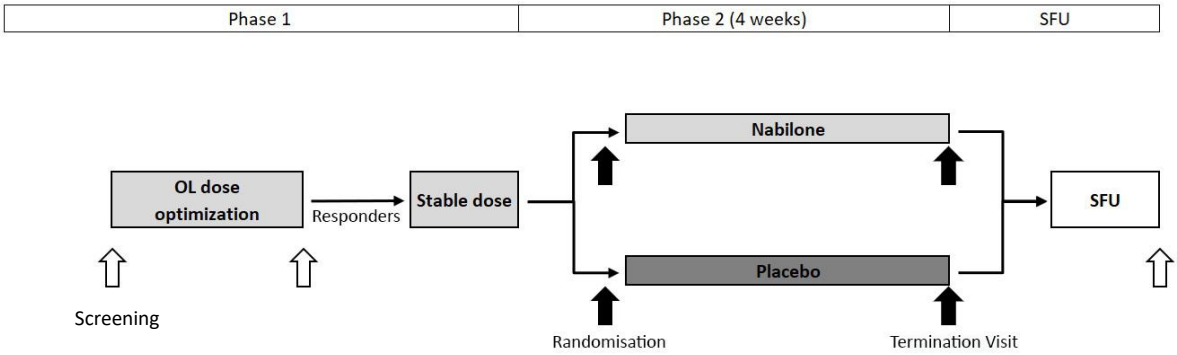


Figure 1: Schedule of trial activities
Abbreviations: OL, open-label; SFU, Safety Follow-Up.

Outcomes

The primary endpoint of the study was the change from randomisation to week four visit in the MDS-UPDRS Part I (non-motor Experiences of daily living) score. Scores for all thirteen items range from 0 to 4 points (Total MDS-UPDRS Part I: 0 to 52 points) with higher scores indicating greater symptom severity. Secondary efficacy outcomes were the change from randomisation to the termination visit in all other clinical scales and questionnaires assessed. CGI-I ratings were evaluated at week four. On an exploratory basis, we also assessed treatment effects on the single items of the MDS-UPDRS Part I and the domains of the NMSS as well as changes of scales and questionnaires in the open-label phase of the trial. Safety and tolerability outcomes were evaluated with reference to the number of subjects (%) who discontinue the study due to an AE, the number of subjects (%) who discontinue the study due to other reasons, AEs, clinical and laboratory measurements, urinalysis, ECG results, vital signs including OH, compliance, prior and concomitant medication use, the C-SSRS as well as the hallucination, OH, and day-time sleepiness items of the MDS-UPDRS.

Statistical analysis

We planned to enrol 48 patients to account for dropouts and include 19 patients per treatment group in the randomised trial phase, which was considered sufficient to detect a treatment difference of 2.5 points in the primary endpoint (standard deviation 2.4) with 80% power and a two-sided α-level of 0.05 (Mann–Whitney U test; nQuery Advisor Version 7). The primary, secondary, and exploratory endpoints of this study were analysed separately for the nabilone and the placebo group using a Wilcoxon matched-pairs test for within-group comparison (with correction for multiple comparisons with a factor of two) and a Mann–Whitney U test for between-group comparisons.

No interim analysis was planned and performed.

4. Discussion of Study Design, including the Choice of Control Groups

Evidence from preclinical and clinical trials suggest a rationale for the use of cannabinoids in NMS due to the influence of the ECS on processing of nociception and mood, as well as on sleep. Moreover, the overactivity of the ECS in PD patients and shared pathways of the cannabinoid and dopaminergic systems in the basal ganglia as presented in these studies justify its use in PD patients. Treatment with cannabinoids is considered to be safe and seems to be well-tolerated in clinical trials and routine use in other indications. We believe that the use of cannabinoids can be an additional

treatment option for symptoms not concerning motor control of PD. Data from randomised-controlled trials (RCTs) of cannabinoids in PD are limited and mostly focus on motor abnormalities. Therefore, we have decided to perform this phase II randomized clinical trial that uses an EERW design to evaluate the effects of continuous nabilone therapy versus withdrawal to placebo in patients with PD suffering from NMS followed by an OL treatment phase. The natural evolution of NMS is not well established over short durations and data on changes in MDS-UPDRS ratings are limited. The withdrawal design enrolling only responders provides an enrichment strategy for efficacy testing. Thus, the study evaluation will be based on the amelioration and/or recurrence of NMS of PD in the randomised withdrawal phase of the study to show efficacy of the treatment (7-9). This is based on the assumption that if the treatment is beneficial, the withdrawal group will return to baseline values, and/or show higher drop-out rates, more adverse events, and/or a deterioration of symptom scores and CGI-I ratings compared to the treatment group. The difficulty of recruiting patients for placebo-controlled trials, high drop-out rates, and the high placebo effect experienced in clinical studies with PD patients are additional rationales for this study design (7-11). The sample size calculation of this study assumed of a standard deviation of 2.4 points of the change from randomization to week 4. In a standard trial design, the standard deviation should be suggested to be higher due to differences in response of the patients and therefore a higher mean variation. With increasing standard deviation, the sample sizes will increase likewise. Assuming the standard deviation of the change of the values of MDS-UPDRS Part I between baseline and termination visit to be 2.6 points and a power of 80% with a two-sided significance level of 5% in a Wilcoxon rank-sum test, the sample size rises to 21 patients per treatment group. For a standard deviation of 3 points leaving all other parameters unchanged, the sample size would be 27 patients for each group. With drop-out rates of 25%, 53 patients or 68 patients would be needed in total in the randomized withdrawal phase of the trial respectively (Table 1).

Table 1: Estimates of sample size using different standard deviations

	1	**2**	**3**
Difference in means, $\mu 1 - \mu 2$	2.500	2.500	2.500
Common standard deviation, σ	2.400	2.600	3.000
Effect size, $\delta = (\mu 1 - \mu 2) / \sigma$	1,042	0,96	0,833
Test significance level, α	0.050	0.050	0.050
1- or 2- sided test?	2	2	2
Power (%)	80	80	80
Number per group	**19**	**21**	**27**
Total number of participants	**38**	**42**	**54**
Including 25% drop-outs	**47.5**	**52.5**	**67.5**

Furthermore, this trial design protects patients against long-term exposure to an ineffective treatment through early discontinuation of trial participation in case of a deterioration of the severity of the condition (e.g. CGI-I measures deteriorate) (9). On the other hand, selection of OL responders can raise concerns about generalizability of the results and thus affect external validity. However, in the NMS-Nab study, most patients enrolled in the OL part of the study were responders, such that any selection bias was small. Nevertheless, inclusion of OL responders only can lead to overestimation of the effect of a novel treatment. On the other hand, in this study, patients whose NMS had a favourable response on nabilone during the OL part of the trial were switched either to nabilone or placebo during the randomised double-blind phase. Therefore, the design of this study may be associated with a negative expectation related to receiving placebo. Indeed, the non-significant deterioration of single NMS with small effect sizes as measured with the MDS-UPDRS Part

I and the NMSS in the verum-group might be impacted by negative expectations related to receiving placebo (i.e. “lessebo effect”, (12), see Efficacy Variables for results).

Restriction to responders however reflects clinical practice by limiting long-term treatment to patients who might benefit from it, in line with a personalised medicine approach. Heterogeneity of response during the OL phase of the trial reflects individual treatment response as seen in daily clinical routine (8). The OL phase grants the assessment of a dose-response effect and provides a range of doses to be considered when planning a confirmatory study (9). This type of enrichment design has been suggested to be sensitive and efficient for proof of concept studies of new treatment strategies in humans (13).

Although common, there is a paucity of well-performed large-scale RCTs for the treatment of the different NMS in PD (14-16). Unlike most motor features of PD, NMS often have limited treatment options or response (17). Our proof-of-concept study should be the basis for further evaluations of long-term efficacy and safety of the use of cannabinoids in PD patients in multiple clinical sites. The reduction of harm through an ineffective treatment, the reduction of sample size caused by our trial design, and the possible evaluation of the concrete influence of the placebo effect on efficacy outcomes justify this design for a single-centered placebo-controlled investigator-initiated trial of nabilone.

In order to determine improvement or deterioration with nabilone compared to placebo in anxiety, sleep disturbances, orthostatic hypotension, and other NMS, post-hoc analyses may follow the primary and secondary analyses that are defined in the actual study protocol (none yet performed).

5. Selection of Study Population

Inclusion and Exclusion criteria

The diagnosis of PD was based on UK Parkinson’s Disease Society Brain Bank clinical diagnostic criteria and NMS severity was assessed by the non-motor section (Part I) of MDS-UPDRS. To be eligible for participation, male and female PD patients had to be older than thirty years of age and have a score of ≥ 4 points on the MDS-UPDRS Part I with ≥ 2 points in either the item for anxiety (1.4) or pain (1.9). The disease had to be stable with steady medication for at least thirty days prior to screening. All participants had to agree to abstain from recreational use of cannabinoids during study participation. Exclusion criteria included evidence of any form of secondary or atypical parkinsonism (e.g. drug induced, post stroke), a Hoehn and Yahr (H&Y) stage > 3, disturbing motor fluctuations or dyskinesia (MDS-UPDRS Part IV > 1), neurosurgical intervention for PD, evidence of disturbing impulse control disorders as defined by cut-off values of QUIP-RS (18), a known hypersensitivity to any of the components, contemporaneous participation in another interventional trial, and the use of prohibited medication as per protocol. Additionally, PD patients with symptomatic OH, sinus tachycardia, and major psychiatric disorders were not allowed to participate in this trial as these are more vulnerable to possible hazardous adverse reactions that may occur during the intake of nabilone. Patients with at least moderately impaired liver function and/or chronic alcohol or drug abuse were excluded from the trial because the primary route of elimination of nabilone is biliary. Female patients of childbearing potential and men with a potentially fertile partner were required to use adequate contraceptive methods (Table 2).

Table 2: Full list of inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
1. Age ≥30 years	1. Patient previously participated in any study with nabilone.

2. Diagnosis of PD: PD should be either de novo or on stable medication without disturbing motor fluctuations or dyskinesia. 3. NMS with a score of ≥4 on MDS-UPDRS Part 1. One of the following domains must be affected with a score ≥2: 1.4 (anxious mood) or 1.9 (pain) 4. On a stable regimen of anti-Parkinson´s medications for at least 30 days prior to screening and willing to continue the same doses and regimens during study participation 5. Any other current and allowed prescription/non-prescription medications and/or nutritional supplements taken regularly must have been at a stable dose and regimen for at least 30 days prior to screening, and subject must be willing to continue the same doses and regimens during study participation 6. Patient is informed and had enough time and opportunity to think about his/her participation in the study and has signed a current IRB-approved informed consent form 7. Contraception a. Women of childbearing potential must use or attest an acceptable method* of contraception starting 4 weeks prior to study drug administration and for a minimum of 1 month after study completion. b. Men with a potentially fertile partner must be willing to use an acceptable method* of contraception for the duration of the study and for 3 months after study drug discontinuation or have had a vasectomy.	2. Current use of cannabinoids or use of cannabinoids within 30 days prior to screening. 3. Patient is currently participating in or has participated in another study of investigational products within 30 days prior to screening. 4. Patient has any form of secondary or atypical parkinsonism (e.g., drug-induced, post stroke). 5. Patient presents with motor complications which are, based on the investigator's judgment, not adequately controlled (i.e. a score ≥2 on one of the items of the MDS-UPDRS Part IV at screening) 6. H&Y stage > 3 7. Evidence of disturbing (i.e. requiring treatment) impulse control disorder in the participant. Can be resolved through a structural interview during screening period. 8. History of neurosurgical intervention for PD 9. Presence of symptomatic orthostatic hypotension at screening (MDS-UPDRS 1.12 > 2) 10. Use of prohibited medication as listed in the protocol 11. Patients with laboratory values that are out-of-range at Screening (or within 4 weeks prior to Screening) and haven´t been reviewed and documented as not clinically significant by the investigator. Lab Tests can be repeated for confirmation. 12. Patients with known or newly diagnosed sinus tachycardia in ECG evaluation at Screening or within 4 weeks prior to Screening. 13. Presence of an acute or chronic major psychiatric disorder (e.g., Major Depressive Disorder, psychosis) or symptom (e.g., hallucinations, agitation, paranoia) (MDS-UPDRS 1.2 and/or 1.3 > 2) 14. Patients who had a recent suicidal attempt (active, interrupted, aborted) within the past five years or report suicidal ideation within the past 6 months. 15. Presence of dementia (MDS-UPDRS 1.1 > 2, MMSE of <24 at the Screening visit) 16. Clinically significant or unstable medical or surgical condition at Screening or Baseline visit that may preclude safety and the completion of the study participation (based on the investigator's judgment). 17. Patients with moderate or severe hepatic or renal impairment. 18. Patient has a history of chronic alcohol or drug abuse within the last 2 years.

	19. Women of child-bearing potential who do not practice an acceptable method of birth control 20. Pregnant women or women planning to become pregnant during the study and nursing women. 21. Patients who are knowingly hypersensitive to any of the components of the IMP or excipients. 22. Patient is legally incapacitated, or persons held in an institution by legal or official order 23. Persons with any kind of dependency on the investigator or employed by the Sponsor or investigator

Removal of patients from therapy or assessment

Subjects have the right to withdraw fully or partially from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution. Withdrawal of full consent for a study means that the subject does not wish to receive further investigational treatment and does not wish or is unable to continue further study participation. Subject data up to withdrawal of consent was included in the subject's study data, but no further information was collected (no separate consent given).

Withdrawal of partial consent means that the subject does not wish to take the protocol-specified product any longer but is still willing to collaborate in providing further data by continuing the study (no patient).

The investigator had right to discontinue a patient from IMP or withdraw a patient from the study at any time. The primary reason for withdrawal from the study was documented. Patients were discontinued if they experienced intolerable side effects believed to be related to the study drug or if they did not meet the responder criterion at the previous dose or the maximum permitted dose. The principal investigator must be informed without delay if any investigator has ethical concerns about continuation of the trial.

The Sponsor had the right to discontinue the trial at any time, even prematurely. The Sponsor must notify the investigator of this decision. Reasons for the decision to discontinue the trial include any relevant medical or ethical concerns, or if completing the trial would not have been practicable any longer. If such action would have been taken, the reasons for terminating the trial must´ve been documented in detail. All trial subjects still under treatment at the time of termination would have needed to undergo a final examination (Early Termination Visit (ET) as soon as possible and SFU Visit 2 weeks + 2 days after the ET (except when the ET was performed more than 5 days after the last intake of study drug)).

In case of discontinuation of the trial the IEC and competent regulatory authority must be informed within 15 days of early termination.

6. Treatments

Test product, dose and mode of administration, batch number:

Synthetic cannabinoid nabilone, other components: Polyvinylpyrollidone (Povidone) pregelatinized starch, yellow iron oxide (E 172), titanium dioxide (E 171), gelatin
Manufactured by AOP Orphan Pharmaceuticals AG, Vienna, Austria, in 0.25 mg dosage strength
Mode of administration: oral
Administration form: capsules
Dose: 0.25 – 2 mg per day
Bottles of 28 capsules each
Packaging, labelling and distribution of the IMP was performed by the company Kwizda.

Information on the test and control substance can be found in the SmPC (for nabilone only) and the respective investigational medicinal product dossier (IMPD) for nabilone or placebo. The SmPC used in this study concerns the registered product Nabilon 1 mg, because the two forms are made from the same granulate and differ only in their fill weight, which can be found in the IMPD (enclosed).
"Nabilone capsules are manufactured in two different strengths. Both strengths are produced out of the same granulate and are only differing by the filling weight.
For the Nabilone 1.0 mg capsules 147.1 mg of granules is filled into yellow / white hard gelatin capsules size 2.
For Nabilone 0.25 mg capsules 36.78 mg of granules is filled into white / white hard gelatin capsules size 4. "
(Page 6, 2.1.P.1 Description and Composition of the Drug Product (Nabilone, 1 mg capsules and Nabilone, 0.25 mg capsules)

Phase 1 of the study was an OL dose titration phase. Eligible patients received 0.25 mg nabilone orally starting in the evening after the screening visit. Nabilone was titrated in 0.25 mg-increments every one to four days (max. 2 mg per day). During the double-blind phase of the trial, patients in the nabilone group received their optimal dose defined in phase 1 (OL titration) of the study.

Median daily dose of nabilone was 1 mg at the beginning of the double-blind study phase (range 0.25–1.75 mg).

Duration of treatment:
see above

Reference therapy, dose and mode of administration, batch number:

Placebo capsules to be used in the double-blind treatment phase are visually and physically indistinguishable from the active drug product and contain no active ingredient. They consist of corn starch.
Manufactured by AOP Orphan Pharmaceuticals AG, Vienna, Austria
Mode of administration: oral
Administration form: capsules
Bottles of 28 capsules each
Packaging, labelling and distribution of placebo capsules was performed by the company Kwizda.

During the double-blind phase of the trial, patients randomized to placebo received the same number of capsules as during the OL titration phase, however without active ingredient.

Reference substance:
Placebo (corn starch)

The SmPC of nabilone 1 mg and the IMPDs of nabilone and the placebo capsules are enclosed to this final report as PDF-Files.

Method of assigning patients to treatment groups

See above

The Sponsor has separate documentation concerning the randomisation which is kept in the Trial Master File (TMF) and stored at a locked cabinet of the Sponsor. No data collected in the study offers evidence of a participant's assignment to a study arm. The patients received a screening number at the Screening Visit and were randomised according to the randomisation list. No patient was informed about the assigned treatment group.

A table exhibiting the randomisation codes, patient identifier, and treatment assigned can be found in the Appendix (PDF-File).

Selection of doses in the study

See above

Selection and timing of dose for each patient

See above

Dosing Instructions

During titration phases nabilone was started with a dosage of 0.25 mg in the evening orally and titrated by 0.25 mg increments every one- to four- daily. Dose adjustments were performed as follows:
First dose to be implemented: 0.25 mg orally in the evening once a day (0-0-1)
Increase in one- to four-day- steps, according to the investigator´s decision:
2. 0.25 mg by mouth BID (1-0-1),
3. 0.25 mg 1-0-2 orally,
4. 0.25 mg 2-0-2 orally,
5. 0.25 mg 2-0-3 by mouth,
6. 0.25 mg 3-0-3 orally,
7. 0.25 mg 3-0-4 p.o.,
8. 0.25 mg 4-0-4 orally

A maximum of 1 mg twice a day should not have been exceeded. Between morning dose an evening dose a time interval of 12 hours should have been meet. Tablets should have been taken at the same time each day. In case a participant missed a dose, he/she was instructed to take their next dose of nabilone at the normally scheduled time. The increment of dosage took place until the patient has much (CGI- I Rating Scale: 2) or very much (CGI-I Rating Scale: 1) improved, reached a maximum dose of 1 mg twice daily or experiences intolerable AEs that are believed to be related to the study drug. In the double-blinded withdrawal phase of the study, the participants received nabilone 0.25 mg–1 mg twice daily or matching placebo (administered orally once or twice daily). During this phase the fixed dosage of the study drug did not changed.

Blinding

See above
Emergency envelopes containing the patient´s name, number in the trial, and the assigned treatment group were provided in case of need. These emergency envelopes were provided by the CTC and stored on-site separately from study documentation in a locked cabinet. In case of an emergency, a member of the study team would have been allowed to open the emergency envelope on behalf of the principal investigator. Authorized members are displayed in the Delegation Log. Opening the emergency envelopes must be documented in the patient´s records and the Sponsor or its designee be informed.

All patients were unblinded after the end of the trial (official closure of the study) by providing the documentation to the authorized investigators on-site. Authorization is shown in the Delegation Log. A list including the patient identifier and treatment assignment is attached to this report (PDF-File).

Prior and concomitant therapy

Allowed Anti-PD Medications/Treatments

All Anti-PD Medications were allowed in this study preconditioned the patient had a stable disease and that the regimens of Anti-Parkinson´s medications, other current prescribed/non-prescribed medications or dietary supplements were stable for at least 30 days prior to screening. The addition of any new anti-PD medication or other prescribed / non-prescribed drugs were prohibited during the study as well as changes to frequency or intervals between doses. Participants were advised to refrain from the use of any concomitant medication during their participation in the study without prior permission by the investigator. The use and the reason for the use of any additional medication was recorded in source documents.

Prohibited Concomitant Medications/Treatments

Nabilone has an addictive and central nervous system- depressing effect if taken together with diazepam, Na-Secobarbital, alcohol and codeine. Interactions between nabilone and the following medications have been observed. Therefore, the intake of these drugs during the clinical trial was prohibited for participants of this study.

- amphetamine, cocaine, other sympathomimetics
- atropine, scopolamine, antihistaminics, other anticholinergic substances
- amitriptyline, amoxapine, desipramine, other tricyclic antidepressants
- barbiturates, benzodiazepines (except for clonazepam up to a maximum of 1.5 mg per d), lithium, opioids, buspirone, muscle relaxing agents, CNS depressing substances
- disulfiram
- fluoxetine
- antipyrines
- theophylline
- naltrexone

Concomitant Non-Pharmacologic Therapies

All non-pharmacological therapies (i.e. physical therapy, exercise, yoga) the patient performs to improve PD symptoms could be continued during participation in the study. During the trial, however, such non-pharmacological therapies were not to be started. All non-pharmacological therapies were documented in the source documents at the Screening Visit. The concomitant non-pharmacological therapies were to be kept on the same levels during the study.

Treatment compliance

Drug Accountability and Treatment Compliance

The receipt of medication and the condition of it as well as the loss or damage of medication were recorded in the source documents. The dispensing and return of medication were documented in the Drug Accountability Section and the patient´s record. Both these records and the medication supplies were/are available to be reviewed by the study Sponsor or designee at any time requested. The investigator was/is responsible for appropriate storage of used, unused, and partially used study drug supplies on-site until they are returned for destruction or destructed on-site upon completion of the

study (last patient last visit, LPLV).

Supplies of nabilone intended for this study were only to be used for the purpose of the study and adhering to this protocol. It is prohibited to apply for any other purpose. The investigator is responsible that the use of the study drug is strictly in accordance with the study protocol.

Procedures for Monitoring Patient Compliance

Procedures for the verification and documentation of the compliance were as follows:

- The patients only received the amount of medication units at each visit that was needed until the next visit.
- The Investigator took back the empty containers or non-used units.

The patient had to return all used, unused, and partially used study drug supplies at the planned visits in the study course. Drug accountability was done in the presence of the participant. Thus, discrepancies between the dosing regime and the patient´s compliance could be clarified directly. Drug Accountability was recorded in the source documents and the Drug Accountability Log in the Investigator Site File.
The end of treatment for the patient was documented at the Termination visit (week 4).
In case of persistent noncompliance of a patient (<80% to >120% of the assigned dose), the Sponsor or its designee had to be informed to decide together with the investigator whether the patient should be discontinued or not.

7. Efficacy and Safety Variables

Efficacy and safety measurements assessed and flow chart

Assessments of Efficacy

The primary efficacy criterion was measured as the change of the *MDS-UPDRS Part I* between randomisation and week 4 / termination visit as determined by the investigator. The change is given in points in the scale. The subscale provides score values from 0 to 52 points in which 0 means that all measured values appear normal and 52 points that all domains are severely impaired.

Currently, the MDS-UPDRS Scale is the most common used scale in evaluation motor symptoms in patients with PD. The Movement Disorder Society (MDS)-sponsored new version of the UPDRS was published in 2003 with respect to the Task Force for Rating Scales´ proposed criticism of the original UPDRS concerning issues of weakness and ambiguities. The scale consists of four components with each part addressing different domains of symptoms of PD and its therapy (Part I: Non-Motor Experiences of Daily living; Part II: Motor experiences of daily living; Part III: Motor Examination; Part IV: Motor Complications). Each section was written by appropriate members of the subcommittees, reviewed, and ratified by the subcommittee. Part I of the MDS-sponsored new version of the UPDRS consists of one part (Part IA) containing the observations of the investigator regarding behaviours based on information from patients and caregivers, and one part (Part IB) to be self-administered by the patient alone or with help of the caregiver without cooperation with the investigator. The rater can solely review this part to ensure that all items are rated and questions for understanding can be addressed to him/her. Part II is also based on the patient´s self-evaluation. Part III needs to be demonstrated or performed by the rater. Part IV consists of instructions for the investigator and the patients to combine clinical observations with information provided by the patient and it is executed by the rater. Only qualified and trained raters (online training, MDS Website) administered the MDS-UPDRS subscales in accordance with requirements for background and experience in research settings. Trainings were documented by providing a Certificate of Rater Approval. The MDS-UPDRS Scale was first measured before the patient received nabilone and in subsequent visits after the patient´s morning dose of nabilone.

The key secondary efficacy criteria were measured as the change in the other clinical scales and questionnaires regarding motor symptoms and different domains of non-motor symptoms in Parkinson´s Disease between baseline and week 4. Therefore, the *total MDS-UPDRS Part I, II, III, and IV* (total MDS-UPDRS: 50 items, Part I: 0 to 52 points, Part II: 0 – 52 points, Part III: 0 – 132 points plus Hoehn and Yahr Scale 0 - 5 points, Part IV: 0-24 points), the *NMSS* (4 domains, 15 items, points from 0 – 12x15 with the latter being severely impaired daily or always), the *HADS* (14 items, values from 0 – 42 points), *the PDQ – 39* (8 domains, 39 items), the *MoCA* (8 items, score ranges from 0 – 30 points), the *ESS* (8 items, ranges from 0 – 24 points), the *FSS* (9 items, 9 – 63 points), the *VAS of Pain*, the *KPPS* (7 domains, 14 items, 0 – 168 points), and the *QUIP-RS* (7 domains, 0 – 122 points) were performed. The results of the *CGI-I* (ratings from 1 to 7) at the termination visit were additionally used as a key secondary efficacy criterion. All presented scales are measured in points given above.

The *NMSS* was developed by an international multidisciplinary PD-NMS group in order to create a comprehensive questionnaire to assess symptoms of PD that are not affecting movement. Symptoms included in the scale range from vertigo and other symptoms of OH, falls, daytime sleepiness and subsequent loss of energy, sleep disturbances at night, restlessness in the legs to psychiatric and cognitive symptoms like apathy, loss of motivation and interest, nervousness, anxiety, worry,

sadness, depression, mood swings, loss of joy in usual activities, and symptoms of delusion, hallucinations, and double vision.

The *HADS* was developed in 1983 from Ziegmond und Snaith which edited a longer version of the questionnaire and published this 14-items-long tool. The Scale aims to assess symptoms of anxiety and depression and was generated as a screening tool. 7 items address symptoms of anxiety and the other 7 items assess depression in patients. Therefore, a subscore for anxiety and depression can be generated. Questions regarding physical symptoms and intrusive items are not included to avoid confounding of the result by organic diseases.

The *PDQ-39* is the most widely used PD specific measure of health status and functional capacity. Its 39 questions cover eight aspects of quality of life. The instrument was developed based on interviews with people diagnosed with PD and it has been widely validated. The questions relate to mobility, activities of daily living, emotional well-being, social support, cognition, communication, and bodily discomfort. The patient is asked to rate each question regarding his/her PD symptoms over the past month.

Nasreddine et. al created the *MoCA* in 1996 in Montreal, Quebec to assess symptoms of mild cognitive impairment. The test assesses several cognitive domains through its task for orientation to time and place (6 points), its learning task (five nouns) to assess short-term memory recall (5 points), a task to assess visuospatial / executive functions (task adapted from trail making B task, clock-drawing task, and drawing a three-dimensional cube, 5 points), and a phonemic fluency task (1 point), and a two-item verbal abstraction task (2 points). Cognitive function and working memory are evaluated using a sustained attention task (target detection using tapping,1 point), a serial number subtraction task (3 points), and a task where digits are repeated forwards and backwards (1 point each). Verbal skills are assessed by using a confrontation naming task with animals with low familiarity (lion, camel, rhinoceros, 3 points), by letting the patient repeat two sentences with complex syntax (2 points), and the fluency task described above.

Daytime sleepiness is assessed by the *ESS*, which is a short, self-administered scale asking for the probability of dozing in eight different situations during the day. Answers can range from no chance of dozing to high chance of dozing in the following scenarios: sitting and reading, watching TV, sitting in a public space, being an assistant driver in a one-hour ride without a break, relaxing in the evening, sitting and talking to another person, sitting still after lunch without intake of alcohol and stopping the car at a traffic light.

The *VAS of Pain* is a tool to measure pain by indicating a position along a continuous line between two end-points (0-100 millimetres). There is evidence that shows that the VAS as continuous scales have superior metrical characteristics than discrete scales and a wider range of statistical methods can be applied to its results.

Chaudhuri et al. initially published the *KPPS* to be a reliable and valid scale to rate different types of pain in PD in 2015. Its aim is to evaluate the global and bedside burden of pain and to characterize various phenotypes of pain in PD patients. The scale consists of seven domains including 14 items, with each item scored by severity (0-3) multiplied by frequency (0-4), resulting in a subscore of 0 to 12, with a total possible score range from 0 to 168. The KPPS provides questions for musculoskeletal pain, chronic pain, fluctuation-related pain, nocturnal pain, oro-facial pain, discolouration, oedema / swelling and radicular pain. The contact information for this questionnaire and the permission to use for this study was granted by: Mapi Research Trust, Lyon, France – Internet: https://eprovide.mapi-trust.org

To evaluate the level and severity of fatigue of patients during the past week the *FSS* was used in this study. It consists of nine statements with levels ranging from 0 to 7 points whereat a low value

indicates a strong disagreement with the statement and a high value a strong approval of it. The scale pays attention to motivation, the impact of exercise on fatigue, the impact of fatigue on (physical) functioning, work, family or social life, and problems and disability arising from fatigue.

The *CGI-I* is used by the investigator to rate the patient´s total improvement based on a 1 to 7-point weighted scale at which 1 point means "very much improved" and 7 points indicate a status of being "very much worse". If the scale has not been assessed, a zero score will be given. The rater had to evaluate the improvement with regards to the patient´s NMS.

The *QUIP-RS* is a measurement designed to support the diagnosis and to measure the severity of symptoms of impulse control disorders and related disorders in PD in the last four weeks. The QUIP-RS consists of 4 primary questions addressed to commonly reported thoughts, urges/desires, and behaviours associated with impulse control disorders each applied to 4 domains of impulse control disorders and 3 domains of related disorders. These 4 domains are: compulsive gambling, buying, eating, and sexual behaviour. The 3 domains of related disorders are medication use, punding, and hobbyism. Each question can have a score from 0 to 4 assessing the frequency of thoughts, urges, or behaviours. The scores for each impulse control disorder and related disease can range from 0 to 16 points, with a higher score indicating a greater severity of symptoms. The total QUIP-RS score for all ICDs and related disorders combined can have values from 0 to 112 points. © University of Pennsylvania

Safety Assessments

Tolerability was described through the: Number of subjects (%) who discontinue the study and the number of subjects (%) who discontinue the study due to AE

Safety Measures included the following: AEs, SAEs, SUSARs, Clinical and laboratory assessment, Vital signs including performance of active orthostatism (measurement of heart rate and blood pressure after 10 minutes of quiet rest in the supine position and at 1, 2, 3, 5, and 10 minutes of active standing), ECG results, Patient´s Compliance, Prior and Concomitant Medication Use, Hallucination item (1.2), OH item (1.12), and Day-time sleepiness item (1.8) of the MDS-UPDRS, C-SSRS

Adverse Events, Serious Adverse Events, Adverse Drug Reaction, Suspected unexpected serious adverse reactions

Safety assessment can be implemented by monitoring and recording of AEs including adverse drug reactions, SAEs, and SUSARs. For a description of the terms, documentation, and reporting see 8 of the study protocol (Appendix). The patients were questioned for adverse reactions at any visit and telephone call. This was reported on the CRF and in the patient´s record. In case of an SAE or SUSAR, an immediate (within 24 hours of receipt) reporting to the Sponsor and the competent authorities would have been obligatory.

Description of other safety measures

Demographics
At Screening, the patient was asked for ethnicity, sex, age at examination, year and age of symptom onset, marital state, education (years), profession, family history (brief), and social history (brief).

Physical and neurological examination
A brief physical and neurological examination of the patient was held at the Screening Visit, randomisation Visit, V 1, the SFU, and an ET (if applicable) and documented in the patient´s record. All physical examinations were performed by trained medical personnel only. Any new abnormal findings were recorded as AEs. Physical examination had to at least include assessment of the

vigilance and orientation, general condition, nutritional condition, HEENT (head, eyes, ears, nose and throat), respiratory system, heart, abdomen, extremities, and visible skin and mucous membrane. Patients should be questioned for defecation and the act of urination. Neurological examination had to include standard neurological assessment of vigilance, orientation, mental status (e.g. consciousness), meningism, cranial nerves, the motor system and sensory system of both upper and lower extremities, reflexes (including pathological reflexes), cerebellar signs, gait, tandem gait, and postural stability, as well as special tests for parkinsonism (e.g. finger tapping, toe tapping, facial expression, … - assessed with the MDS-UPDRS III).

Laboratory assessments and Urinalysis

All laboratory assessments were made at the central laboratory of the MUI to ensure the patient´s safety and for early detection of changes in the course of the clinical trial. All members of the study team that were authorized by the principal investigator obtained blood samples. In total 8.2 ml of blood were withdrawn in 2 tubes at one visit. After withdrawal of blood, it was sent to the central laboratory and processed via standard methods. Date of collection was provided in the patient´s records. The laboratory results were displayed in the clinical information system, printed, reviewed by the principal investigator or authorized medical personnel, signed, dated and filed in the patient´s chart. An interpretation by the principal investigator or authorized medical personnel (clinically significant (c.s.) or non-clinically significant (n.c.s)) was provided.

Urinalysis was performed by authorized members of the study team using the Combur 10 Test M (Roche®) and reviewed by the investigator or authorized medical personnel. Date of collection was provided in the patient´s records. The results were written down on the Test Result Pads which are stored in the patient´s folder. Date and signature as well as an interpretation of the results by the principal investigator or authorized medical personnel (clinically significant (c.s.) or non-clinically significant (n.c.s)) were provided.

Laboratory assessments included standard hematology, chemistry, and urinalysis as outline in the schedule of events table (see Protocol) and were performed using standard kits of outpatient´s department. The following laboratory parameters were measured:

- Haematology: red blood cell count, white blood cell count, Haematocrit, Haemoglobin, MCV: mean corpuscular volume, MCH: mean corpuscular haemoglobin, MCHC: mean corpuscular haemoglobin concentration, Platelets
- Chemistry: alanine transaminase, aspartate transaminase, Troponin-I, creatine phosphokinase-MB, Creatinine, gamma-glutamyl transpeptidase, Electrolytes, Total conjugated and unconjugated bilirubin, lactate dehydrogenase, alkaline phosphatase, blood urea nitrogen
- Urinalysis: Leucocytes, Nitrite, Protein, Glucose, pH, Ketones, Urobilinogene, Bilirubin, Blood, Haemoglobin, Urine pregnancy test (females of childbearing potential, only)

If an abnormal laboratory measurement or result at urinalysis was detected, further measures and care were performed to ensure the patient´s safety. The abnormal finding was recorded and reported as an AE, SAE, or SUSAR if clinically significant. In case of SAEs or SUSARs, further participation of the patient in the trial would have been discussed with the Medical Monitor.

Vital signs

Vital signs including the evaluation of weight, height (only at screening), temperature, and active orthostatism were performed at all visits during the course of the study. The latter was assessed by measuring the heart rate and blood pressure after 10 minutes of quiet rest in a supine position and at 1, 2, 3, 5, and 10 min after active standing. Blood pressure and pulse rate were obtained in a quiet room at a comfortable temperature, with the patient's arm unconstrained by clothing or other material, and with an appropriate cuff size. In this study, an automatic blood pressure cuff

(sphygmomanometer) with digital advert was used. Patients with symptomatic OH were excluded from the study.

Concomitant medications
The patients were asked for concomitant medication on every visit and telephone call and assessed about permitted and prohibited concomitant medication.

Twelve-lead ECG
For ECG analyses the patient was sent to the cardiologic outpatient´s department of the MUI at Screening (if not performed within 4 weeks prior to SCR), randomisation and ET (if applicable). The ECG was reviewed by a cardiologist and displayed in the information system of the clinic. Members of the study team printed it, the investigator or a designee reviewed it, and the copy was filed in the patient´s records. If an abnormal ECG was detected, necessary procedures to ensure the safety of the patient were performed and an AE, SAE, or SUSAR was recorded and reported as described in 6.2 of the protocol (Appendix of this report). A standard 12-lead ECG was performed in a supine position after at least 10 minutes of resting to minimize variability at the study visits outlined in the Schedule of Events table of the protocol. ECGs for each patient were obtained from the same machine whenever possible. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. For safety monitoring purposes, the investigator or designee reviewed, signed, and dated all ECG tracings. The 12-lead ECG includes standard PR, QRS, QT, and QTc (heart-rate corrected QT) intervals as read by the machine. Fridericia's correction (QTcF) must be used for correction of the QT interval. The recorded ECG was used to determine eligibility at the Screening visit and to supervise the heart rhythm through the course of the study. Tachycardia is defined as a pulse rate above 100 bpm and by its characteristic changes in ECG waves.

Patient´s Compliance
The patient´s compliance was assessed by open questions from the investigator at every on-site visit and phone call.

Hallucination item (1.2) of MDS-UPDRS
Day-time sleepiness item (1.8) of MDS-UPDRS
OH item (1.12) of MDS-UPDRS
These items are part of the MDS-UPDRS Part I and refer to delusions and hallucinations of all sensations and to the loss of insight of the patient, to day-time sleepiness and its frequency while reading or watching TV, while having a discussion or during the meal, and to the sensation of drowsiness and vertigo and its consequences, like falls during the last week. The items were assessed to detect potential side effects that may occur due to drug treatment. They were assessed at every clinical visit and during all phone calls and documented in the source documents.

C-SSRS
The C-SSRS has shown overall successful prediction of suicidal behaviour in adolescences and adults. It is the only screening tool to assess the full range of suicidal ideation and behaviour including criteria for the next steps (e.g. referral to a mental health professional). In this study the scale was used by trained study personnel only (online training, Posner et. al, 2011) at all visits and telephone calls as a measurement for safety. The scale consists of 4 categories: suicidal ideation, intensity of suicidal ideation, suicidal behaviour, and actual/potential lethality which can be answered by Yes or No. At Screening Visit the questionnaire for the past 6 months was used and for all other visits and phone calls the version "Since the last visit" was administered. © 2008 The Research Foundation for Mental Hygiene, Inc.

Assessment of exploratory endpoint

Eye-tracking: Measurement of eye-movements with the Tobii TX-300 Eye-tracking provides a fast and non-invasive method for various examinations. In this study we measured the reaction time using prosaccade and antisaccade tasks. Moreover, we assessed attention spans and the ability to concentrate using a customized saccade task and a test involving task-switching. The examination was performed at the Screening Visit and the Termination Visit (Week 4). Examinations took place in a quiet room and were conducted by trained personnel only.

Appropriateness of measurements

All measures used were standard, i.e., widely used and generally recognised as reliable, accurate, and relevant (able to discriminate between effective and ineffective agents), except for the Eyetracking. No surrogate end point was used.

Primary efficacy variable

The primary efficacy endpoint was measured as the change of the MDS-UPDRS Part I between randomisation and week 4. Significance of the MDS-UPDRS Part I as globally used assessment tool for NMS in PD patients: see above

Drug concentration measurements

No drug concentration measurement was performed in this study.

8. Data Quality Assurance

Training, monitoring, and audits are performed for quality assurance reasons within this clinical study. Monitoring and auditing procedures developed or endorsed by the Sponsor complied with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use – Good Clinical Practice (ICH-GCP) guidelines and local legal requirements to ensure acceptability of the study data and patient´s safety.

Qualifications

The Sponsor was responsible for selecting the investigator and Institution. Each investigator was qualified by training and experience and had adequate resources. Everyone involved in conducting the trial was qualified by education, training, and experience to perform his or her respective task(s) (see ICH GCP E6). To meet those objectives, every member of the study team is GCP-trained. A Certificate of MDS-UPDRS Training, a C-SSRS Training Certificate, and experience in using the other scales (e.g. QUIP-RS) was provided by every investigator in the trial who intended to use these scales. The members of the study team were trained on the trial´s protocol and the completion of the source data entry (case report form and patient´s record) by the principal investigator or designee. This process was documented in the Investigator Site File (ISF). Authorization of a member of the study team to perform study related tasks were reported in the Delegation Log of the ISF.

Monitoring

A study monitor from the CTC performed source document verification at regular intervals in accordance with GCP and ICH guidelines. The objectives of the monitoring procedures were to ensure that the trial subject's safety and rights as a study participant are respected, that accurate, valid and complete data are collected, used, and stored, and that the trial is conducted in accordance to the trial protocol, the principles of GCP and local legislation. All investigators agreed that the monitor regularly visits the trial site. For monitoring, all study-related documents were given access to the monitor by the investigator for confirmation of data. Moreover, the investigators assured that

the monitor received appropriate support in his/her activities at the trial site, as agreed in separate contracts. The Informed Consent Form (ICF) included a statement that the monitor has the right – while observing the provisions of data protection legislation – to compare case report forms with the trial subject's medical records (doctor's notes, ECGs, laboratory printouts etc.). A study specific monitoring plan was established, and the study was monitored in agreement with it. All representatives from regulatory authorities and the EC/IRB would have been gained access to the study-related documents needed for their investigation. Protection of the patient´s personal data is/was guaranteed to the extent possible.

Audits and Inspections

During a study, a Quality Assurance audit or inspection can be performed by regulatory authorities, the ethics committees, or the Sponsor's delegates. Therefore, the investigator must grant direct access to all data and must always provide support. The aim of an audit is to verify the validity, accuracy and completeness of data, to establish the credibility of the clinical trial, and to check whether the trial subject's rights and trial subject safety are being maintained. The Sponsor may assign these activities to persons otherwise not involved in the trial (Auditors). These persons are allowed access to all trial documentation (especially the trial protocol, case report forms, trial subject´s medical records, drug accountability documentation, and trial-related correspondence). After each external audit an audit-certificate by the Auditor must be delivered to the investigator. This certificate must be kept in the ISF to evidence the audit to the regulatory authorities in the case of an inspection by them. The audit-report is delivered to the Sponsor of the study. Additionally, according to the Austrian Medicines Law audits and inspections by regulatory authorities may be performed. All persons conducting audits undertake to keep all trial subject data and other trial data confidential.

No audit or inspection of this study was performed until the date of this final report.

Statistical Methods Planned in the Protocol and Determination of Sample Size

Statistical and analytical plans

Data were entered into a database and manually controlled by two independent study team members. A descriptive analysis of demographic and clinical data at baseline was performed using the full dataset of all patients that have ever taken nabilone in this trial (n=47). Analyses of the primary and secondary efficacy endpoints included all randomised subjects with scoring of MDS-UPDRS I at randomisation and the termination visit. Safety and tolerability summaries were based on the safety set which includes all patients receiving at least one dose of study medication during both trial phases. The changes of all outcome variables during phase 1 of the trial were assessed using a Wilcoxon matched-pairs test for within group comparison. The primary, secondary, and exploratory endpoints of this study were analysed separately for the nabilone and the placebo group using a Wilcoxon matched-pairs test for within-group comparison (with correction for multiple comparisons with a factor of two) and a Mann–Whitney U test for between-group comparisons. For all analyses, statistical significance was set at a two-sided 5% level. For CGI analysis, distributions of dichotomized ratings (deterioration versus no-deterioration) in the nabilone and placebo groups at the termination visit was compared by Fisher's exact test. Effect sizes for the different primary, secondary, and exploratory endpoints were calculated according to Cohen´s D (19), except for the efficacy analyses of the single items of the MDS-UPDRS I and the CGI where $r_{contrast}$ and ϕ coefficient (20, 21) were used, respectively. Cohen´s D of 0.2, 0.5, and 0.8 as well as $r_{contrast}$ and ϕ coefficient of 0.1, 0.3, and 0.5 were considered 'small', 'medium', and 'large' effect sizes, respectively.

As a sensitivity analysis, we fitted a repeated measures mixed model with MDS-UPDRS Part I sum score as dependent variable and a factorial interaction between group assignment and time as independent variable. We applied an unstructured within-subject covariance matrix assuming that each timepoint and each pair of time points have their own variance and co-variance, respectively. SPSS 22.0 for windows (SPSS Inc., IBM Corporation and other(s) 1989, 2013, Chicago, IL) was used to tabulate and analyse data.

No changes to the statistical plans were made before outcome variables were available. There was no data monitoring committee for this trial. No interim analysis was planned or conducted.

Determination of sample size

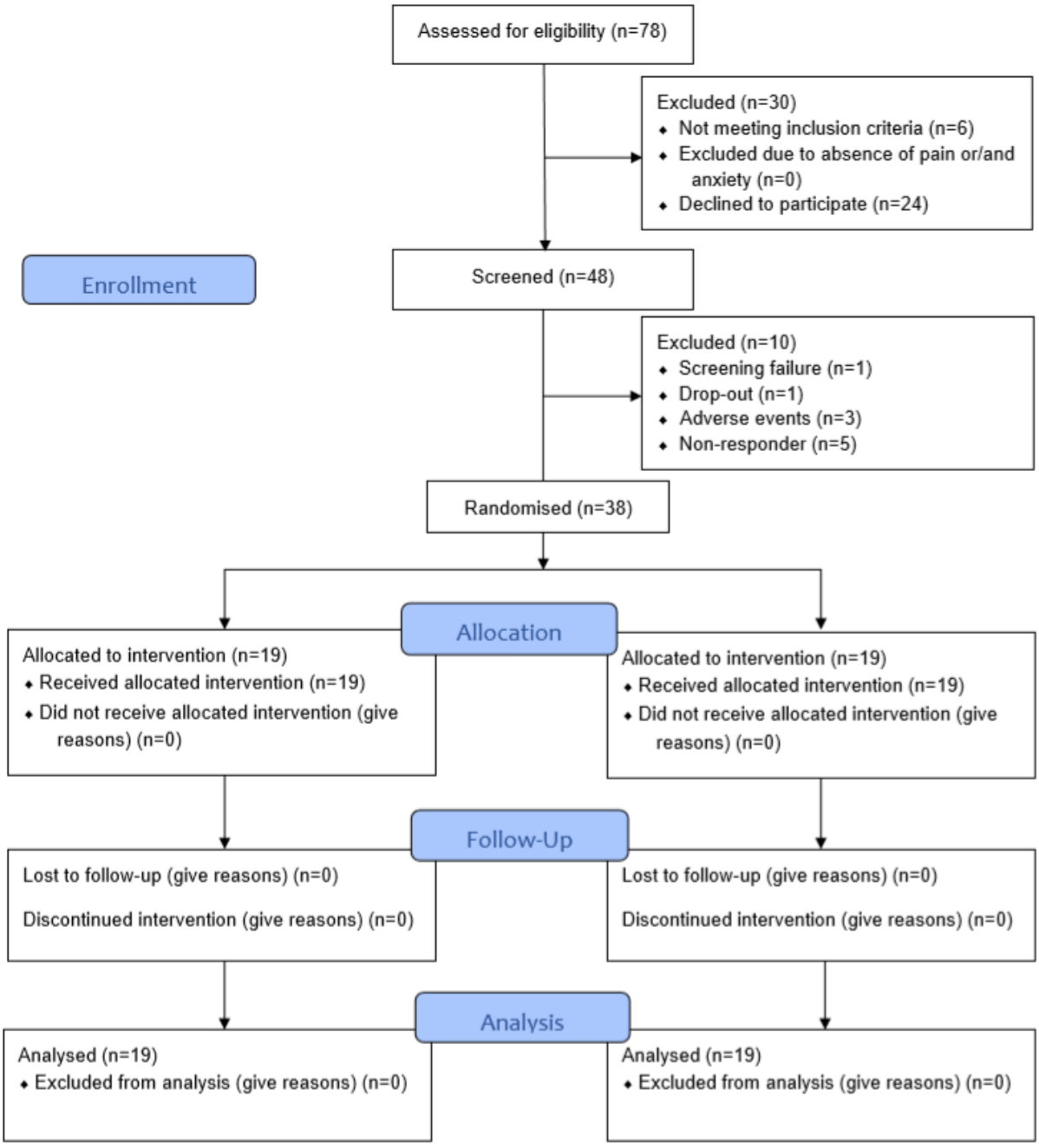
We planned to enrol 48 patients to account for dropouts and include 19 patients per treatment group in the randomised trial phase, which was considered sufficient to detect a treatment difference of 2.5 points in the primary endpoint (standard deviation 2.4) with 80% power and a two-sided α-level of 0.05 (Mann–Whitney U test; nQuery Advisor Version 7 (3)).

Changes in the Conduct of the Study or Planned Analyses

Not applicable

9. Study Patients

Disposition of Patients



Flow Chart (adapted from CONSORT 2010)
Abbreviations: n, number.

Between October 17, 2017, and July 15, 2019 (last patient last visit), 48 participants were screened. There was one screening failure due to the use of prohibited concomitant medication. During open-label titration (phase 1) nine patients were either non-responder as defined per protocol (n=5, 10.42%) or discontinued (n=4, 8.33%, 1 drop-out, 3 due to AEs, Flow chart). Thirty-eight patients

entered phase 2 and were randomised 1:1 to the placebo or nabilone arm (n=19 each). No patient discontinued phase 2 and all patients were included in the final analyses (Flow chart).

Protocol Deviations

No patient entered the study without satisfying the entry criteria. No patient developed withdrawal criteria during the study but was not withdrawn. No patient received the wrong treatment. No patient received an excluded concomitant treatment permanently.

Most protocol deviations were due to deviations in the visit windows or a change in concomitant medication during the double-blind treatment phase (e.g. due to infection). A copy of the Protocol Deviation Log from the ISF is attached to this report.

10. Efficacy Evaluation

Data Sets Analysed

See above

No treatment responder during the open-label phase of the trial was excluded from analyses of the double-blind treatment phase (see Flow chart).

Demographic and Other Baseline Characteristics

Demographic and clinical characteristics were balanced between treatment groups (Table 3).

Table 1: Demographics and results at baseline

	Total (n=47)	**Placebo group (n=19)**	**Nabilone group (n=19)**
Age (years)	65.05 ±8.12 (66.83)	63.95 ±8.04 (65.92)	65.38 ±7.94 (66.83)
Females	19 (40%)	5 (26%)	9 (47%)
Disease duration (years)	7.86 ±5.17 (7.00)	7.39 ±5.14 (5.75)	7.83 ±5.47 (7.25)
Daily nabilone dose (mg)[a] at randomization	0.86 ±0.40 (0.75)	0.80 ±0.41 (0.75)	0.91 ±0.40 (1.00)
Charlson Comorbidity Index	0.43 ±0.77 (0.00)	0.47 ±0.84 (0.00)	0.32 ±0.75 (0.00)
Education (years)	12.85 ±2.71 (12.00)	13.08 ±3.19 (12.00)	12.87 ±2.78 (12.00)
H&Y scale	1.89 ±0.43 (2.00) (95% CI 1.77; 2.02)	1.95 ±0.41 (2.00) (95% CI 1.75; 2.14)	1.84 ±0.50 (2.00) (95% CI 1.60; 2.08)
MDS-UPDRS-I	12.36 ±4.92 (12.00)	12.26 ±5.85 (12.00)	13.53 ±4.39 (15.0)
MDS-UPDRS-II	9.83 ±5.12 (9.00)	10.47 ±4.50 (10.00)	10.37 ±6.24 (9.00)
MDS-UPDRS-III	26.70 ±11.22 (26.0)	27.90 ±9.98 (27.00)	26.00 ±13.25 (25.00)
MDS-UPDRS-IV	1.68 ±2.13 (0.00)	1.42 ±1.92 (0.00)	2.16 ±2.34 (2.00)
MDS-UPDRS Total Score	51.81 ±18.88 (50.00)	52.05 ±14.75 (53.00)	52.05 ±22.97 (49.00)
MDS-UPDRS Motor Score	36.53±14.79 (37.00)	38.37 ±11.93 (39.00)	36.37 ±18.64 (37.00)
MoCA	27.94 ±1.81 (28.0)	27.95 ±1.47 (28.00)	28.11 ±1.27 (28.00)
PDQ-39 SI	22.97 ±15.41 (20.94)	25.18 ±16.38 (21.25)	21.11 ±11.69 (21.04)

Data is given for all patients that have ever taken nabilone in this trial (full dataset). Data are presented as mean ± standard deviation (median) for continuous variables and number (percent) for categorical variables. For the H&Y scale, the 95% CI is also given. [a] Data on nabilone dose refers to the 38 randomized patients. Abbreviations: mg, milligrams; H&Y, Hoehn and Yahr; CI, confidence interval; MDS-UPDRS, Movement Disorders Society- Unified Parkinson´s Disease Rating Scale; MoCA, Montreal Cognitive Assessment; PDQ-39, Parkinson´s Disease Questionnaire-39; SI, Summary Index. Higher Score values indicate worse outcome in all scales and questionnaires but in the MoCA.

Demographic and baseline values of individual patients at the screening visit are attached as PDF-File.

Measurements of Treatment Compliance

One patient had a treatment compliance out of range in the open-label phase of the trial (patient ID 037, non-responder, early termination visit performed, see Protocol Deviation Log attached to this report). No randomised patient had a treatment compliance out of range during the double-blind phase of the trial. For measurements of compliance: see above

Efficacy Results and Tabulations of Individual Patient Data

Analysis of efficacy: OL phase

In the OL phase, both the MDS-UPDRS Part I and the NMSS decreased significantly in all patients (Table 4).

Table 3: Change in endpoint scores during open-label administration of nabilone, patients n=38

	Baseline	Randomization	Mean change (95% CI) from BL to R	p-value [1]
MDS-UPDRS-I	12.90 ±5.14	9.11 ±5.54	-3.79 (-4.97; -2.61)	<0.001
NMSS Total Score	49.82 ±31.03	39.79 ±27.48	-10.03 (-16.65; -3.40)	0.002
MDS-UPDRS-II	10.42 ±5.37	10.03 ±5.09	-0.40 (-1.42; 0.63)	0.406
MDS-UPDRS-III	26.95 ±11.61	24.71 ±10.36	-2.24 (-4.90; 0.42)	0.058
MDS-UPDRS Motor Score	37.37 ±15.47	34.74 ±13.95	-2.63 (-5.72; 0.45)	0.085
ESS	8.00 ±3.95	8.47 ±4.16	0.47 (-0.29; 1.24)	0.308
FSS	34.08 ±13.73	34.08 ±11.05	0.00 (-3.22; 3.22)	0.941
HADS-A	5.39 ±3.58	5.50 ±3.53	0.26 (-0.48; 1.01)	0.793
HADS-D	5.05 ±3.21	5.32 ±3.47	0.11 (-0.70; 0.91)	0.500
MoCA	28.03 ±1.37	28.08 ±2.11	0.05 (-0.48; 0.59)	0.646
PDQ-39 SI	23.14 ±14.18	23.16 ±14.02	0.02 (-2.42; 2.45)	0.521
KPPS Total Score	21.24 ±14.61	17.47 ±13.65	-3.76 (-7.33; -0.20)	0.022
QUIP-RS Total Score	0.71 ±1.29	0.95 ±2.04	0.24 (-0.38; 0.86)	0.482
VAS of Pain (mm)	47.16 ±21.92	35.05 ±24.44	-12.11 (-18.68; -5.53)	0.001

Data of continuous variables are presented as mean ± standard deviation (endpoint scores at baseline and randomization) or mean (95% CI) (change of endpoint scores). [1] Within group comparison. For all p-values, significance level was set at p≤0.05. Abbreviations: MDS-UPDRS, Movement Disorder Society- Unified Parkinson´s Disease Rating Scale; NMSS, Non-Motor Symptoms Scale; CGI-I, Clinical Global Impression – Improvement Scale; ESS, Epworth Sleepiness Scale; FSS, Fatigue Severity Scale; HADS-A/D, Hospital anxiety and depression scale- Anxiety/Depression; MoCA, Montreal Cognitive Assessment; PDQ-39, Parkinson´s Disease Questionnaire-39; SI, Summary Index; KPPS, King´s Parkinson´s Disease Pain Scale; QUIP-RS, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale; VAS, Visual Analogue Scale; mm, millimeters; BL, Baseline; R, Randomization; CI, confidence interval. Higher Score values indicate worse outcome in all scales and questionnaires but in the MoCA.

Analysis of efficacy: Double-blind phase

Mean change of the MDS-UPDRS part I score during the randomised double-blind phase was 2.63 points (95%CI 1.53 to 3.74, p=0.002, effect size 1.15) in the placebo versus 1.00 points (95%CI -0.16 to 2.16, p=0.280, effect size 0.42) in the nabilone group (difference: 1.63, 95%CI 0.09 to 3.18, p=0.030, effect size 0.66, Figure 2). The change of the MDS-UPDRS part I score was not significant in the nabilone group which is reflected by the small effect size. The placebo group deteriorated significantly with a large effect size (Table 5.1 and 5.2). Additionally, there was a significant between-group difference for the MDS-UPDRS I, which was medium to the disadvantage of the placebo arm (Table 5.1 and 5.2). The sensitivity analyses (mixed model as described above) showed a significant partial interaction between treatment and time (from randomisation to the termination visit). Mean change of the NMSS at the termination visit was 11.00 points (95%CI 4.68 to 17.32, p=0.004, effect size 0.84) in the placebo versus 4.05 points (95%CI -0.65 to 8.75, p=0.096, effect size 0.42) in the nabilone group (difference: 6.95, 95%CI -0.66 to 14.55, p=0.147, effect size 0.58, Table 5.1 and 5.2).

The change of the NMSS during the randomised double-blind phase was not significant in the nabilone group, but there was a trend for deterioration (p=0.096). This is reflected by the small effect size of the change in the nabilone group. The placebo group however worsened significantly, reflected by a large effect size (Table 5.1 and 5.2). Of note, the between-group effect size of deterioration was also medium to the disadvantage of the placebo arm for the NMSS (Table 5). Quite in line with this, there was a significant deterioration with a medium effect size also for the CGI-I to the disadvantage of the placebo arm (Table 5.1 and 5.2). Fourteen patients in the placebo-group (73.68%) rated themselves as worsened during the double-blind period, compared to only seven patients in the nabilone group (36.84%, p=0.049, Figure 3), revealing a ϕ coefficient of 0.37.

Table 4.1: Change in primary and secondary endpoint scores during double-blind treatment, within-group comparisons

		Randomisation	Termination visit	Mean change (95% CI) from R to TV	p-value *	Effect size **
MDS-UPDRS I	P	8.58 ±5.81	11.21 ± 6.20	2.63 (1.53; 3.74)	0.002	1.15
	V	9.63 ±5.35	10.63 ±5.64	1.00 (-0.16; 2.16)	0.280	0.42
NMSS	P	35.16 ±24.07	46.16 ±29.47	11.00 (4.68; 17.32)	0.004	0.84
	V	44.42 ±30.45	48.47 ±31.12	4.05 (-0.65; 8.75)	0.096	0.42
CGI	P	NA	4.95 ±0.71	NA	NA	NA
	V	NA	4.42 ±0.61	NA	NA	NA
MDS-UPDRS II	P	10.11 ±4.37	11.00 ±5.37	0.90 (-0.35; 2.14)	0.234	0.35
	V	9.95 ±5.85	10.42 ±5.92	0.47 (-0.37; 1.31)	0.458	0.27
MDS-UPDRS III	P	24.47 ±9.52	27.11 ±7.66	2.63 (0.25; 5.02)	0.034	0.53
	V	24.95 ±11.39	25.47 ±11.47	0.53 (-2.24; 3.29)	1.000	0.09
MDS-UPDRS Motor Score	P	34.58 ±11.76	38.11 ±10.99	3.53 (0.78; 6.28)	0.018	0.62
	V	34.90 ±16.17	35.89 ±16.58	1.00 (-2.16; 4.16)	0.790	0.15
ESS	P	8.26 ±4.64	7.47 ±4.36	-0.79 (-1.85; 0.27)	0.260	-0.36
	V	8.68 ±3.74	7.95 ±4.06	-0.74 (-1.87; 0.40)	0.368	-0.31
FSS	P	34.11 ±13.10	34.11 ±17.56	0.00 (-5.26; 5.26)	1.000	0.00
	V	34.05 ±8.92	30.05 ±10.14	-4.00 (-9.77; 1.77)	0.358	-0.33
HADS-A	P	4.74 ±3.96	4.79 ±4.09	0.05 (-1.09 1.19)	1.000	0.02
	V	6.26 ±2.96	6.53 ±4.65	0.26 (-0.87; 1.40)	1.000	0.11
HADS-D	P	5.00 ±2.93	5.16 ±3.70	0.16 (-0.71; 1.03)	1.000	0.09
	V	5.63 ±4.00	5.95 ±3.89	0.32 (-1.11; 1.74)	1.000	0.11
MoCA	P	28.11 ±2.13	28.11 ±1.45	0.00 (-0.63; 0.62)	1.000	0.00
	V	28.05 ±2.15	28.79 ±1.36	0.74 (-0.18; 1.66)	0.112	0.39
PDQ-39 SI	P	23.26 ±16.73	22.57 ±12.83	-0.47 (-3.21; 2.28)	1.000	-0.08
	V	23.06 ±11.13	22.57 ±12.83	-0.49 (-3.04; 2.05)	0.842	-0.09
KPPS Total Score	P	18.53 ±16.18	21.37 ±20.62	2.84 (-5.19; 10.87)	1.000	0.17
	V	16.42 ±10.89	18.00 ±13.00	1.58 (-2.73; 5.89)	1.000	0.18
QUIP-RS Total Score	P	1.00 ±2.33	1.05 ±3.21	0.05 (-0.64; 0.74)	1.000	0.04
	V	0.89 ±1.76	0.21 ±0.63	-0.68 (-1.49; 0.12)	0.186	-0.41
VAS of Pain (mm)	P	36.42 ±25.26	38.58 ±25.30	2.16 (-8.40; 12.71)	1.000	0.10
	V	33.68±24.21	40.26 ±23.91	6.58 (-5.65; 18.81)	1.000	0.26

Data of continuous variables are presented as mean ± standard deviation (endpoint scores at randomisation and termination) or mean (95% CI) (change of endpoint scores). *p-value corrected for multiple testing (multiplied by 2). For all p-values, significance level was set at p≤0.05. **Effect size according to Cohen´s d for all variables except for the CGI-I (ϕ coefficient). Abbreviations: MDS-UPDRS, Movement Disorder Society- Unified Parkinson´s Disease Rating Scale; NMSS, Non-Motor Symptoms Scale; CGI-I, Clinical Global Impression – Improvement Scale; ESS, Epworth Sleepiness Scale; FSS, Fatigue Severity Scale; HADS-A/D, Hospital anxiety and depression scale- Anxiety/Depression; MoCA, Montreal Cognitive Assessment; PDQ-39, Parkinson´s Disease Questionnaire-39; SI, Summary Index; Dim., Dimension; KPPS, King´s Parkinson´s Disease Pain Scale; D, (Sub-)Domain; QUIP-RS, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale; VAS, Visual Analogue Scale; mm, millimetres; R, Randomisation; TV, Termination Visit; CI, confidence interval; P, Placebo; V, Verum; NA, not applicable. Higher Score values indicate worse outcome in all scales and questionnaires but in the MoCA.

Table 5.2: Change in primary and secondary endpoint scores during double-blind treatment, between-group comparisons

		Randomisation	Termination visit	Mean difference (95% CI)	p-value	Effect size*
MDS-UPDRS I	P	8.58 ±5.81	11.21 ± 6.20	1.63 (0.09; 3.18)	0.030	0.66
	V	9.63 ±5.35	10.63 ±5.64			
NMSS	P	35.16 ±24.07	46.16 ±29.47	6.95 (-0.66; 14.55)	0.147	0.58
	V	44.42 ±30.45	48.47 ±31.12			
CGI	P	NA	4.95 ±0.71	0.53 (0.09; 0.96)	0.019	0.37
	V	NA	4.42 ±0.61			
MDS-UPDRS II	P	10.11 ±4.37	11.00 ±5.37	0.42 (-1.03; 1.87)	0.584	0.19
	V	9.95 ±5.85	10.42 ±5.92			
MDS-UPDRS III	P	24.47 ±9.52	27.11 ±7.66	2.11 (-1.42; 5.63)	0.420	0.39
	V	24.95 ±11.39	25.47 ±11.47			
MDS-UPDRS Motor Score	P	34.58 ±11.76	38.11 ±10.99	2.53 (-1.52; 6.57)	0.339	0.44
	V	34.90 ±16.17	35.89 ±16.58			
ESS	P	8.26 ±4.64	7.47 ±4.36	-0.05 (-1.55; 1.45)	0.918	-0.02
	V	8.68 ±3.74	7.95 ±4.06			
FSS	P	34.11 ±13.10	34.11 ±17.56	4.00 (-3.53; 11.53)	0.364	0.35
	V	34.05 ±8.92	30.05 ±10.14			
HADS-A	P	4.74 ±3.96	4.79 ±4.09	0.21 (-1.34; 1.76)	0.779	-0.09
	V	6.26 ±2.96	6.53 ±4.65			
HADS-D	P	5.00 ±2.93	5.16 ±3.70	0.16 (-1.46; 1.77)	0.790	-0.07
	V	5.63 ±4.00	5.95 ±3.89			
MoCA	P	28.11 ±2.13	28.11 ±1.45	-0.74 (-1.81; 0.46)	0.053	-0.44
	V	28.05 ±2.15	28.79 ±1.36			
PDQ-39 SI	P	23.26 ±16.73	22.57 ±12.83	0.03 (-3.59; 3.64)	0.907	0.00
	V	23.06 ±11.13	22.57 ±12.83			
KPPS Total Score	P	18.53 ±16.18	21.37 ±20.62	1.00 (-7.76; 9.76)	0.671	0.10
	V	16.42 ±10.89	18.00 ±13.00			
QUIP-RS Total Score	P	1.00 ±2.33	1.05 ±3.21	0.74 (-0.29; 1.76)	0.181	0.47
	V	0.89 ±1.76	0.21 ±0.63			
VAS of Pain (mm)	P	36.42 ±25.26	38.58 ±25.30	-4.42 (-20.02; 11.17)	0.965	-0.19
	V	33.68±24.21	40.26 ±23.91			

Data of continuous variables are presented as mean ± standard deviation (endpoint scores at randomisation and termination) or mean (95% CI) (change of endpoint scores). *Effect size according to Cohen´s d for all variables except for the CGI-I (ϕ coefficient). For all p-values, significance level was set at p≤0.05. Abbreviations: MDS-UPDRS, Movement Disorder Society- Unified Parkinson´s Disease Rating Scale; NMSS, Non-Motor Symptoms Scale; CGI-I, Clinical Global Impression – Improvement Scale; ESS, Epworth Sleepiness Scale; FSS, Fatigue Severity Scale; HADS-A/D, Hospital anxiety and depression scale- Anxiety/Depression; MoCA, Montreal Cognitive Assessment; PDQ-39, Parkinson´s Disease Questionnaire-39; SI, Summary Index; Dim., Dimension; KPPS, King´s Parkinson´s Disease Pain Scale; D, (Sub-)Domain; QUIP-RS, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale; VAS, Visual Analogue Scale; mm, millimetres; R, Randomisation; TV, Termination Visit; CI, confidence interval; P, Placebo; V, Verum; NA, not applicable. Higher Score values indicate worse outcome in all scales and questionnaires but in the MoCA.

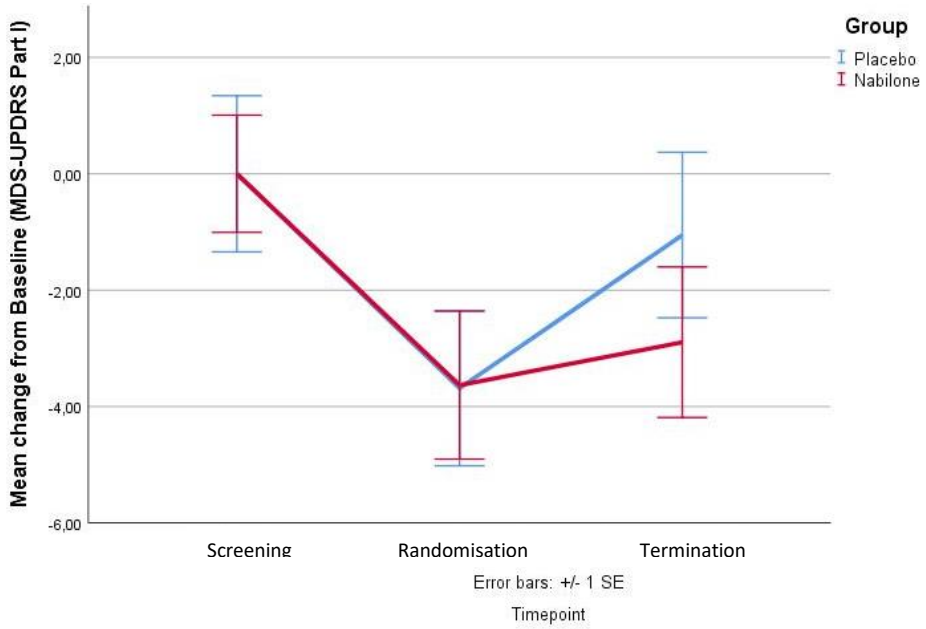


Figure 2: Changes of MDS-UPDRS Part I during the study
Abbreviations: MDS-UPDRS, Movement Disorder Society- Unified Parkinson´s Disease Rating Scale; SE, standard error.

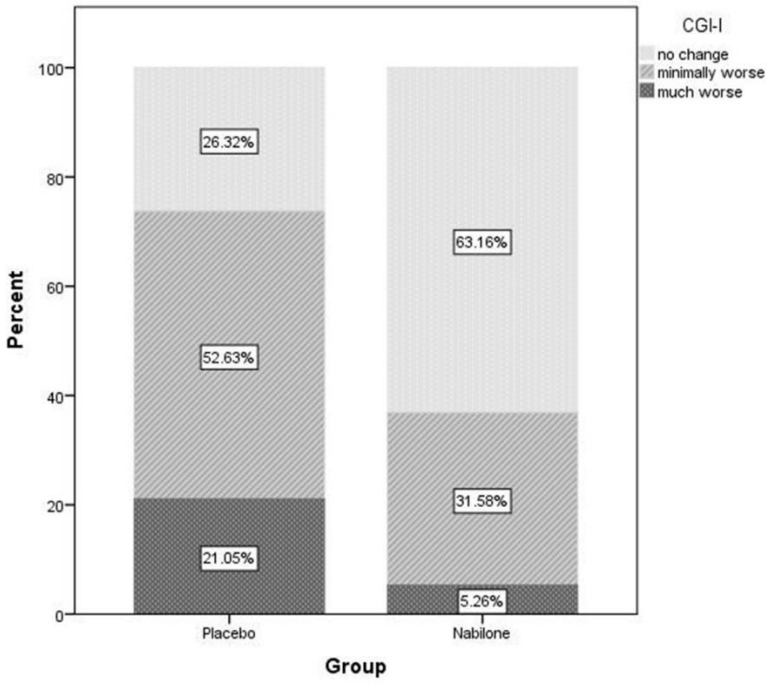


Figure 3: Changes of CGI-I during double-blind treatment
Abbreviation: CGI-I, Clinical Global Impression – Improvement Scale.

Table 5.1 and 5.2 also shows the main results of the other secondary efficacy analyses of the randomised phase of the trial. The MDS-UPDRS Part III and the motor sum score of the MDS-UPDRS worsened in the placebo arm, while the between-group differences were not significant with medium effect sizes of 0.39 and 0.44 (Table 5.1 and 5.2). None of the further secondary outcome

measures showed significant within- or between-group differences and none of their effect sizes exceeded 0.5. Although pain-related endpoints (KPPS Total Score and Pain VAS) improved significantly during the open-label phase of the trial (Table 4), the change during the randomised phase of the trial was not significant (Table 5.1 and 5.2).

Analysis of efficacy: single items of the MDS-UPDRS and NMSS

Results of analyses of the single items of the MDS-UPDRS I are given in Tables 6.1, 6.2, 7.1, and 7.2. These analyses revealed significant between-group changes for items 1.4 (i.e. anxious mood: p=0.044 with a $r_{contrast}$ of 0.33) and 1.7 (i.e. night-time sleeping problems: p<0.001 with a $r_{contrast}$ of 0.61) to the advantage of the nabilone group. The deterioration of these two items in the placebo arm was significant only for item 1.7 (Table 6.1 and 6.2). In line with the single item analysis of the MDS-UPDRS I, there was also a significant worsening of the NMSS Domain 2 (i.e. Sleep/Fatigue) in the placebo group with a significant between-group difference (p=0.023 with a Cohen's D of 0.81, Table 7.1 and 7.2).

Table 6.1: Change in MDS-UPDRS Subitems during double-blind treatment, within-group comparisons

MDS-UPDRS Sub-Item		Randomisation	Termination visit	Mean change (95% CI) from R to TV	p-value *	Effect size **
1.1	P	0.58 ±0.69	0.68 ±0.75	0.11 (-0.15; 0.33)	0.634	0.16
	V	0.68 ±0.67	0.74 ±0.73	0.05 (-0.14; 0.25)	1.000	0.09
1.2	P	NA	NA	NA	NA	NA
	V	NA	NA	NA	NA	NA
1.3	P	0.53 ±0.70	0.68 ±0.58	0.16 (-0.08; 0.40)	0.360	0.22
	V	0.53 ±0.70	0.63 ±0.90	0.11 (-0.17; 0.38)	0.828	0.13
1.4	P	0.68 ±1.00	0.89 ±0.88	0.21 (-0.05; 0.47)	0.204	0.27
	V	0.89 ±0.94	0.74 ±1.05	-0.16 (-0.53; 0.21)	0.816	-0.13
1.5	P	0.53 ±0.96	0.53 ±0.91	0.00 (-0.23; 0.23)	1.000	0.00
	V	0.68 ±0.89	0.84 ±0.90	0.16 (-0.13; 0.45)	0.514	0.18
1.6	P	NA	NA	NA	NA	NA
	V	NA	NA	NA	NA	NA
1.7	P	0.58 ±1.02	2.37 ±1.38	1.79 (1.15; 2.42)	0.002	0.56
	V	0.95 ±0.91	1.00 ±1.11	0.05 (-0.47; 0.57)	1.000	0.01
1.8	P	0.95 ±0.78	1.05 ±0.71	0.11 (-0.21; 0.42)	0.960	0.12
	V	0.95 ±0.78	1.21 ±0.79	0.26 (-0.01; 0.53)	0.118	0.29
1.9	P	1.79 ±1.13	2.11 ±1.05	0.32 (-0.14; 0.78)	0.306	0.23
	V	1.58 ±0.96	1.95 ±1.08	0.37 (-0.06; 0.80)	0.166	0.28
1.10	P	0.84 ±1.17	1.00 ±1.25	0.16 (-0.41; 0.72)	1.000	0.10
	V	1.16 ±1.39	1.32 ±1.53	0.16 (-0.17; 0.49)	0.634	0.16
1.11	P	0.74 ±0.87	0.74 ±1.05	0.00 (-0.28; 0.28)	1.000	0.00
	V	0.53 ±0.84	0.53 ±0.70	0.00 (-0.36; 0.36)	1.000	0.00
1.12	P	0.68 ±0.75	0.42 ±0.77	-0.26 (-0.65; 0.13)	0.332	-0.23
	V	0.74 ±0.65	0.95 ±0.97	0.21 (-0.13; 0.55)	0.412	0.21
1.13	P	0.42 ±0.84	0.53 ±1.02	0.11 (-0.21; 0.42)	0.960	0.12
	V	0.68 ±0.82	0.68 ±0.82	0.00 (-0.28; 0.28)	1.000	0.00

Data are presented as mean ± standard deviation (endpoint scores at randomisation and termination) or mean (95% CI) (change of endpoint scores). As only 2 and 7 patients scored on MDS-UPDRS 1.2 and 1.6, respectively, no statistical analysis on these items was performed. *p-value corrected for multiple testing (multiplied by 2). For all p-values, significance level was set at p≤0.05. ** Effect size calculated with $r_{contrast}$, values of 0.1, 0.3 and 0.5 considered as 'small', 'medium' and 'large' effect sizes. Abbreviations: MDS-UPDRS, Movement Disorder Society- Unified Parkinson´s Disease Rating Scale; R, Randomisation; TV, Termination Visit; CI, confidence interval; P, Placebo; V, Verum; NA, not applicable.
MDS-UPDRS items: 1.1: Cognitive impairment, 1.2: Hallucinations and psychosis, 1.3: Depressed Mood, 1.4: Anxious Mood, 1.5: Apathy, 1.6: Features of dopamine dysregulation syndrome, 1.7: Nighttime sleep problems, 1.8: Daytime sleepiness, 1.9: Pain and other sensations, 1.10: Urinary problems, 1.11: Constipation problems, 1.12: Lightheadedness on standing, 1.13: Fatigue.

Table 6.2: Change in MDS-UPDRS Subitems during double-blind treatment, between-group comparisons

MDS-UPDRS Sub-Item		Randomisation	Termination visit	Mean difference (95% CI)	p-value	Effect size *
1.1	P	0.58 ±0.69	0.68 ±0.75	0.05 (-023; 0.34)	0.697	0.06
	V	0.68 ±0.67	0.74 ±0.73			
1.2	P	NA	NA	NA	NA	NA
	V	NA	NA			
1.3	P	0.53 ±0.70	0.68 ±0.58	0.05 (-0.30; 0.41)	0.783	0.05
	V	0.53 ±0.70	0.63 ±0.90			
1.4	P	0.68 ±1.00	0.89 ±0.88	0.37 (-0.07; 0.80)	0.044	0.33
	V	0.89 ±0.94	0.74 ±1.05			
1.5	P	0.53 ±0.96	0.53 ±0.91	-0.16 (-0.51; 0.20)	0.460	-0.12
	V	0.68 ±0.89	0.84 ±0.90			
1.6	P	NA	NA	NA	NA	NA
	V	NA	NA			
1.7	P	0.58 ±1.02	2.37 ±1.38	1.74 (0.95; 2.53)	<0.001	0.61
	V	0.95 ±0.91	1.00 ±1.11			
1.8	P	0.95 ±0.78	1.05 ±0.71	-0.21 (-0.63; 0.21)	0.459	-0.12
	V	0.95 ±0.78	1.21 ±0.79			
1.9	P	1.79 ±1.13	2.11 ±1.05	-0.05 (-0.66, 0.55)	0.950	-0.01
	V	1.58 ±0.96	1.95 ±1.08			
1.10	P	0.84 ±1.17	1.00 ±1.25	0.00 (-0.63; 0.63)	0.958	0.01
	V	1.16 ±1.39	1.32 ±1.53			
1.11	P	0.74 ±0.87	0.74 ±1.05	0.00 (-0.44; 0.44)	0.821	0.02
	V	0.53 ±0.84	0.53 ±0.70			
1.12	P	0.68 ±0.75	0.42 ±0.77	-0.47 (-0.97; 0.03)	0.078	-0.29
	V	0.74 ±0.65	0.95 ±0.97			
1.13	P	0.42 ±0.84	0.53 ±1.02	0.11 (-0.30; 0.51)	0.728	0.06
	V	0.68 ±0.82	0.68 ±0.82			

Data are presented as mean ± standard deviation (endpoint scores at randomisation and termination) or mean (95% CI) (change of endpoint scores). As only 2 and 7 patients scored on MDS-UPDRS 1.2 and 1.6, respectively, no statistical analysis on these items was performed. * Effect size calculated with $r_{contrast}$, values of 0.1, 0.3 and 0.5 considered as 'small', 'medium' and 'large' effect sizes. For all p-values, significance level was set at p≤0.05. Abbreviations: MDS-UPDRS, Movement Disorder Society- Unified Parkinson´s Disease Rating Scale; R, Randomisation; TV, Termination Visit; CI, confidence interval; P, Placebo; V, Verum; NA, not applicable.
MDS-UPDRS items: 1.1: Cognitive impairment, 1.2: Hallucinations and psychosis, 1.3: Depressed Mood, 1.4: Anxious Mood, 1.5: Apathy, 1.6: Features of dopamine dysregulation syndrome, 1.7: Nighttime sleep problems, 1.8: Daytime sleepiness, 1.9: Pain and other sensations, 1.10: Urinary problems, 1.11: Constipation problems, 1.12: Lightheadedness on standing, 1.13: Fatigue.

Table 7.1: Change in NMSS Items and Subdomains during double-blind treatment, within-group comparison

NMSS		Randomisation	Termination Visit	Mean change (95% CI) from R to TV	p-value *	Effect size **
D 1	P	1.89 ±2.26	1.58 ±2.69	0.32 (-1.61; 0.98)	1.000	-0.11
	V	1.63 ±2.17	2.63 ±3.15	1.00 (-0.15; 2.15)	0.182	0.42
D 2	P	6.32 ±6.66	14.32 ±11.74	8.00 (2.88; 13.12)	0.002	0.75
	V	10.53 ±8.29	11.00 ±8.91	0.47 (-2.39; 3.34)	1.000	0.08
D 3	P	6.53 ±7.68	6.16 ±7.34	-0.37 (-2.30; 1.56)	1.000	-0.09
	V	8.00 ±9.98	8.89 ±11.76	0.90 (-1.12; 2.91)	1.000	0.21
D 4	P	0.05 ±0.23	0.05 ±0.23	NA	1.000	NA
	V	1.79 ±4.22	1.63 ±4.23	-0.16 (-0.49; 0.17)	0.634	-0.23
D 5	P	3.37 ±4.76	3.58 ±5.15	0.21 (-0.48; 0.90)	1.000	0.15
	V	3.63 ±4.72	4.26 ±4.79	0.63 (-0.98; 2.24)	0.688	0.19
D 6	P	2.89 ±4.11	3.42 ±4.53	0.53 (-0.46; 1.51)	0.516	0.26
	V	2.89 ±3.00	3.26 ±3.59	0.37 (-0.41; 1.14)	0.640	0.23
D 7	P	5.58 ±6.85	6.32 ±8.09	0.74 (-1.11; 2.58)	0.648	0.19

	V	7.16 ±7.46	7.05 ±6.57	-0.11 (-1.21; 1.00)	1.000	-0.05
D 8	P	0.21 ±0.63	0.84 ±2.77	0.63 (-0.70; 1.96)	0.634	0.23
	V	0.21 ±0.92	0.00 ±0.00	-0.21 (-0.65; 0.23)	0.634	-0.23
D 9	P	8.32 ±5.76	9.89 ±6.94	1.58 (-0.99; 4.15)	0.654	0.30
	V	8.58 ±6.12	9.74 ±5.86	1.16 (-1.25; 3.56)	0.658	0.23

Data of continuous variables are presented as mean ± standard deviation (endpoint scores at randomisation and termination) or mean (95% CI) (change of endpoint scores). *p-value corrected for multiple testing (multiplied by 2). For all p-values, significance level was set at p≤0.05. **Effect size according to Cohen´s d. Abbreviations: NMSS, Non-Motor Symptoms Scale; D, (Sub-)Domain; R, Randomisation; TV, Termination Visit; CI, confidence interval; P, Placebo; V, Verum; NA, not applicable.
Domain 1: Cardiovascular: Item 1: Light-headedness, Item 2: Fainting. Domain 2: Sleep/Fatigue: Item 3: Daytime sleepiness, Item 4: Fatigue, Item 5: Difficulty falling asleep, Item 6: Restless legs. Domain 3: Mood/Apathy: Item 7: Lost interest in surroundings, Item 8: Lack motivation, Item 9: Feel nervous, Item 10: Seem sad, Item 11: Flat mood, Item 12: Difficulty experiencing pleasure. Domain 4: Perceptual problems/Hallucinations: Item 13: Hallucinations, Item 14: Delusions, Item 15: Double vision. Domain 5: Attention/Memory: Item 16: Concentration, Item 17: Forget things or events, Item 18: Forget to do things. Domain 6: Gastrointestinal: Item 19: Saliva, Item 20: Swallowing, Item 21: Constipation. Domain 7: Urinary: Item 22: Urgency, Item 23: Frequency, Item 24: Nocturia. Domain 8: Sexual dysfunction: Item 25: Interest in sex, Item 26: Problems having sex. Domain 9: Miscellaneous: Item 27: Pain, Item 28: Taste or smell, Item 29: Weight change, Item 30: Excessive sweating.

Table 7.2: Change in NMSS Items and Subdomains during double-blind treatment, between-group comparison

NMSS		Randomisation	Termination Visit	Mean difference (95% CI)	p-value	Effect size *
D 1	P	1.89 ±2.26	1.58 ±2.69	-1.32 (-2.99; 0.36)	0.137	-0.51
	V	1.63 ±2.17	2.63 ±3.15			
D 2	P	6.32 ±6.66	14.32 ±11.74	7.53 (1.86; 13.19)	0.023	0.81
	V	10.53 ±8.29	11.00 ±8.91			
D 3	P	6.53 ±7.68	6.16 ±7.34	-1.26 (-3.96; 1.43)	0.836	-0.31
	V	8.00 ±9.98	8.89 ±11.76			
D 4	P	0.05 ±0.23	0.05 ±0.23	0.16 (-0.17; 0.49)	0.317	0.32
	V	1.79 ±4.22	1.63 ±4.23			
D 5	P	3.37 ±4.76	3.58 ±5.15	-0.42 (-2.11; 1.27)	0.447	-0.17
	V	3.63 ±4.72	4.26 ±4.79			
D 6	P	2.89 ±4.11	3.42 ±4.53	0.16 (-1.05; 1.37)	0.646	0.09
	V	2.89 ±3.00	3.26 ±3.59			
D 7	P	5.58 ±6.85	6.32 ±8.09	0.84 (-1.23; 2.92)	0.330	0.27
	V	7.16 ±7.46	7.05 ±6.57			
D 8	P	0.21 ±0.63	0.84 ±2.77	0.84 (-0.51; 2.19)	0.163	0.41
	V	0.21 ±0.92	0.00 ±0.00			
D 9	P	8.32 ±5.76	9.89 ±6.94	0.42 (-2.98; 3.82)	0.743	0.08
	V	8.58 ±6.12	9.74 ±5.86			

Data of continuous variables are presented as mean ± standard deviation (endpoint scores at randomisation and termination) or mean (95% CI) (change of endpoint scores). *Effect size according to Cohen´s d. For all p-values, significance level was set at p≤0.05. Abbreviations: NMSS, Non-Motor Symptoms Scale; D, (Sub-)Domain; R, Randomisation; TV, Termination Visit; CI, confidence interval; P, Placebo; V, Verum; NA, not applicable.
Domain 1: Cardiovascular: Item 1: Light-headedness, Item 2: Fainting. Domain 2: Sleep/Fatigue: Item 3: Daytime sleepiness, Item 4: Fatigue, Item 5: Difficulty falling asleep, Item 6: Restless legs. Domain 3: Mood/Apathy: Item 7: Lost interest in surroundings, Item 8: Lack motivation, Item 9: Feel nervous, Item 10: Seem sad, Item 11: Flat mood, Item 12: Difficulty experiencing pleasure. Domain 4: Perceptual problems/Hallucinations: Item 13: Hallucinations, Item 14: Delusions, Item 15: Double vision. Domain 5: Attention/Memory: Item 16: Concentration, Item 17: Forget things or events, Item 18: Forget to do things. Domain 6: Gastrointestinal: Item 19: Saliva, Item 20: Swallowing, Item 21: Constipation. Domain 7: Urinary: Item 22: Urgency, Item 23: Frequency, Item 24: Nocturia. Domain 8: Sexual dysfunction: Item 25: Interest in sex, Item 26: Problems having sex. Domain 9: Miscellaneous: Item 27: Pain, Item 28: Taste or smell, Item 29: Weight change, Item 30: Excessive sweating.

Statistical/analytical issues

See text above and table legends

Because an interpolation of data was not planned or performed in case of a drop-out, the primary analysis is a per-protocol analysis. Missing data was kept as such. Analytical methods were not

adjusted. No interim analyses were performed. For adjustments of multiple comparisons: see table legends. No changes in the analyses were made after blind-breaking.

Adjustments for Covariates

As a sensitivity analysis, we fitted a repeated measures mixed model with MDS-UPDRS Part I sum score as dependent variable and a factorial interaction between group assignment and time as independent variable. We applied an unstructured within-subject covariance matrix assuming that each timepoint and each pair of time points have their own variance and co-variance, respectively.

Handling of Dropouts or Missing Data

See above for number of drop-outs and reason for it as well as statistical considerations (no interpolation). No patient dropped-out during the double-blind phase of the trial, which is the period the primary endpoint/ efficacy criterion refers to.

Interim Analyses and Data Monitoring

See above

Multicentre Studies

Not applicable

Multiple Comparisons/Multiplicity

See above and table legends

Use of an "Efficacy Subset" of Patients

No patients with available data from analyses was dropped because of poor compliance, missed visits, ineligibility, or any other reason. The study participants represent the standard patient population.

Active-Control Studies Intended to Show Equivalence

Not applicable

Examination of Subgroups

See above (separate summaries for the two study groups)

Due to the small sample size and exploratory character of the study, further subset analyses (e.g. sex-specific efficacy and safety analyses or analyses of patients with specific NMS at screening) were not feasable.

Drug dose, drug concentration, and relationships to response

Table 85: Dose regimen of randomised patients during double-blind treatment phase

Patient Identifier at screening	Assigned treatment group	Dose regimen at randomisation (capsules)	Nabilone daily dose (in mg)
002	Verum	2-0-2	1.00
003	Placebo	1-0-1	Not applicable
004	Verum	1-0-1	0.50
005	Placebo	1-0-1	Not applicable
006	Placebo	2-0-3	Not applicable
008	Verum	2-0-2	1.00
009	Placebo	1-0-1	Not applicable
010	Verum	1-0-1	0.50
012	Placebo	1-0-2	Not applicable
013	Verum	1-0-2	0.75
015	Verum	2-0-3	1.25
016	Placebo	1-0-2	Not applicable
017	Placebo	0-0-1	Not applicable
018	Placebo	2-0-3	Not applicable
019	Verum	1-0-1	0.50
020	Placebo	3-0-3	Not applicable
021	Verum	3-0-3	1.50
022	Verum	1-0-1	0.50
026	Placebo	2-0-3	Not applicable
027	Verum	1-0-2	0.75

028	Placebo	2-0-2	Not applicable
029	Placebo	1-0-1	Not applicable
030	Verum	0-0-1	0.25
031	Verum	2-0-3	1.25
032	Placebo	3-0-3	Not applicable
034	Verum	1-0-1	0.50
036	Placebo	2-0-2	Not applicable
038	Placebo	0-0-1	Not applicable
039	Verum	2-0-2	1.00
040	Verum	2-0-2	1.00
041	Verum	2-0-3	1.25
042	Placebo	1-0-2	Not applicable
043	Placebo	1-0-2	Not applicable
044	Verum	3-0-4	1.75
045	Verum	1-0-2	0.75
046	Placebo	0-0-1	Not applicable
047	Placebo	1-0-2	Not applicable
048	Verum	2-0-3	1.25

Drug-drug and drug-disease interactions

Not applicable. No relevant safety concern due to concomitant treatment or illness was noted during the trial.

Efficacy conclusions

In this randomised placebo-controlled, double-blind, parallel-group, EERW trial, we examined the efficacy and safety of the synthetic cannabinoid nabilone in PD patients suffering from troublesome NMS. To our knowledge, this is the first study evaluating the effect of cannabinoids on NMS in PD in a controlled fashion. The primary endpoint of the study, assessing differences in change of NMS between the two treatment arms using Part I of the MDS-UPDRS, was met. NMS scores of the MDS-UPDRS-I deteriorated significantly less in the nabilone group compared to those switched to placebo with a medium effect size, most likely due to a positive effect of nabilone on anxious mood and night-time sleep problems. Positive treatment effects of nabilone were also reflected in patient´s self-rating (CGI-I). In line with this, there was also a deterioration of the NMSS with a medium effect to the disadvantage of the placebo compared to the nabilone arm, although the between-group difference was not significant. Differences in the construct of the MDS-UPDRS-I and the NMSS (22) may explain that the between-group difference was not significant for the NMSS although it was for the MDS-UPDRS-I. Nevertheless, positive treatment effects of nabilone were reflected in medium effect sizes as assessed by both scales, most probably because a strong convergent validity between the MDS-UPDRS-I and NMSS has been reported (22).

Noteworthy, most PD patients responded to a dose up to 1 mg of nabilone per day, indicating a benefit from even a small dose of cannabinoids. Observational studies assessing the use of non-prescribed cannabis in PD patients reported lower levels of disability and positive effects on mood, fatigue, sleep, and pain (23-26). In line with this, we observed beneficial effects of nabilone on anxious mood and night-time sleep problems in the double-blind phase of the trial.

11. Safety Evaluation

Extent of exposure

Duration: (mean ±standard deviation)
Mean duration of titration phase of all drop-outs and non-responder was 36.44 (±17.81) years. Mean duration of the open-label titration phase for all patients that have been randomised was 39.90 (±12.10) days. Mean duration of the double-blind treatment phase was 28.37 (±3.23) years.

Table 9: Demographic and other Baseline Characteristics of Drop-outs and Non-responder

Female (n,%)				5 (55.6%)
	Minimum	**Maximum**	**Mean**	**Standard deviation**
Age at exam (years)	50.17	75.33	66.69	9.24
Disease duration (years)	1.00	20.00	8.89	5.01
Education (years)	11.00	15.00	12.33	1.32
Charlson Comorbidity Index	0	2	0.56	0.73
H&Y Scale	1	2	1.89 (1.63, 2.15)	0.33
MoCA	20.00	31.00	27.56	3.17
MDS-UPDRS Part I	7.00	17.00	10.11	3.18
MDS-UPDRS Part II	3.00	13.00	7.3	3.00
MDS-UPDRS Part II	12.00	44.00	25.67	9.96
MDS-UPDRS Part IV	0.00	6.00	1.22	2.11
MDS-UPDRS Total Sum Score	31.00	96.00	50.78	19.30
MDS-UPDRS Motor Sum Score	19.00	52.00	33.00	11.55
PDQ-39 SI	0.00	58.33	22.22	20.83

Data is given for the patients that dropped-out or were non-responders. Data are presented as minimum, maximum, mean, and standard deviation for continuous variables and number (percent) for categorical variables. For the H&Y scale, the 95% CI is also given. Data represent values at the screening visit.
Abbreviations: H&Y, Hoehn and Yahr; MDS-UPDRS, Movement Disorders Society- Unified Parkinson´s Disease Rating Scale; MoCA, Montreal Cognitive Assessment; PDQ-39, Parkinson´s Disease Questionnaire-39; SI, Summary Index. Higher Score values indicate worse outcome in all scales and questionnaires but in the MoCA.

Dose: Cumulative Subject Exposure
The NMS-Nab study has an OL and double-blind phase. According to the World Health Organisation, there is no defined daily dose for nabilone. In the OL phase of the study, the cumulative subject exposure was 5589 units, where one unit represents 0,25 mg of nabilone (Table 10, A).
In the double-blind phase of the study, subjects are randomized in a 1:1 ratio at the randomisation visit. For daily doses of individual patients, dose ranges, and demographic data by treatment group: see above (Table 3 and Table 8). Out of the 38 subjects randomised, 63% of subjects are male, and 58% of subjects are age 65 and older. 100% of subjects are Caucasian. The cumulative subject exposure for the nabilone group in the double-blind phase and the follow-up period of the trial was 1841 units, where one unit represents 0,25 mg of nabilone (Table 10, B).

Table 10: Cumulative Subject Exposure

A) OL phase

Subject # (ID at screening)	**Units***
001**	0
002	97
003	72
004	50
005	53
006	119

Subject # (ID at screening)	Units*
007	93
008	108****
009	41
010	65
011	11
012	109
013	63
014	48
015	199
016	161
017	46
018	215
019	69
020	220
021	138 (140 in drug account.)***
022	63
023	1
024	230
025	140****
026	199
027	98
028	155
029	99
030	30
031	312
032	200 (203 in drug account.)***
033	113
034	61
035	91
036	154
037	84
038	149
039	212****
040	122
041	221
042	108
043	114
044	210
045	101
046	45
047	96
048	204
Total	**5589**

*1 unit=1 capsule=0,25 mg nabilone
**subject was screen failure
***patient lost 2 capsules due to difficulties with their small size
****maximum score, patient did not return all bottles for final drug accountability

B) Double-blind phase and follow-up period

(Nabilone group, n=19)

Randomisation ID (Nabilone group)	Units*
IBK-001	99
IBK-003	58
IBK-006	70*
IBK-008	58
IBK-010	82
IBK-011	145
IBK-014	57
IBK-015	161
IBK-017	42
IBK-019	86
IBK-022	33
IBK-024	193
IBK-025	53
IBK-028	126
IBK-030	168
IBK-031	124
IBK-034	112**
IBK-035	86
IBK-038	88
Total	**1841**

*1 unit=1 capsule=0,25 mg nabilone
**Patient did not return all bottles for final drug accountability.

Drug concentration
Not applicable

Adverse events

Brief summary of adverse events
During the OL phase of the trial, one patient declined further participation (2.08% of all 48 patients) and three (6.25% of all 48 patients) discontinued due to AEs (gonarthrosis leading to knee-replacement surgery, migraine after intake of the first nabilone dose, and confusion). The latter two AEs were of moderate severity, but only confusion was rated possibly related to the intake of the IMP by the investigators.
Common AEs (>1 patient) are given in Tables 11 and 12 (see supplemental for a full list of AEs). During the OL phase, the most common treatment-related adverse events were transient mild fatigue, dizziness, dry mouth, and sleepiness (Table 11). During the randomised phase of the trial, the overall incidences of all-cause AEs and treatment-related AEs were similar between groups (Table 12). Table 13 displays a full list of the AEs. MDS-UPDRS items considered as safety parameters (1.2 (hallucinations), 1.8 (day-time sleepiness) and 1.12 (OH)) did not change during the randomised phase of the trial (Table 4). There was, however, a medium effect size of 0.51 for the NMSS Domain 1 (Cardiovascular: Light-headedness and Fainting) to the disadvantage of the nabilone arm, although the difference was not significant. Table 14 summarizes blood pressure readings in both phases of the trial as well as differences between the two groups. There were no significant within- or between-group differences in systolic and diastolic blood pressure readings in supine positions and in their postural changes after 3 minutes in standing position, except for a difference in the mean change of supine diastolic blood pressure between the nabilone and the placebo group in the double-blind treatment phase (Table 14). No severe AE, SAE, or SUSAR were reported in any patient in this trial. We did not record any clinically relevant changes in laboratory measures or ECG

recordings. Suicidality according to C-SSRS did not occur in any patient during the study and follow-up period.

Table 11: Safety Analysis of the OL phase

Most common AEs (n>1) during the OL phase			
AE	**total (n)**	**Severity of AE (n)**	
		mild [a]	**moderate** [a]
Fatigue	17	15 (4/6/5/0)	2 (1/0/1/0)
Dizziness	9	8 (5/1/1/1)	1 (0/1/0/0)
Daytime sleepiness	5	4 (0/3/1/0)	1 (0/1/0/0)
Upper respiratory tract infection	5	4 (0/0/0/4)	1 (0/0/0/1)
Dry mouth	4	4 (0/3/1/0)	0
Confusion and disorientation	3	1 (0/1/0/0) [b]	2 (0/2/0/0) [c]
Gastro-esophageal reflux	2	2 (0/0/0/2)	0
Fall	2	2 (0/0/0/2)	0
Headache	2	1 (0/0/0/1)	1 (0/0/0/1) [d]

[a] (definitely related to treatment/ probably related/ possibly related/ not related)
[b] Resolved after down-titration from nabilone 0.25 mg b.i.d. to 0.25 mg q.d.
[c] Confusion leading to study discontinuation of one patient (resolved after discontinuation), the other patient was a non-responder suffering from confusion (resolved after discontinuation).
[d] Migraine leading to study discontinuation of one patient.
No severe AE or SAEs were reported during both phases of the trial.
Abbreviations: n, number; AE, adverse event; SAE, serious adverse event; q.d., “quaque die" (once a day); b.i.d. "bis in die" (2 times a day).

Table 12: Safety Analysis of the double-blind phase

Most common AEs (n>1) during the double-blind phase					
AE	**total (n)**	**Nabilone (n)**		**Placebo (n)**	
		mild	**moderate**	**mild**	**moderate**
Insomnia	4	2	0	0	2
Upper respiratory tract infection	3	0	0	3	0
Pain (including worsening)	3	0	1	1	1
Fall (including recurrent falls)	2	1	0	1	0
Syncope	2	0	0	0	2

No severe AE or SAEs were reported in any group of patients. AEs during the double-blind phase of the trial listed in the table were rated as unrelated to treatment. Abbreviations: n, number; AE, adverse event; SAE, serious adverse event

Display of adverse events
See above and Table 13

Table 13: Safety Analyses: Full list of AEs

OL phase (Patients: n=47)*
AEs (n=65)
Mild
Fatigue (n=15): definitely related (n=4), probably related (n=6), possibly related (n=5)
Dizziness (n=8): definitely related (n=5), probably related, possibly related, not related (each n=1)
Dry mouth (n=4): probably related (n=3), possibly related (n=1)
Daytime Sleepiness (n=4): probably related (n=3), possibly related (n=1)
Upper respiratory tract infection (n=4): not related
Gastro-oesophageal reflux (n=2): not related
Drowsiness (n=1): definitely related

Disorientation (n=1): probably related
Delusion (n=1): possibly related
Headache (n=1): possibly related
Restlessness (n=1): possibly related
Chest pain (n=1): not related
Skin reaction due to spider bites (n=1): not related
Iron deficiency (n=1): not related
Gastroenteritis (n=1): not related
Nausea and vomiting (n=1): not related
Meralgia paresthetica (n=1): not related
Fall (n=2): not related
Olecranon bursitis (n=1): not related

Moderate
Fatigue (n=2): definitely related (n=1), possibly related (n=1)
Dizziness (n=1): probably related
Daytime sleepiness (n=1): probably related
Confusion (n=1): possibly related, resulted in discontinuation
Disorientation (n=1): possibly related
One episode of symptomatic orthostatic hypotension (n=1): possibly related
Migraine (n=1): not related, resulted in discontinuation
Tooth ache, resulting in teeth extraction (n=1): not related
Erythema migrans (n=1): not related
Upper respiratory tract infection (bacterial, n=1): not related
Conjunctivitis (n=1): not related
Fracture of lumbar vertebrae (n=1): not related

Gonarthrosis, resulting in knee replacement surgery (n=1): not related, resulted in discontinuation

Double-blind phase: Nabilone group (Patients: n=19)*

AEs (n=8)

Mild
Sleeping disturbances (insomnia, n=2): not related
Fall (n=1): not related
Muscle cramps (n=1): not related
Essential hypertension (n=1): not related

Moderate
Panic attack (n=1): possibly related
Pain (right hip joint and lumbar spine, n=1): not related
Inflammation of the jaw bone (below tooth, n=1): not related

Double-blind phase: Placebo group (Patients: n=19)*

AEs (n=15)

Mild
Upper respiratory tract infection (n=3): not related
Livedo reticularis (n=1): not related
Recurrent falls (n=1): not related
Depressive episode (due to worsening of pain, n=1): not related
Nausea and vomiting (n=1): not related
Worsening of respiratory function (n=1): not related
Pain (n=1): not related

Moderate
Syncope (n=2): not related
Sleeping disturbances (insomnia, n=1): not related
Sleeping disturbances (falling asleep and insomnia, n=1): not related
Worsening of pain (implant, n=1): not related
Helicobacter pylori associated gastritis (n=1): not related

Safety Follow-Up (Patients: n=38)*
new AEs (n=7)
Mild Gastroenteritis (n=1): not related (nabilone group) Pain (torn muscle, n=1): not related (nabilone group) Constipation (n=1): not related (nabilone group) Fall (n=2): not related (placebo group) Dry skin (head, n=1): not related (placebo group) **Moderate** Panic attack (n=1): possibly related (nabilone group)

*No severe AE or SAEs were reported in any group of patients.
Abbreviations: OL, open-label; n, number; AE, adverse event; SAE, serious adverse event.

Table 14: Change in blood pressure readings during open-label administration of nabilone and during double-blind treatment

Visit		BP readings (mmHg)			
		SBP supine [1]	DBP supine [1]	SBP change [2]	DBP change [2]
Open-label phase					
Baseline		135.66 ±15.89	83.61 ±10.90	-1.45 ±10.63	3.24 ±7.93
Randomization		134.92 ±17.34	83.08 ±10.55	-1.29 ±12.89	3.47 ±5.88
Mean change [3]		-0.74 (-5.63; 4.15)	-0.53 (-3.53; 2.47)	0.16 (-4.33; 4.65)	0.24 (-2.39; 2.87)
p-value [4]		0.812	0.629	0.910	0.896
Double-blind phase					
Randomization	P	132.21 ±18.41	80.89 ±10.37	-4.05 ±11.53	3.16 ±6.07
	V	137.63 ±16.24	85.26 ±10.55	1.47 ±13.88	3.79 ±5.84
Termination	P	127.53 ±15.19	83.16 ±8.95	-2.95 ±17.96	-0.79 ±7.90
	V	137.16 ±14.02	81.58 ±12.32	-1.84 ±10.68	4.11 ±5.95
Mean change [5]	P	-4.68 (-13.40; 4.03)	2.26 (-1.58; 3.11)	1.11 (-5.20; 7.41)	-3.95 (-8.26; 0.37)
	V	-0.47 (-6.18; 5.24)	-3.68 (-7.54; 0-18)	-3.32 (-10.63; 4.00)	0.32 (-3.34; 3.97)
p-value [4.a]	P	0.214	0.686	1.000	0.086
	V	1.000	0.139	0.774	1.000
p-value [6]		0.121	0.047	0.286	0.077

Data are presented as mean ±standard deviation or 95% confidence interval. Blood pressure was measured in supine position (after having been in supine position for at least 10 minutes; [1] "supine") and after 3 minutes in standing position after postural change ([2] "change"). [3] from BL to R, with (95% CI). [4] Within-group comparison. [5] from R to TV, with (95% CI). [6] Between-group comparison. [a] p-value corrected for multiple testing (multiplied by 2). Abbreviations: mmHg, millimeter of mercury; SBP, systolic blood pressure; DBP, diastolic blood pressure; BL, Baseline; R, Randomization; TV, Termination Visit; CI, confidence interval; P, placebo; V, verum.

An excel file including AEs separated by patients with original terms used by the investigators is available in the attachment.

Analysis of adverse events
See above
Listing of adverse events by patient
See attached Excel File, see Tables for demographics of all patients. Demographic and baseline values of individual patients at the screening visit are attached as PDF-File. Separate data of AEs of each patient are stored as source documents (direct entry electronically and printed) at the study centre.
Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No participant died during the study. There were no SAE or other significant AE reported by any patient during the conduct of this trial.

Safety Conclusions

Symptoms of OH worsened moderately on nabilone as assessed with the NMSS, which is not surprising since OH is a well-known side effect of treatment with cannabinoids. Dizziness was indeed reported commonly as an AE by patients in this study. However, the assessment of active orthostatism was mostly unremarkable. PD patients with symptomatic orthostatic hypotension might therefore possibly not be good candidates for the use of nabilone.
Overall, nabilone treatment was well tolerated. During the OL phase, the most common treatment-related AES were transient mild fatigue, dizziness, dry mouth, and somnolence, which is in line with information from the SmPC and other controlled trials using nabilone (27). In the randomised phase of the trial, no difference in AEs or tolerability issues was found between the two study arms. Most AEs were of mild severity and unrelated to the intake of the study drug. Two of the oldest PD patients reported confusion and delusions during the titration phase of the trial. The first patient (age 71.7 years) was maintained in the study after down-titration to a single dose of nabilone 0.25 mg in the evening resolved the AE. The other patient (age 74.5 years) was discontinued from further study participation and confusion resolved after three weeks. Some observational studies reported of confusion and hallucination after smoking cannabinoids in PD patients (23). Although extensive use of cannabis was reported to impair verbal and working memory as well as cognitive processing, no worsening of cognitive function was observed subjectively or objectively (as assessed with MoCA) in our PD patients.

12. Discussion and overall conclusions

The ECS plays a significant part in motor control and the regulation of various non-motor functions including mood, attention and concentration, eating habits, sleep, and pain (4, 5), although the exact details of the neural circuitry through which the ECS modulates these functions remain uncertain. In animal models, a high amount of CB1 receptors is found in presynaptic nerve terminals of GABA-ergic synapses and in cortical and limbic serotoninergic, noradrenergic, dopaminergic neurons as well as neurons with μ-opioid receptors. Moreover, structures of the ECS co-localise with nociceptive pathways in the spinal cord. Consequently, cannabinoids are believed to modulate monoaminergic, GABA-ergic, glutamatergic, and opioid signalling (28-30). Data from animal studies and human PET studies reveal a high density of CB receptors in the basal ganglia where the ECS is believed to function as a regulator of dopamine release and uptake (31-36). Following the loss of dopamine, the ECS is overactive in the striatum of PD patients with upregulation of its neurotransmitter and receptor levels possibly reflecting a compensational mechanism (5, 33, 35, 37). With respect to these findings, a positive effect of nabilone on NMS in PD is not surprising. Only a few studies have assessed the ECS and sleep and showed that exogenous cannabinoids promote sleep, REM sleep, and the stability of non-REM sleep (38). In PD patients, an influence of cholinergic neurons in brain areas involved in the regulation of sleep and sleep-wake cycle has been proposed as possible underlying mechanism (39). Besides symptomatic treatment, preclinical research revealing neuroprotective properties of cannabinoids gains interest in clinicians dealing with patients with movement disorders (6).

Overall, the study has several strengths and limitations. Although presence of significant anxiety or pain were chosen as inclusion criteria, none of our consecutively screened patients had to be excluded because of these criteria. Therefore, we conclude that our study population is representative for PD patients of a tertiary care centre. The study´s withdrawal design is inevitably

associated with a negative expectation related to receiving placebo. Indeed, the non-significant deterioration of single NMS with small effect sizes as measured with the MDS-UPDRS Part I and the NMSS in the nabilone-group might be impacted by negative expectations related to receiving placebo (i.e. “lessebo effect” (12)). Selection of open-label responders can raise concerns about generalizability of the results and thus affect external validity. In this study, most patients enrolled in the open-label phase were responders, therefore selection bias can be considered small. Inclusion of responders only can lead to overestimation of the effect of a novel treatment. However, restriction to responders reflects clinical practice by limiting long-term treatment to patients who might benefit from it, in line with a personalized medicine approach. The enrichment design has been suggested to be sensitive and efficient for proof-of-concept studies of new treatment strategies in humans (13). With our trial design, total exposure to placebo is reduced compared to a standard randomized controlled trial. The open-label phase grants the assessment of a dose-response effect and provides a range of doses to be considered when planning a confirmatory study. Heterogeneity of response during the open-label phase of the trial reflects individual treatment response as seen in daily clinical routine.

To the best of our knowledge, this is the first study to evaluate the efficacy and safety of cannabinoids for the treatment of NMS in PD, making this a unique pilot trial. Our findings show an improvement of overall NMS burden with nabilone, especially reflected by amelioration of anxiety and sleeping problems. The treatment was well tolerated. This study adds to the limited evidence of safety and efficacy of cannabinoid-based treatment in PD patients with troublesome NMS. Further and larger controlled trials assessing the effects of cannabinoids on PD symptoms are clearly needed.

PRINCIPAL OR COORDINATING INVESTIGATOR(S) SIGNATURE(S)

OR SPONSOR'S RESPONSIBLE MEDICAL OFFICER

STUDY TITLE: Nabilone for non-motor symptoms in Parkinson's disease: A Randomized Placebo-controlled, double-blind, parallel-group, enriched enrolment randomized withdrawal Study

STUDY AUTHOR(S): Klaus Seppi (PI), Marina Peball

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study

INVESTIGATOR OR SPONSOR'S RESPONSIBLE MEDICAL OFFICER: Klaus Seppi (PI) SIGNATURE(S): SEPPI

AFFILIATION: Department of Neurology, Medical University of Innsbruck, Austria

DATE: IBK, 17. Jul 2020

13. Legend of Figures

14. Legend of Tables

15. Tables and Figures referred to but not included in the text

All included in the text or Appendix

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17. Appendix

Study Information

Protocol and protocol amendments

The latest protocol version is attached to this final report (PDF-File). Sample case report form are not attached separately as they were submitted to the IEC and regulatory authorities before.

Ethics Revision Chronology	26th June 2017: Original, Protocol Version 1.2 26th January, 2018: Amendment 1: Primary reason for the amendment: Eye-tracking was added as an exploratory endpoint. A change in the list of prohibited medication was made. Protocol Version 1.3 13th July, 2018: Amendment 2: Primary reason for the amendment: The protocol was adapted to reflect changes in EU data protection regulations. Protocol Version 1.4
Suspensions:	There were no interruptions or suspensions of the study.
Early Termination:	The study was not terminated early.

Full list of study team members and involved facilities

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Statistics	Qualified members of the study team with support from the **Department of Medical Statistics, Informatics and Health Economics, Innsbruck Medical University** Head: ao. Univ.-Prof. Mag. Dr. Hanno Ulmer Schöpfstraße 41/1 6020 Innsbruck Austria **Contactperson**: ao. Univ.-Prof. Mag. Dr. Hanno Ulmer (Sample size calculation) hanno.ulmer@i-med.ac.at Assoz.-Prof. Priv.-Doz. Mag. Dr. rer.nat. Georg Göbel (repeated measures mixed model) georg.goebel@i-med.ac.at

Publications based on the study

In Submission

Peball M, Werkmann M, Ellmerer P, Stolz R, Valent D, Knaus HG, et al. Nabilone for non-motor symptoms of Parkinson's disease: a randomized placebo-controlled, double-blind, parallel-group, enriched enrolment randomized withdrawal study (The NMS-Nab Study). J Neural Transm (Vienna). 2019 Aug;126(8):1061-72. PubMed PMID: 31129719. PMCID: PMC6647387.

Documents submitted with this report

Clinical study protocol, version 1.4, dated 06th June 2018 (PDF-File)

Investigational medicinal product dossier (IMPD) of nabilone and the placebo capsules, as well as SmPC of nabilone 1 mg (PDF-Files)

Table exhibiting the randomisation codes, patient identifier, and treatment assigned (PDF-File)

Protocol Deviation Log (PDF-File, copy of the original file in the ISF)

Report of Data Safety Board Meeting, 22th October 2018 (PDF-File)

Demographic and baseline values of individual patients at the screening visit (PDF-File)

File including all AEs separated by patients with original terms used by the investigators (Excel Sheet)