Title page

Nabilone for non-motor symptoms in Parkinson's disease: An open-label study to evaluate long-term safety and efficacy

(NMS-Nab2 Study)

Name of test drug/investigational product: Nabilone

Indication: Parkinson´s disease

Name of the sponsor: Medical University of Innsbruck

Development phase of study: III

Protocol identification (code or number): 1.3

Study initiation date: 6th August 2018

Study completion date (last patient last visit): 31st January 2020

Name and affiliation of principal or coordinating investigator: Klaus Seppi

Author: Marina Peball

Contact: Klaus Seppi (Klaus.seppi@tirol-kliniken.at)

Marina Peball (Marina.peball@i-med.ac.at)

Medical University of Innsbruck

Telephone: 0043-512-504-81553

Fax: 0043-512-504-25819

Medical University of Innsbruck

Department of Neurology

Medical University of Innsbruck

Anichstraße 35

6020 Innsbruck

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

Date of the report: 26th January 2021

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:
O.Univ.-Prof. Dr. Werner Poewe
Department of Neurology
Anichstraße 35
6020 Innsbruck
Austria
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: An open-label study to evaluate long-term safety and efficacy
(NMS-Nab2 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: None</td></tr>
<tr><td>Studied period (years)
first patient in: 10th August 2018
last patient out: 31st January 2020 (LPLV)</td><td>Phase: III</td></tr>
<tr><td colspan="2">Objectives
<u>Primary Objective</u>
The primary objective was the long-term safety and tolerability of nabilone based on the following measurements:
1. Tolerability
• Number of subjects (%) who discontinue the study
• Number of subjects (%) who discontinue the study due to AE
2. Safety Measures
• Adverse Events (AE)
• Physical and neurological examination findings
• Vital signs assessment including assessment 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)
• Subjects compliance
• Prior and concomitant medication use
• Hallucination item (1.2) of Movement Disorders Society – Unified Parkinson´s Disease Rating Scale (MDS-UPDRS)
• Orthostatic hypotension (OH) item (1.12) of the MDS-UPDRS
• Day-time sleepiness item (1.8) of the MDS-UPDRS
• Suicidality as assessed with the Columbia-Suicide Severity Rating Scale (C-SSRS)

<u>Secondary Efficacy Objectives</u>
The secondary objectives were the assessment of long-term efficacy of open-label nabilone therapy with regards to non-motor symptoms (NMS) and quality of life (QoL) in patients with Parkinson´s disease (PD). Efficacy endpoints included changes in the following assessments:

• Total and different parts of the MDS-UPDRS
• Different domains of the MDS-UPDRS Part I
• Non Motor Symptoms Scale (NMSS)</td></tr>
</table>

- Hospital anxiety and depression scale (HADS)
- Parkinson´s Disease Questionnaire – 8 (PDQ-8)
- Epworth Sleepiness Scale (ESS)
- Fatigue Severity Scale (FSS)
- King's Parkinson's disease pain scale (KPPS)
- Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale (QUIP-RS)
- Clinical Global Impression – Global Improvement (CGI-I)

The change of the Mini Mental State Exam (MMSE) and the Montreal Cognitive Assessment (MoCA) score values between the Screening Visit of the NMS-Nab Study (before the first intake of nabilone medication) and the termination visit of this study was also assessed as secondary efficacy endpoints.

Exploratory Objective

The exploratory objective of this study was an Eye-tracking evaluation in PD patients taking nabilone. The following measurements were taken during the Eye-tracking evaluation at V 2:

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

Methodology:

Study design and participants

This was a single-centre phase III, open-label extension study for participants of the randomized placebo-controlled, double-blind, parallel-group, enriched enrolment randomized withdrawal trial, the NMS-Nab Study. The goals were to assess long-term safety and efficacy in PD patients taking nabilone. 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

Not applicable

Procedures

Eligible subjects, who have signed the informed consent form at the first visit, were re-tapered with daily orally nabilone, manufactured by AOP Orphan Pharmaceuticals AG (Vienna, Austria), starting with a dose of 0.25 milligrams (mg, one capsule) in the evening after the baseline visit. Nabilone was titrated in 0.25 mg-increments every one to four days after consultation with the study team during regular telephone calls, optimally up to the dose the patient had in the open-label titration phase of the randomized placebo-controlled, double-blind, parallel-group, enriched enrolment randomized withdrawal trial (NMS-Nab study). If necessary, modification of this dose was possible upon the investigator´s decision. The re-tapering was performed up to a maximum dose of 1 mg twice daily (dose increments: 1: 0.25 mg 0-0-1; 2: 0.25 mg 1-0-1; 3: 0.25 mg 1-0-2; 4: 0.25 mg 2-0-2; 5: 0.25 mg 2-0-3; 6: 0.25 mg 3-0-3; 7: 0.25 mg 3-0-4; 8: 0.25 mg 4-0-4). 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 responder 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. The titration phase lasted up to 28 days and responders proceeded into an open-label treatment period of six months.

Visits were performed every three months in the context of the patient´s regularly scheduled visits in the specialized outpatient department. This period ended with a termination visit from which on the investigational medicinal product (IMP) was tapered in all patients in 0.25 mg two-daily decrements. During this period the patients received phone calls every other day. A Safety Telephone Call and a Safety Follow-Up Visit were executed 5 days ± 2 days and 2 weeks + 2 days after the last intake of study drug.

This study comprised of five on-site study visits and regular telephone calls during titration phases (Figure of trial schedule). Safety parameters were monitored throughout the study via telephone calls and at on-site visits. Clinical assessments included the MDS-UPDRS, the NMSS, the HADS, the PDQ-8, the MoCA, the ESS, the FSS, the KPPS, the CGI-I, and the QUIP-RS. Assessment of safety and tolerability was performed during trial conduction via the safety data monitoring board (HGK, KS, MP).

Number of patients (planned and analysed):

Planned: Maximally 48 responders of the randomized placebo-controlled, double-blind, parallel-group, enriched enrolment randomized withdrawal Study

Analysed: 22 patients
Diagnosis and main criteria for inclusion: The diagnosis of PD was based on UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria. To be eligible for participation, male and female PD patients must have completed the double-blind phase of the NMS-Nab trial as responders without a drug-related SAE or drug-related moderate or severe AE. Moreover, patients had to be willing and able to take oral medication and able to comply with the study specific procedures. Patients had to be in good health at screening as determined by medical examination. (see Table 1 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. This study had an open-label dose titration phase followed by an open-label nabilone treatment 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 open-label treatment phase of the trial, patients received their optimal nabilone dose as defined during titration.
Duration of treatment: see above
Reference therapy, dose and mode of administration, batch number: Not applicable.
Reference substance: Not applicable.
Unblinding: Not applicable.
Criteria for evaluation: Efficacy Endpoints *Primary Endpoint:* The primary objective was the long-term safety and tolerability of nabilone between V 1 and the termination visit based on the measures described in "Objectives". *Secondary Efficacy Endpoints:* The change in the other assessments listed above between V 1 and the termination visit were the secondary efficacy criteria. The change of the MMSE and MoCA score values between the Screening Visit of the NMS-Nab Study (before the first intake of nabilone medication) and the termination visit of this study was also assessed as secondary efficacy endpoints. Exploratory Endpoint The change of the reaction time, attention span, and ability to concentrate between the Screening or Termination visit of the randomized placebo-controlled, double-blind, parallel-group, enriched enrolment randomized withdrawal study (before the first intake of nabilone) and V 2 of this study as measured by the Eye-tracking examination were exploratory endpoints.
Statistical Methods: Up to 48 subjects who completed the preceding randomized placebo-controlled, double-blind, parallel-group, enriched enrolment randomized withdrawal study (NMS-Nab Study) and met patient exclusion/inclusion criteria were planned to be enrolled. No power calculation was performed for this open-label extension of the NMS-Nab Study. The NMS-Nab2 Study was as a mono-centric Phase II, open-label trial. The primary efficacy criterion was safety and tolerability between V 1 and the termination visit. 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 clinical scales and questionnaires between V 1 and the termination visit. The safety analyses were performed on all events and tolerability issues, as well as the hallucination item, orthostatic hypotension item, the day-time sleepiness item of Part I of MDS-UPDRS, and C-SSRS occurring through the overall course of the study. This was a descriptive analysis reporting overall number,

frequencies, and percentage of AEs and serious AEs (SAEs) in all patients taking nabilone, patients withdrawn from the study, and patients withdrawn due to an AE. For the study's secondary efficacy objectives, mean changes from V 1 of this study to the termination visit were analysed by Wilcoxon matched-pairs tests. To estimate the treatment effect, we compared mean change from V 1 to month six visit using analysis of covariance, with value at V 1 as covariate and the treatment group as main effect. Moreover, sensitivity to treatment was assessed using effect sizes of the different outcome variables when using nabilone to treat non-motor symptoms in Parkinson´s disease. For the change in cognition, the score values of MMSE and MoCA were compared to the values of these scores at the Screening visit of the randomized placebo-controlled, double-blind, parallel-group, enriched enrolment randomized withdrawal study using the Wilcoxon matched-pairs test. For the Eye-tracking analyses, mean changes from the evaluations of the Screening (and the Termination Visit) of the randomized placebo-controlled, double-blind, parallel-group, enriched enrolment randomized withdrawal study to V 2 of this study were compared using the Wilcoxon matched-pairs test.
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 August 10, 2018 and January 31, 2020 (last patient last visit), 22 patients were screened. There were no screening failures. During open-label titration one patient was a non-responder as defined per protocol (n=1, 4.55%). Twenty-one patients entered the open-label treatment phase. Two patients discontinued this phase, one due to an adverse event and the other one on his own will.
Median daily dose of nabilone was 0.75 mg at the beginning of the open-label treatment phase (range 0.25 – 1.50 mg). The primary endpoint of this study was the assessment of long-term safety of nabilone treatment in PD patients. Overall, nabilone was well tolerated with most AEs being unrelated to the study drug. The most common and related AEs were concentration difficulties in two patients. Efficacy analyses showed a significant difference in patient´s CGI-I ratings, reflected by a moderate effect size. This study adds to the limited evidence of cannabinoid-based treatment in PD patients.

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List of abbreviations (alphabetical order)

AE	Adverse event
CB	Cannabinoid
CI	Confidence interval
CGI-I	Clinical Global Impression of Improvement
C-SSRS	Columbia Suicide Severity Rating scale
ECS	Endocannabinoid system
ESS	Epworth Sleepiness Scale
EU	European Union
ET	Early Termination Visit
FSS	Fatigue Severity Scale
GABA	gamma-Aminobutyric acid
GCP	Good Clinical Practice
HADS-A/-D	Hospital anxiety and depression scale -anxiety/-depression
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
MMSE	Mini Mental State Exam
MoCA	Montreal Cognitive Assessment
MUI	Medical University of Innsbruck
NA	Not applicable
NMS	Non-motor symptoms
NMSS	Non Motor Symptoms Scale
OH	Orthostatic hypotension
OL	open-label
PD	Parkinson´s Diseases
PDQ-8 (SI)	Parkinson´s Disease Questionnaire – 8 (Summary Index)
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
SFU	Safety Follow-Up visit
SUSARs	Suspected unexpected serious adverse reactions
THC	tetrahydrocannabinol
TMF	Trial Master File
V	Visit

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 February 07th, 2018 (reference number: 1214/2017) and the Austrian regulatory authorities approved the study on the 13th of April 2018. One substantial amendment with changes in prohibited concomitant medication, study team members, and to conform to the EU Data Protection Law 2018 have been approved by the EC of the MUI and non-prohibited by the regulatory authorities. Two amendments for changes in study team members were approved by the EC of the MUI. 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 1214/2017 and the national regulatory authorities) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Patient recruitment was started in August 2018 and ended in January 2020. The study was registered on ClinicalTrials.gov.

The results of this study 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-Nab2 Study was performed at one clinical site, the MUI (Austria, urban and rural setting) which was 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 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 monitoring of the study was conducted by a member of the study team that was not involved in patient recruitment, assessment, data curation, or analyses. 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 was conducted by qualified members of the study team of the neurological study centre Innsbruck.
Patients were seen in the outpatient department on-site. 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, usually during the last visit of the preceding NMS-Nab study. 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 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 long-term safety and efficacy of the synthetic cannabinoid nabilone for the treatment of NMS in PD. 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 long-term nabilone treatment will have a favourable safety profile and improve NMS in patients with PD. The primary endpoint of the study combined safety and tolerability measures between V 1 and the termination visit six months thereafter. The outcome of this trial may contribute to a better understanding of the value of cannabinoids for treatment in PD patients.

2. Study objectives

Primary Objective

The primary objective of this study was to assess the long-term safety and tolerability of nabilone as a treatment in PD patients. Assessment was based on the following measurements:

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

2. Safety Measures
- Adverse Events (AE)
- Physical and neurological examination findings
- Vital signs assessment including assessment 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)
- Subjects compliance
- Prior and concomitant medication use
- Hallucination item (1.2) of Movement Disorders Society – Unified Parkinson´s Disease Rating Scale (MDS-UPDRS)
- Orthostatic hypotension (OH) item (1.12) of the MDS-UPDRS
- Day-time sleepiness item (1.8) of the MDS-UPDRS
- Suicidality as assessed with the Columbia-Suicide Severity Rating Scale (C-SSRS)

Key Secondary Efficacy Objectives

The secondary objectives of this study were to evaluate the long-term efficacy of nabilone on PD motor and non-motor symptoms and QoL of with the following scales and questionnaires:

- Total and different parts of the MDS-UPDRS
- Different domains of the MDS-UPDRS Part I

- Non Motor Symptoms Scale (NMSS)
- Hospital anxiety and depression scale (HADS)
- Parkinson´s Disease Questionnaire – 8 (PDQ-8)
- Epworth Sleepiness Scale (ESS)
- Fatigue Severity Scale (FSS)
- King's PD pain scale (KPPS)
- Questionnaire for Impulsive-Compulsive Disorders in PD–Rating Scale (QUIP-RS)
- Clinical Global Impression – Global Improvement (CGI-I)

The change of the Mini Mental State Exam (MMSE) and the Montreal Cognitive Assessment (MoCA) score values between the Screening Visit of the NMS-Nab Study (before the first intake of nabilone medication) and the termination visit of this study was also assessed as secondary efficacy endpoints

Exploratory Objective

The exploratory objective of this study was an Eye-tracking evaluation in PD patients taking nabilone. The following measurements were taken during the Eye-tracking evaluation at V 2:

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

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.1.3, dated 04JUNE2019).

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 III, open-label extension study for participants of the preceding randomized placebo-controlled, double-blind, parallel-group, enriched enrolment randomized withdrawal trial (NMS-Nab Study) to assess long-term safety and efficacy of treatment with nabilone in PD patients.

Randomisation and masking, Unblinding

Not applicable.

Procedures

Eligible subjects, who signed the informed consent form at the first visit, were re-tapered with daily orally nabilone, manufactured by AOP Orphan Pharmaceuticals AG (Vienna, Austria), starting with a dose of 0.25 milligrams (mg, one capsule) in the evening after the baseline visit. Nabilone was titrated in 0.25 mg-increments every one to four days after consultation with the study team during regular telephone calls, optimally up to the dose the patient had in the open-label titration phase of the preceding NMS-Nab study. If necessary, modification of this dose was possible upon the investigator´s decision. The re-tapering was performed up to a maximum dose of 1 mg twice daily (dose increments: 1: 0.25 mg 0-0-1; 2: 0.25 mg 1-0-1; 3: 0.25 mg 1-0-2; 4: 0.25 mg 2-0-2; 5: 0.25 mg 2-0-3; 6: 0.25 mg 3-0-3; 7: 0.25 mg 3-0-4; 8: 0.25 mg 4-0-4). 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 responder 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. The titration phase lasted up to 28 days (V 1) and responders proceeded into an open-label treatment period of six months on a stable nabilone dose. Dose adjustments were only possible after consultation with the study team and if CGI-I deteriorated. Patients were able to continue as per protocol thereafter (Protocol page 71).

Visits were performed every three months (V 2, V 3) in the context of the patient´s regularly scheduled visits in the specialized outpatient department. This period ended with a termination visit (V 3) from which on study drug was tapered in all patients in 0.25 mg two-daily decrements. During tapering, the patients received phone calls every other day. A Safety Telephone Call and a Safety Follow-Up Visit were executed 5 days ± 2 days and 2 weeks + 2 days after the last intake of study drug. In summary, this study comprised of five on-site study visits and regular telephone calls during titration phases (Figure of trial schedule). Safety parameters were monitored throughout the study via telephone calls and at on-site visits. Clinical assessments included the MDS-UPDRS, the NMSS, the HADS, the PDQ-8, the MoCA, the ESS, the FSS, the KPPS, the CGI-I, and the QUIP-RS. The safety data monitoring board (HGK, KS, MP) had a 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.

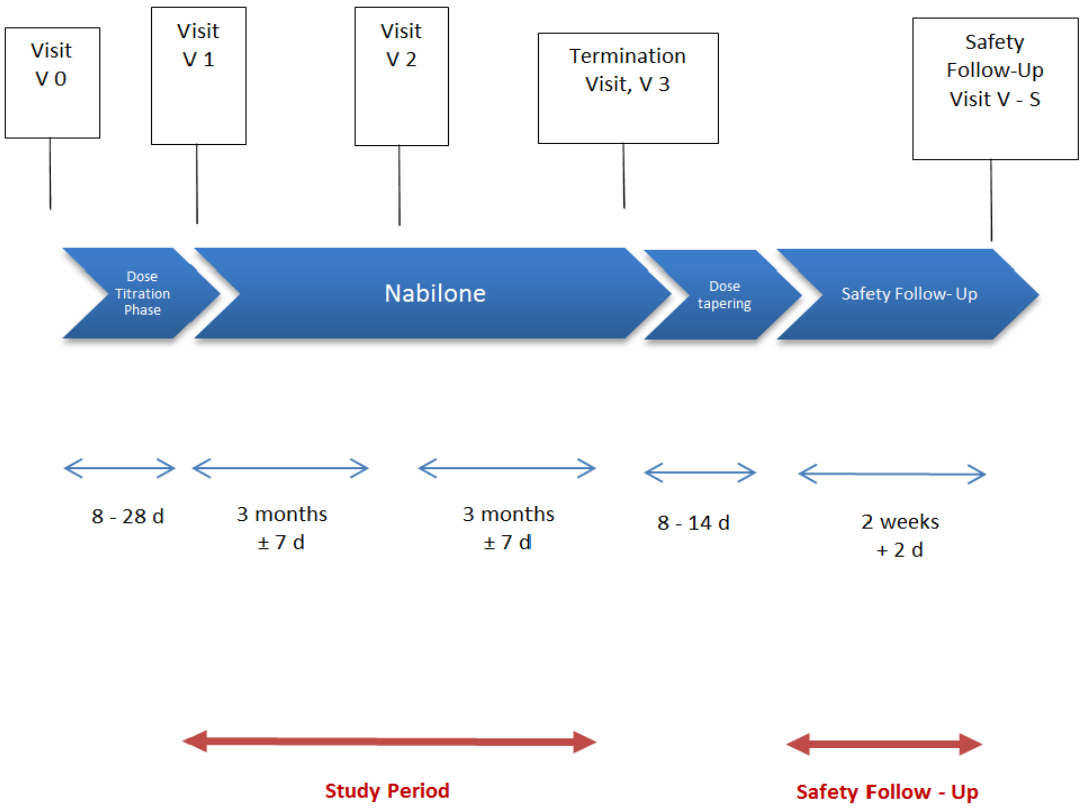


Figure 1: Schedule of trial activities
Abbreviations: V, visit; d, days.

Outcomes

The primary endpoint of the study was the long-term safety and tolerability of nabilone in PD patients between V 1 and the termination visit 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 examination findings, 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. Secondary outcomes were the change from V 1 to the termination visit in other clinical scales and questionnaires assessed. The change of the MMSE and MoCA score values between the Screening Visit of the NMS-Nab Study (before the first intake of nabilone medication) and the termination visit of this study was also assessed as secondary efficacy endpoints.

Statistical analysis

The sample size for this open-label study is not based on statistical considerations. Up to 48 subjects who completed the preceding randomized placebo-controlled, double-blind, parallel-group, enriched enrolment randomized withdrawal study (NMS-Nab Study) and met patient exclusion/inclusion criteria were planned to be enrolled.

The safety analyses were performed on all events and tolerability issues, as well as the hallucination item, orthostatic hypotension item, the day-time sleepiness item of Part I of MDS-UPDRS, and C-SSRS occurring through the overall course of the study. This was a descriptive analysis reporting overall number, frequencies, and percentage of AEs and SAEs in all patients taking nabilone, patients withdrawn from the study, and patients withdrawn due to an AE. For the study's secondary efficacy objectives, mean changes from V 1 to the termination visit were analysed by Wilcoxon matched-pairs

test. To estimate the treatment effect, we compared mean change from V 1 to month 6 visit using analysis of covariance, with value at V 1 as covariate and the treatment group as main effect. For the change in cognition, the score values of MMSE and MoCA were compared to the values of these scores at the Screening visit of the randomized placebo-controlled, double-blind, parallel-group, enriched enrolment randomized withdrawal study using the Wilcoxon matched-pairs test.

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 and performed.

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.

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 performed a phase II randomized clinical trial that used an enriched-enrolment randomized withdrawal design to evaluate the effects of continuous nabilone therapy versus withdrawal to placebo in patients with PD and troublesome NMS. Participants of this preceding trial were able to continue nabilone treatment in the open-label phase III extension study (NMS-Nab2). After screening, a re-titration of nabilone was performed and responders were continued on a stable nabilone dose for a period of six months. Safety, tolerability, and efficacy of long-term treatment were assessed during this six months-period.
Selection of open-label responders may raise concerns about generalizability of the results and thus affect external validity. However, all of our patients were responders in the preceding NMS-Nab study as defined by the study protocol and all but one were responding to treatment during titration. Therefore, selection bias was small. Restriction to responders also 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 open-label phase of the trial reflects individual treatment response as seen in daily clinical routine (7).
The long follow-up periods allow for the assessment of patients during their usual daily routines. Rare AEs or AEs associated with chronic use may be unmasked during long follow-up periods, which is important if regular prescription of the study drug should be considered in the future.

Although common, there is a paucity of well-performed trials for the treatment of different NMS in PD (8-10). Unlike most motor features of PD, NMS often have limited treatment options or response (11). Our study adds long-term data to the scarce evidence of cannabis-based treatment in PD patients. It should be the basis for further evaluations of the use of cannabinoids in this patient population. The possibility of long-term follow up in a controlled setting justifies this study design for a single-centred investigator-initiated trial of nabilone.

In order to determine improvement or deterioration with nabilone in single NMS (e.g. anxiety, sleep disturbances, orthostatic hypotension), 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 PD Society Brain Bank clinical diagnostic criteria. In order to be eligible for the study, patients had to have completed the double-blind phase of the NMS-Nab trial as responders without experiencing a drug-related SAE or drug-related moderate or severe AE. Additionally, patients had to be able and willing to take oral medication and to comply with the study specific procedures. Participants had to be in good health as determined by medical examination.

Inclusion criteria (as given in the study protocol)
1. In order to be eligible for the study, patients must have completed the double-blind phase of the NMS-Nab trial as responders within the last 2 months.
2. For patients that completed NMS-Nab Study over 2 months prior to the Screening / Baseline Visit, and meet all other inclusion criteria, eligibility should be discussed on a case-by-case basis.
3. Only patients without a drug-related SAE or (drug-related) moderate or severe AE during the NMS-Nab Study can be included in the study.
4. Patients must be able and willing to provide written informed consent prior to any study related procedure being performed. Patients with a legal guardian should be consented according to local requirements.
5. Patients must be willing and able to take oral medication and able to comply with the study specific procedures.
6. The patient is in good health as determined by medical examination and based on the investigator's judgement

Patients were not eligible for this study if they had not participated in the randomized double-blind phase of the NMS-Nab Study, had experienced a drug-related moderate or severe AE or SAE during the NMS-Nab Study, or if they had any clinically significant or unstable medical or surgical condition at the Screening / Baseline Visit that might had precluded safety and the completion of the study participation (based on the investigator's judgement, e.g. impaired liver function, sinus tachycardia, OH, a known hypersensitivity to any of the components). Patients with symptomatic OH, sinus tachycardia, and major psychiatric disorders were not allowed to participate in this trial as they are more vulnerable to possible hazardous adverse reactions that may occur during the intake of nabilone. Female patients of childbearing potential and men with a potentially fertile partner were required to use adequate contraceptive methods (according to the protocol of the NMS-Nab study).

Exclusion criteria (as given in the study protocol)
1. Patients with PD who have not participated in the randomized double-blind phase of the previous NMS-Nab Study.
2. Patients that experienced a drug-related SAE or had a (drug-related) moderate or severe AE during the NMS-Nab Study will be excluded in the study.
3. Patients who are unable or unwilling to comply with the study procedures in the investigator´s opinion.
4. Patients with any clinically significant or unstable medical or surgical condition at the Screening / Baseline Visit that may preclude safety and the completion of the study participation (based on the investigator's judgement).

The inclusion and exclusion criteria of the preceding NMS-Nab study are shown in the table below (Table 1).

Table 1: Full list of inclusion and exclusion criteria of the NMS-Nab study (as given in the study protocol)

Inclusion Criteria	**Exclusion Criteria**
1. Age ≥30 years 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.	1. Patient previously participated in any study with nabilone. 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 had 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 meant that the subject did not wish to receive further investigational treatment and did not wish or was 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 meant that the subject did not wish to take the protocol-specified product any longer but still wanted 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 had to be 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 had to be informed without delay if any investigator had ethical concerns about continuation of the trial.

The Sponsor had the right to discontinue the trial at any time, even prematurely. The Sponsor had to notify the investigator of this decision. Reasons for the decision to discontinue the trial included 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 had to be 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 would have had to 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 substance can be found in the SmPC and the respective investigational medicinal product dossier (IMPD) for nabilone. 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)

The study started with an open-label 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) until the optimal dose for the patient was found. Responders proceeded into a phase of nabilone treatment on a stable dose for six months.

Median daily dose of nabilone was 0.75 mg at the beginning of the six-months period (range 0.25–1.50 mg).

Duration of treatment:
see above

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

Not applicable.

Method of assigning patients to treatment groups

Not applicable.
Due to the open-label design of this study, no documentation on randomisation codes or assigned treatments was needed.

Selection of doses in the study

See above

Selection and timing of dose for each patient

See above

Dosing Instructions

After screening, nabilone was started in eligible patients 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 daily should not have been exceeded. Patients were instructed to meet a time interval of 12 hours between morning dose and evening dose. Capsules should have been taken at the same time each day. In case a participant should have 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 had 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 experienced intolerable AEs that were believed to be related to the study drug. During the six months of open-label treatment, participants received nabilone 0.25 mg–1 mg twice daily at their optimal dose defined in the titration phase. During this phase the fixed dosage of the study should not have been changed. However, if CGI-I deteriorated, a modification was possible after consultation with the study team (Protocol page 71). This was performed in two patients (003 and 008). However, one patient autonomously increased the daily dose from 5x0.25 mg (2-0-3) to 6x0.25 mg (3-0-3) shortly after V 1 due to an even higher benefit for controlling his NMS. The patient did not experience any drug-related adverse effects. Therefore, he was maintained in the study on the higher dose.

Blinding

Not applicable.

Prior and concomitant therapy

Allowed Anti-PD Medications/Treatments

All Anti-PD Medications were allowed in this study. Patients should have had stable disease. Moreover, the regimens of Anti-PD medications, other current prescribed/non-prescribed medications or dietary supplements should have been stable for at least 30 days prior to screening, except for the nabilone down-titration of the NMS-Nab Study. The addition of any new anti-PD medication or other prescribed / non-prescribed drugs were allowed 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 (e.g., physical therapy, exercise, yoga) the patient wanted to perform to improve his/her Parkinson symptoms were allowed to be continued during participation in the study. During the trial, such non-pharmacological therapies were allowed to be started as well. All non-pharmacological therapies had to be documented in the source documents at the Screening / Baseline Visit. The concomitant non-pharmacological therapies should have been kept on the same level 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 available to be reviewed by the study Sponsor or designee at any time requested. The investigator was responsible for appropriate storage of used, unused, and partially used study drug supplies on-site until they were returned for destruction or destructed on-site upon completion of the study (last patient last visit, LPLV).

The principal investigator was responsible that the use of the study drug was 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.
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

Safety Assessments

Tolerability was described through the: Number of subjects (%) who discontinued the study and the number of subjects (%) who discontinued the study due to AEs.

Safety Measures included the following: AEs, SAEs, Suspected unexpected serious adverse reactions (SUSARs), Clinical 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), 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 were implemented by monitoring and recording of AEs including adverse drug reactions, SAEs, and SUSARs. Description of the terms, documentation, and reporting are summarized in chapter 8 of the study protocol (starting at page 75). The patients were asked for adverse reactions at any study 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 was performed.

Description of other safety measures

Demographics

At Screening/Baseline, 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 / Baseline Visit, the Visits V 1, V 2, V 3, the Safety Follow-up Visit, and an ET Visit (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. History of defecation and of the act of urination was assessed. Neurological examination included 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, assessment of rigidity, testing for postural stability - Assessment of parkinsonism was performed in accordance with the MDS-UPDRS III).

Vital signs

Vital signs including the evaluation of weight, height (only at screening/baseline), 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.

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 of nabilone. 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 a 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.

Assessments of Efficacy

The 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 V 1 and V 3. 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, 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 – 8* (8 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 *KPPS* (7 domains, 14 items, 0 – 168 points), and the *QUIP-RS* (7 domains, 0 – 122 points) were performed. All presented scales are measured in points given above. The results of the *CGI-I* (ratings from 1 to 7) were additionally used as a secondary efficacy criterion.

All scales at screening were measured before the patient received nabilone and in subsequent visits after the patient´s morning dose of nabilone.

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. Currently, the *MDS-UPDRS* is the most common used scale in evaluation symptoms in patients with PD. 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 *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-9* is the short version of the longer PDQ-39 scale and was created to measure the health status and functional capacity of patients with PD. Its eight questions cover eight aspects of quality of life. The instrument was developed on the basis of 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.

Folstein et al. developed the *MMSE* in 1975. The MMSE consists of 30 items and was designed to be a brief global cognitive screening measure. It assesses attention, memory, language, and visuospatial abilities, as well as orientation to person, place, and time. A cut-off of 24 points (23 and below) is defined as cognitive impairment.

Daytime sleepiness was 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.

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* was used by the investigator to rate the patient´s total improvementbased 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”. 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

Assessment of the 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 V 2 and were compared to the termination visit or the screening visit (i.e., prior to

the first ever intake of nabilone) of the preceding NMS-Nab study. 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 Eye-tracking. No surrogate end point was used.

Primary safety variables

The primary endpoint was the long-term safety of nabilone treatment in PD patients as measured by safety and tolerability parameters during the trial. Assessing safety and tolerability is of utmost importance in drug testing. Using AEs, SAEs, SUSARs, and assessments of OH and single items of the MDS-UPDRS Part I is only feasible for this trial and population. Significance of the MDS-UPDRS 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

For data quality assurance procedures we refer to chapter 13 (starting at page 96) in the protocol. Training and monitoring were performed for quality assurance reasons within this clinical study. Monitoring 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. No audit of this study was performed until the date of this final report.

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 these objectives, every member of the study team was 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 used the respective 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 (member of the study team not involved in other study-related procedures) 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 were respected, that accurate, valid and complete data are collected, used, and stored, and that the trial was conducted in accordance with the trial protocol, the principles of GCP and local legislation. All investigators agreed that the monitor regularly visited 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 her activities at the trial site, as agreed in separate contracts. The Informed

Consent Form (ICF) included a statement that the monitor had the right – while observing the provisions of data protection legislation – to compare case report forms with the trial subject's medical records (e.g. doctor's notes). 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 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 independent study team members. Safety and tolerability summaries were based on a safety set which included all patients receiving at least one dose of study medication and completing at least V 1. Additionally, summaries of baseline and demographic data were produced out of the safety set. The efficacy analyses for the secondary endpoints included all screened subjects with at least one visit after screening.

The safety analyses were performed on all events and tolerability issues, as well as the hallucination item, orthostatic hypotension item, the day-time sleepiness item of Part I of MDS-UPDRS, and C-SSRS occurring through the overall course of the study. This was a descriptive analysis reporting overall number, frequencies, and percentage of AEs and serious AEs (SAEs) in all patients taking nabilone, patients withdrawn from the study, and patients withdrawn due to an AE. According to the study protocol, mean changes from V 1 to the termination visit were analysed by Wilcoxon matched-pairs test for the study's secondary efficacy objectives. To estimate the treatment effect, we compared mean change from V 1 to month six visit using analysis of covariance, with value at V 1 as covariate. Moreover, sensitivity to treatment was assessed using effect sizes of the different outcome variables when using nabilone to treat non-motor symptoms in Parkinson´s disease. For the change in cognition, the score values of MMSE and MoCA were compared to the values of these scores at the Screening visit of the randomized placebo-controlled, double-blind, parallel-group, enriched enrolment randomized withdrawal study using the Wilcoxon matched-pairs test. For the Eye-tracking analyses, mean changes from the evaluations of the Screening (and the Termination Visit) of the

randomized placebo-controlled, double-blind, parallel-group, enriched enrolment randomized withdrawal study to V 2 of this study were compared using the Wilcoxon matched-pairs test. 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.

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. As all patients were on nabilone at V 1, any change of the efficacy assessments during the trial until termination visit was not expected. For this reason, we have also performed a post-hoc analysis comparing mean change from V 0 to month six visit for the different efficacy variables including the MDS-UPDRS-I and NMSS.

Determination of sample size

The sample size for this open-label study was not based on statistical considerations. Up to 48 subjects who completed the preceding randomized placebo-controlled, double-blind, parallel-group, enriched enrolment randomized withdrawal study (NMS-Nab Study) and met patient exclusion/inclusion criteria could be enrolled.

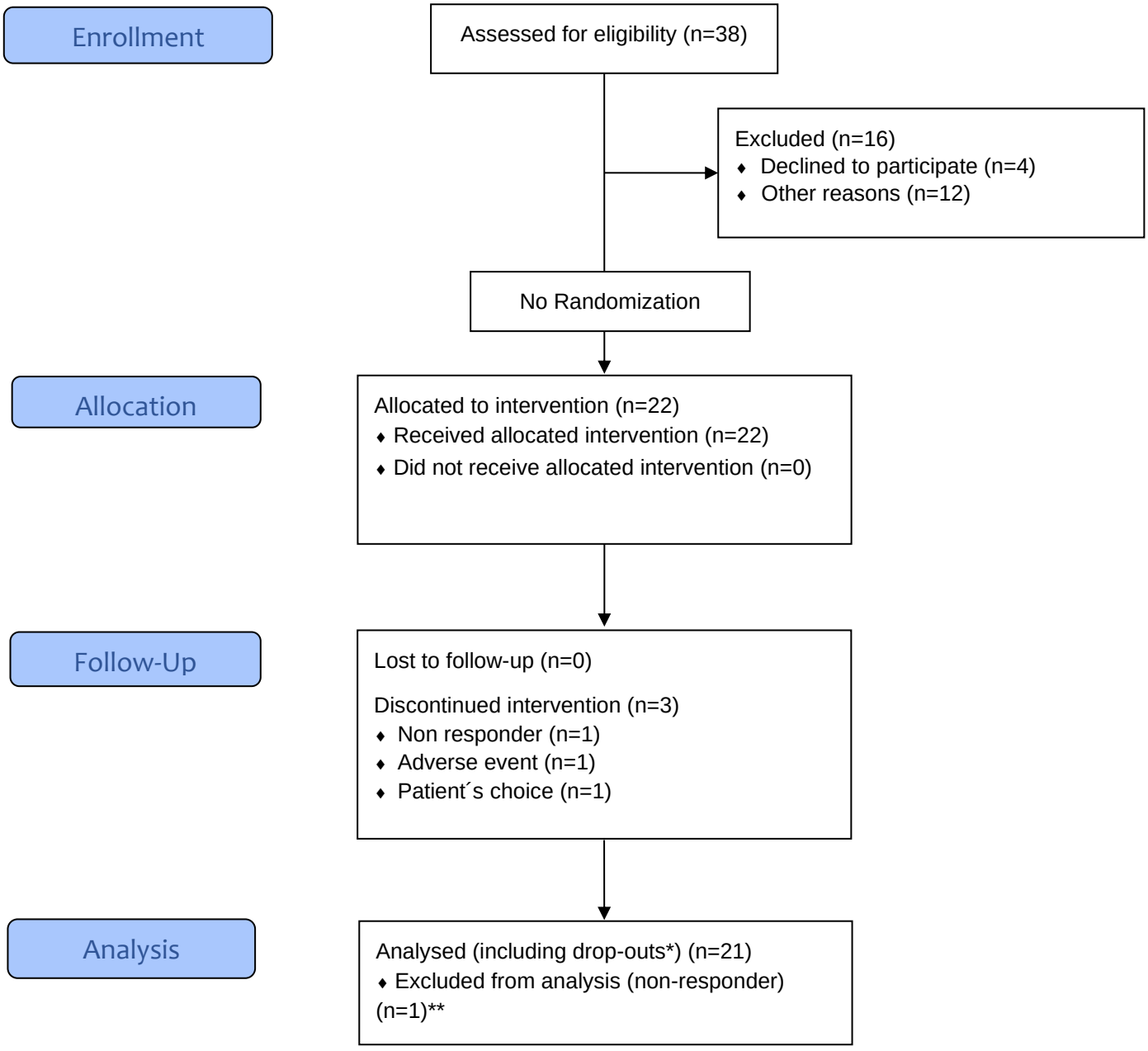
Changes in the Conduct of the Study or Planned Analyses

Not applicable

9. Study Patients

Disposition of Patients

CONSORT 2010 Flow Diagram



Flow Chart (adapted from CONSORT 2010)

* Data of regular visits were included up to the point of discontinuation (before V 2 in both drop-outs). ** The non-responder discontinued study participation before V 1 and was therefore excluded from analysis. Abbreviation: n, number.

All 38 patients that finished the double-blind phase of the preceding NMS-Nab study were assessed for eligibility. Four patients declined participation in the NMS-Nab2 study, because they were satisfied with their symptomatic control at that time. In 12 patients, other reasons prevented them from taking part in this study: planned surgery (n=2), wish for modification of treatment regime of PD symptoms with other treatment strategies than nabilone (n=4), wish for introduction of cannabinoid treatment outside of a study (n=2), scheduling difficulties (mostly with work, n=3), other reason (n=1).

Twenty-two patients participated in the NMS-Nab2 study between August 10, 2018, and January 31, 2020 (last patient last visit). There was no screening failure. Up-titration was started in all patients. One patient was a non-responder and therefore discontinued before V 1. Two patients were drop-outs, one due to an adverse event (problems with night-time sleep) for which a prohibited concomitant medication (brotizolam 0.25 mg 0-0-0-1/2) needed to be introduced. The other patient discontinued the therapy without consultation with the study team because of deterioration of a pre-existing mild cognitive impairment (medical history). This did not resolve after IMP discontinuation (1 patient of 21 = 4.76%). Nineteen patients finished the six months of continuous nabilone treatment. Data of these 19 patients and of the two drop-outs (up to the point of discontinuation = before V 2) were included in the final analyses (Flow chart). At the safety follow-up, MDS-UPDRS III was not assessed in 3 patients who were unable to attend the visit on-site (visit was performed on the phone, see below).

Protocol Deviations

In two patients, there was a transient change of concomitant medication before the screening visit (e.g., antibiotics), but long-term medication was unchanged. One patient changed his dose regimen autonomously between V 1 and V 2 with higher benefit and no side effects. Therefore, he was kept in the study after consultation with the investigators. Daily dose of nabilone treatment was changed in other patients as well (003 and 008) after the titration phase but with consultation with the study team (no protocol deviation). One patient interrupted the study medication for five days during the open-label trial phase due to vertigo (PI`s decision). One patient discontinued the study treatment on his own will; an ET visit was performed. 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 due to difficulties in scheduling the visits (e.g., at Christmas holidays). Three patients were unable to attend the Safety Follow-up visit, which was therefore performed via a telephone call in all of them (PI´s decision). While all questionnaires could be obtained, physical examinations were not performed during these visits (e.g., MDS-UPDRS Part III).

10. Efficacy Evaluation

Data Sets Analysed

See above

One patient was a non-responder during titration phase and was excluded from the analysis. Two patients discontinued the six-months-open-label treatment phase. Their data of regular visits were included in the final analyses until their discontinuation visit (see Flow chart).

Demographic and Other Baseline Characteristics

Demographic and clinical characteristics are shown in Table 2.

Table 2: Demographics and results at the screening visit

Age at SCR (years)	67.23 ±6.15 (68.33, 62.21 – 71.25)
Daily dose (mg, at V 1)	0.87 ±0.44 (0.75) Range: 0.25 – 1.50
Females	11 (52.38%)
Disease duration (years)	9.30 ±6.04 (7.42, 3.92 – 14.38)
Education (years)	12.81 ±2.53 (12.00, 11.00 – 14.00)

Data of continuous variables are presented as mean ± standard deviation (median, P25-P75). Data of nominal variables are presented as n (%). Abbreviations: SCR, screening; v, visit. Higher Score values indicate worse outcome in all scales and questionnaires.

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

Measurements of Treatment Compliance

No patient had a treatment compliance out of range during this trial. However, one patient autonomously increased the daily dose from 5x0.25 mg (2-0-3) to 6x0.25 mg (3-0-3) shortly after V 1 due to an improved benefit for controlling his NMS. The patient did not experience any drug-related adverse effects. Therefore, he was maintained in the study on the higher dose.
Daily dose of nabilone treatment was changed in other patients as well (003 and 008) after the titration phase but with discussion with the study team. One patient interrupted the study medication for five days during the open-label trial phase due to vertigo (AE, PI´s decision). One patient discontinued the study treatment on his own will; an ET visit was performed.

For measurements of compliance: see above

Efficacy Results and Tabulations of Individual Patient Data

Efficacy data are summarized in Table 3 and 4 and Figure 2 and 3. There were no significant differences in any endpoint scores between V 1 and V3 except for the CGI-I, which is reflected in a moderate effect size ($p = 0.002$, ϕ coefficient = 0.034). Therefore, sensitivity analyses were not performed.

CGI-I was improved after titration phase with a long-lasting benefit over the six months treatment period. While at V 1, all patients reported an amelioration of their burden of NMS compared to screening according to the CGI-I, at V 3, still 78.90 % of the patients did so, while 21.10 % of the patients rated the burden of NMS deteriorated compared to screening.

There was a trend for amelioration of the HADS-D ($p = 0.044$; Effect size according to Cohen´s D = 0.48, Table 4).

The MMSE and MoCa score values of V 3 were compared to those of the screening visit of the preceding NMS-Nab1 study. There was also no significant difference (Table 4).

Table 3: Endpoint scores during the study

	SCR **n=21**	**V 1** **n=21**	**V 2** **n=19**	**V 3** **n=19**	**SFU** **n=19**
MDS-UPDRS I	12.05 ±5.79 (11.00) (8.50 – 14.00)	11.14 ±12.60 (8.00) (4.00 – 15.00)	8.42 ±5.30 (10.00) (3.00 – 12.00)	9.47 ±5.90 (8.00) (4.00 – 14.00)	11.58 ±6.23 (11.00) (6.00 – 16.00)
MDS-UPDRS II	12.29 ±7.21 (12.00) (6.00 – 15.50)	11.24 ±7.49 (11.00) (5.50 – 15.50)	10.53 ±7.24 (10.00) (4.00 – 17.00)	11.11 ±6.82 (8.00) (6.00 – 16.00)	11.32 ±7.30 (10.00) (6.00 – 16.00)

MDS-UPDRS III	28.95 ±11.12 (33.00) (18.50 – 38.50)	27.86 ±11.97 (29.00) (18.00 – 37.50)	27.68 ±11.61 (26.00) (18.00 – 38.00)	29.37 ±10.10 (28.00) (21.00 – 38.00)	27.00 ±8.90 (26.50) (21.25 – 35.75)
MDS-UPDRS IV	2.52 ±3.91 (2.00) (0.00 – 4.00)	2.71 ±3.57 (3.00) (0.00 – 5.00)	2.42 ±3.81 (0.00) (0.00 – 4.00)	2.63 ±3.75 (0.00) (0.00 – 4.00)	2.26 ±3.57 (0.00) (0.00 – 4.00)
MDS-UPDRS Total Score	55.81 ±22.45 (55.00) (38.00 – 69.50)	52.95 ±24.51 (50.00) (39.50 – 69.50)	49.05 ±23.51 (47.00) (35.00 – 63.00)	52.58 ±22.45 (50.00) (37.00 – 58.00)	50.56 ±19.26 (52.00) (34.50 – 59.00)
MDS-UPDRS Sum Score I – III	53.29 ±20.55 (55.00) (38.00 – 65.00)	50.24 ±22.26 (48.00) (39.50 – 65.50)	46.63 ±21.05 (47.00) (30.00 – 59.00)	49.95 ±19.82 (50.00) (34.00 – 58.00)	48.50 ±17.98 (50.50) (33.00 – 58.75)
MDS-UPDRS Motor Sum Score II+III	41.24 ±16.88 (43.00) (27.00 – 52.00)	39.10 ±17.27 (40.00) (25.50 – 52.50)	38.21 ±17.45 (37.00) (26.00 – 49.00)	40.47 ±15.36 (37.00) (30.00 – 46.00)	37.31 ±14.46 (36.00) (27.25 – 47.00)
H&Y	2.05 ±0.38 (2.00) (2.00 – 2.00)	1.95 ±0.22 (2.00) (2.00 – 2.00)	2.00 ±0.33 (2.00) (2.00 – 2.00)	2.11 ±0.32 (2.00) (2.00 – 2.00)	2.06 ±0.44 (2.00) (2.00 – 2.00)
CGI-I	n.a.	2.05 ±0.22 (2.00) (2.00 – 2.00)	2.79 ±1.03 (3.00) (2.00 – 3.00)	3.21 ±1.23 (3.00) (3.00 – 3.00)	3.95 ±0.62 (4.00) (4.00 – 4.00)
NMSS Domain 1	1.29 ±1.35 (1.00) (0.00 – 2.00)	1.57 ±1.86 (1.00) (0.00 – 2.00)	1.74 ±2.35 (1.00) (0.00 – 2.00)	1.84 ±2.52 (1.00) (0.00 – 4.00)	n.a.
NMSS Domain 2	15.48 ±11.38 (12.00) (6.00 – 21.00)	7.57 ±7.69 (5.00) (2.00 -10.50)	5.42 ±5.08 (4.00) (1.00 – 10.00)	7.26 ±7.77 (5.00) (2.00 – 8.00)	n.a.
NMSS Domain 3	6.95 ±7.86 (3.00) (1.50 – 10.50)	4.52 ±5.03 (2.00) (0.00 – 8.00)	6.21 ±8.91 (3.00) (0.00 – 10.00)	6.89 ±8.23 (4.00) (1.00 – 9.00)	n.a.
NMSS Domain 4	0.71 ±2.03 (0.00) (0.00 – 0.00)	0.71 ±2.03 (0.00) (0.00 – 0.00)	0.58 ±1.47 (0.00) (0.00 – 0.00)	0.16 ±0.50 (0.00) (0.00 – 0.00)	n.a.
NMSS Domain 5	3.86 ±6.73 (1.00) (0.00 – 5.00)	3.67 ±6.39 (1.00) (0.00 – 5.00)	4.21 ±7.38 (0.00) (0.00 – 6.00)	3.68 ±6.08 (2.00) (0.00 – 6.00)	n.a.
NMSS Domain 6	3.14 ±3.77 (2.00) (0.00 – 5.50)	3.76 ±4.01 (3.00) (0.00 – 6.00)	2.53 ±3.99 (0.00) (0.00 – 4.00)	3.74 ±4.57 (2.00) (0.00 – 8.00)	n.a.
NMSS Domain 7	6.67 ±6.10 (5.00) (1.00 – 12.00)	6.24 ±6.48 (4.00) (0.00 – 12.50)	5.79 ±6.11 (4.00) (0.00 – 10.00)	6.74 ±5.76 (6.00) (2.00 – 13.00)	n.a.
NMSS Domain 8	0.00 ±0.00 (0.00) (0.00 – 0.00)	0.00 ±0.00 (0.00) (0.00 – 0.00)	0.32 ±0.82 (0.00) (0.00 – 0.00)	0.42 ±1.12 (0.00) (0.00 – 0.00)	n.a.
NMSS Domain 9	10.52 ±8.01 (8.00) (6.00 – 12.00)	7.57 ±5.60 (7.00) (4.00 – 12.00)	7.42 ±5.64 (7.00) (2.00 – 10.00)	8.21 ±5.90 (8.00) (3.00 – 12.00)	n.a.
NMSS Total Score	48.62 ±31.10 (42.00) (20.50 – 74.50)	35.62 ±25.69 (33.00) (14.00 – 52.00)	34.21 ±24.70 (28.00) (13.00 – 52.00)	38.95 ±25.82 (29.00) (18.00 – 62.00)	n.a.
KPPS Total Score	20.86 ±13.66 (17.00) (9.50 – 32.00)	6.95 ±8.29 (4.00) (0.50 – 12.00)	10.89 ±13.13 (8.00) (2.00 – 14.00)	13.42 ±13.60 (8.00) (1.00 – 24.00)	n.a.
HADS-A	5.38 ±4.91 (5.00) (1.00 – 8.50)	4.57 ±3.01 (4.00) (2.00 – 7.00)	4.89 ±3.97 (4.00) (2.00 – 8.00)	4.68 ±3.74 (4.00) (2.00 – 9.00)	n.a.

HADS-D	4.90 ±3.74 (4.00) (2.00 – 8.00)	5.43 ±4.07 (5.00) (1.50 – 9.00)	4.79 ±3.44 (4.00) (2.00 – 9.00)	4.42 ±3.20 (4.00) (2.00 – 7.00)	n.a.
PDQ-8 SI	54.02 ±18.60 (56.25) (37.50 – 75.00)	51.94 ±16.64 (56.25) (34.38 – 64.06)	50.82 ±17.98 (50.00) (37.50 – 62.50)	54.11 ±16.44 (56.25) (40.63 – 68.75)	n.a.
ESS	6.95 ±4.46 (6.00) (5.00 – 9.00)	8.14 ±5.79 (6.00) (3.50 – 13.00)	7.42 ±4.96 (6.00) (4.00 – 9.00)	7.32 ±4.58 (7.00) (4.00 – 8.00)	n.a.
FSS	32.10 ±15.08 (29.00) (21.50 – 43.50)	34.62 ±14.71 (36.00) (26.00 – 45.50)	28.74 ±12.39 (31.00) (20.00 – 35.00)	29.89 ±14.35 (27.00) (19.00 – 39.00)	n.a.
QUIP-RS	0.14 ±0.66 (0.00) (0.00 – 0.00)	0.48 ±1.12 (0.00) (0.00 – 0.00)	0.68 ±1.80 (0.00) (0.00 – 0.00)	0.37 ±1.12 (0.00) (0.00 – 0.00)	n.a.
MMSE	n.a.	n.a.	n.a.	28.95 ±1.31 (29.00) (28.00 - 30.00)	n.a.
MoCA	n.a.	n.a.	n.a.	28.21 ±1.90 (29.00) (27.00 – 30.00)	n.a.

Data of continuous variables are presented as mean ± standard deviation (median) (interquartile range / P25-P75).
Abbreviations: MDS-UPDRS, Movement Disorder Society- Unified Parkinson´s Disease Rating Scale; NMSS, Non-Motor Symptoms Scale; H&Y, Hoehn and Yahr; CGI-I, Clinical Global Impression – Global Improvement; KPPS, King's PD pain scale; HADS-A/-D, Hospital anxiety and depression scale - Anxiety/ - Depression; PDQ-8 SI, Parkinson´s Disease Questionnaire – 8 Summary Index; ESS, Epworth Sleepiness Scale; FSS, Fatigue Severity Scale; QUIP-RS, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale; MMSE, Mini Mental State Exam; MoCA, Montreal Cognitive Assessment; SCR, screening; V, visit; n.a., not assessed, therefore not applicable. Higher score values indicate worse outcome in all scales and questionnaires but the MMSE and MoCA.
NMSS Domains: Domain 1: Cardiovascular, Domain 2: Sleep/Fatigue, Domain 3: Mood/Apathy, Domain 4: Perceptual problems/Hallucinations, Domain 5: Attention/Memory. Domain 6, Domain 7: Urinary, Domain 8: Sexual dysfunction, Domain 9: Miscellaneous.

Table 4: Change in endpoint scores during open-label administration of nabilone, patients n= 19

	Mean change between V 1 and V 3	**p-value**	**Effect size**
MDS-UPDRS I	1.58 ±13.87 (-5.10; 8.26) (0.00, -5.00 – 1.00)	0.489	0.11
MDS-UPDRS II	-0.58 ±3.49 (-2.26; 1.10) (-1.00, -3.00 – 1.00)	0.195	-0.17
MDS-UPDRS III	-1.89 ±6.88 (-5.21; 1.42) (-1.00, -5.00 – 1.00)	0.092	-0.28
MDS-UPDRS IV	-0.16 ±2.14 (-1.19; 0.87) (-1.00, 0.00 – 0.00)	0.724	-0.08
MDS-UPDRS Total Score	-1.05 ±15.90 (-8.71; 6.61) (-1.00, -10.00 – 4.00)	0.600	-0.07
MDS-UPDRS Sum Score I – III	-0.89 ±14.99 (-8.12; 6.33) (-1.00, -10.00 – 4.00)	0.468	-0.06
MDS-UPDRS Motor Sum Score II+III	-2.47 ±7.88 (-6.27; 1.33) (-2.00, -8.00 – 2.00)	0.211	-0.31
H&Y	-0.16 ±0.38 (-0.34; 0.02) (0.00, 0.00 – 0.00)	0.083	-0.42
NMSS Domain 1	-0.63 ±2.75 (-1.96; 0.70) (0.00, -2.00 – 1.00)	0.502	-0.23
NMSS Domain 2	-0.16 ±6.36 (-3.22; 2.91) (1.00, -3.00 – 3.00)	0.855	-0.03

NMSS Domain 3	-2.37 ±7.34 (-5.91; 1.17) (0.00, -3.00 – 2.00)	0.461	-0.32
NMSS Domain 4	0.63 ±2.01 (-0.34; 1.60) (0.00, 0.00 – 0.00)	0.180	0.32
NMSS Domain 5	-0.47 ±2.09 (-1.48; 0.53) (0.00, -1.00 – 0.00)	0.375	-0.23
NMSS Domain 6	0.05 ±3.91 (-1.83; 1.94) (0.00, -2.00 – 3.00)	0.850	0.01
NMSS Domain 7	-0.47 ±4.06 (-2.43; 1.48) (0.00, -4.00 – 2.00)	0.598	-0.12
NMSS Domain 8	-0.42 ±1.12 (-0.96; 0.12) (0.00, 0.00 – 0.00)	0.109	-0.38
NMSS Domain 9	-1.00 ±4.91 (-3.37; 1.37) (-1.00, -4.00 – 1.00)	0.324	-0.20
NMSS Total Score	-4.84 ±18.08 (-13.55; 3.87) (-2.00, -15.00 – 8.00)	0.212	-0.27
CGI-I	-1.16 ±1.30 (-1.79; -0.53) (-1.00, -1.00 – -1.00)	0.002	0.34
KPPS Total Score	-6.84 ±15.12 (-14.13; 0.45) (-4.00, -20.00 – 1.00)	0.073	-0.45
HADS-A	-0.16 ±1.50 (-0.88; 0.57) (0.00, -2.00 – 1.00)	0.560	-0.11
HADS-D	1.00 ±2.08 (0.00; 2.00) (0.00, 0.00 – 3.00)	0.044	0.48
PDQ-8 SI	-2.96 ±9.11 (-7.35; 1.43) (-3.13, -6.25 – 3.13)	0.236	-0.33
ESS	0.11 ±2.75 (-1.22; 1.43) (0.00, -2.00 – 1.00)	0.886	0.04
FSS	4.26 ±10.08 (-0.60; 9.12) (2.00, 0.00 – 10.00)	0.103	0.42
QUIP RS	0.11 ±1.41 (-0.57; 0.78) (0.00, 0.00 – 0.00)	0.785	0.08
	Mean change between NMS-Nab1 SCR Visit and V 3	**p-value**	**Effect size**
MMSE	0.42 ±1.84 (-0.46; 1.31) (0.00, 0.00 – 1.00)	0.298	0.23
MoCA	-0.11 ±1.94 (-1.04; 0.83) (0.00, -2.00 – 1.00)	0.775	-0.05

Data are given as mean ± standard deviation (95% confidence interval) (median, interquartile range / P25-P75).
Abbreviations: CI, confidence interval; MDS-UPDRS, Movement Disorder Society- Unified Parkinson´s Disease Rating Scale; NMSS, Non-Motor Symptoms Scale; CGI-I, Clinical Global Impression – Global Improvement; KPPS, King's PD pain scale; HADS-A/-D, Hospital anxiety and depression scale - Anxiety/ - Depression; PDQ-8 SI, Parkinson´s Disease Questionnaire – 8 Summary Index; ESS, Epworth Sleepiness Scale; FSS, Fatigue Severity Scale; QUIP-RS, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale; MMSE, Mini Mental State Exam; MoCA, Montreal Cognitive Assessment; SCR, screening; V, visit. Higher score values indicate worse outcome in all scales and questionnaires but the MMSE and MoCA.
NMSS Domains: Domain 1: Cardiovascular, Domain 2: Sleep/Fatigue, Domain 3: Mood/Apathy, Domain 4: Perceptual problems/Hallucinations, Domain 5: Attention/Memory. Domain 6, Domain 7: Urinary, Domain 8: Sexual dysfunction, Domain 9: Miscellaneous.
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). Cohen´s D of 0.2, 0.5, and 0.8 and ϕ coefficient of 0.1, 0.3, and 0.5 were considered 'small', 'medium', and 'large' effect sizes.

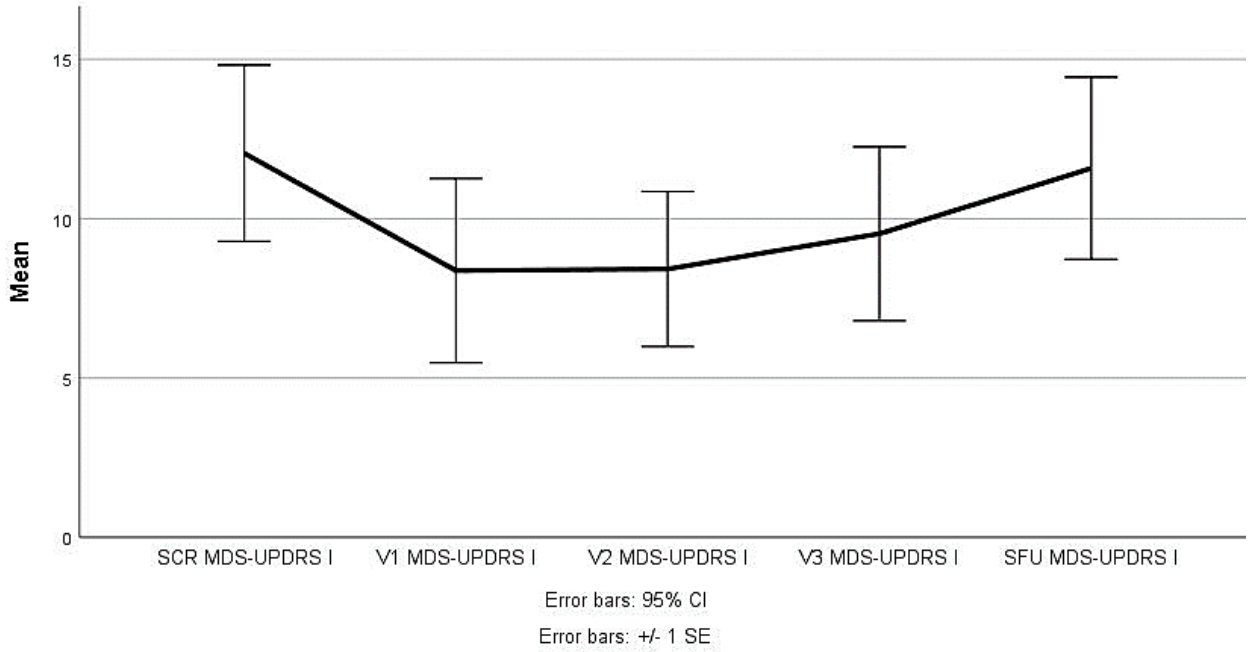


Figure 2: Change of MDS-UPDRS I during the study
Abbreviations: SCR, screening; V, visit; MDS-UPDRS, Movement Disorder Society- Unified Parkinson´s Disease Rating Scale; SFU, Safety Follow-Up; CI, confidence interval; SE, standard error.

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 was a per-protocol analysis. Missing data were kept as such. Analytical methods were not adjusted. No interim analyses were performed. Adjustments of multiple comparisons was not performed. As all patients were on nabilone at V 1, any change of the efficacy assessments during the trial until termination visit was not expected. For this reason, we have also performed a post-hoc analysis comparing mean change from V 0 to month six visit for the different efficacy variables including the MDS-UPDRS-I and NMSS.

Adjustments for Covariates
Because change from V 1 to V 3 was not significant in any of the efficacy variables (except the CGI-I), the planned sensitivity analysis (i.e., analysis of covariance with value at V 1 as covariate) was not performed. The CGI-I describes improvement, deterioration or no change of a treatment compared to the time before treatment (where no CGI-I can be assessed), such as no sensitivity analysis was performed for the CGI-I´s change.

Handling of Dropouts or Missing Data
See above for number of drop-outs and reason for it as well as statistical considerations (no interpolation). Data of drop-outs were included in the final analyses up to the timepoint of study discontinuation as per protocol (defined datasets).
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 were dropped because of poor compliance, missed visits, or ineligibility. The study participants represent the standard patient population.

Active-Control Studies Intended to Show Equivalence

Not applicable

Examination of Subgroups

Not applicable.

Drug dose, drug concentration, and relationships to response

Table 5: Dose regimen of individual patients

Patient Identifier at screening	Dose regimen at V 1 (capsules)	Nabilone daily dose (in mg)
1	2-0-3	1.25
2	0-0-1	.25
3	2-0-2 → 1-0-1*	1.00 → .50
4	2-0-2	1.00
5	1-0-2	.75
6	1-0-1	.50
7	3-0-3	1.50
8	1-0-2 → 1-0-1 → 1-0-2*	.75 → .50 → .75
9	2-0-3	1.25
10	2-0-2	1.00
11	0-0-1***	.25
13	1-0-2	.75
14	2-0-3 → 3-0-3**	1.25 → 1.50
15	1-0-2	.75
16	1-0-1	.50
17	3-0-3	1.50
18	2-0-2	1.00
19	3-0-3	1.50
20	1-0-2	.75
21	0-0-1	.25
22	0-0-1****	.25

* Subjects changed their daily nabilone dose during the open-label trial phase after consultation with the study team.

** Subject changed his dose autonomously shortly after V1.

*** IMP interrupted during titration phase after consultation with the study team.

**** IMP interrupted during open-label phase after consultation with the study team.

Drug-drug and drug-disease interactions

Not applicable. No relevant safety concern due to combination of nabilone with any treatment or illness during this trial was noted.

Post-hoc analysis

As all patients were on nabilone at V 1, any change of the efficacy assessments during the trial until termination visit was not expected. For this reason, we have also performed a post-hoc analysis comparing mean change from V 0 to month six visit for the different efficacy variables including the MDS-UPDRS-I and NMSS. Table 6 summarises the results of the post-hoc analysis.

Table 6: Change in endpoint scores between screening and V 3, patients n= 19

	Mean change (95% CI) between SCR visit and V 3	p-value	Effect size
MDS-UPDRS I	-2.58 (-5.00; -0.16)	0.052	-0.51

MDS-UPDRS II	-0.53 (-2.25; 1.20)	0.958	-0.15
MDS-UPDRS III	1.21 (-1.85; 4.27)	0.513	0.19
MDS-UPDRS IV	0.42 (-0.94; 1.78)	0.538	0.15
MDS-UPDRS Total Score	-1.47 (-6.99; 4.04)	0.376	-0.13
MDS-UPDRS Sum Score I – III	-1.90 (-7.28; 3.49)	0.359	-0.17
MDS-UPDRS Motor Sum Score II+III	0.68 (-3.48; 4.84)	0.763	0.08
H&Y	0.05 (-0.20; 0.31)	0.655	0.10
NMSS Domain 1	0.63 (-0.44; 1.70)	0.365	0.29
NMSS Domain 2	-8.26 (-13.82; -2.71)	0.004	-0.72
NMSS Domain 3	0.79 (-3.80; 5.38)	0.887	0.08
NMSS Domain 4	-0.63 (-1.60; 0.34)	0.180	-0.32
NMSS Domain 5	0.53 (-0.56; 1.61)	0.381	0.23
NMSS Domain 6	0.68 (-1.39; 2.76)	0.624	0.16
NMSS Domain 7	-0.11 (-2.50; 2.29)	0.721	-0.02
NMSS Domain 8	0.42 (-0.12; 0.96)	0.109	0.38
NMSS Domain 9	-1.74 (-5.21; 1.73)	0.279	-0.24
NMSS Total Score	-7.68 (-18.96; 3.59)	0.205	-0.33
KPPS Total Score	-8.00 (-15.05; -0.95)	0.046	-0.55
HADS-A	-0.74 (-1.81; 0.34)	0.216	-0.33
HADS-D	-0.63 (-1.64; 0.38)	0.295	-0.30
PDQ-8 SI	0.00 (-3.82; 3.82)	0.886	0.00
ESS	0.47 (-0.70; 1.65)	0.456	0.20
FSS	-0.63 (-5.26; 3.99)	0.856	-0.07
QUIP RS	0.37 (-0.17; 0.91)	0.180	0.33

Abbreviations: CI, confidence interval; MDS-UPDRS, Movement Disorder Society- Unified Parkinson´s Disease Rating Scale; NMSS, Non-Motor Symptoms Scale; KPPS, King's PD pain scale; HADS-A/-D, Hospital anxiety and depression scale - Anxiety/ - Depression; PDQ-8 SI, Parkinson´s Disease Questionnaire – 8 Summary Index; ESS, Epworth Sleepiness Scale; FSS, Fatigue Severity Scale; QUIP-RS, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale; SCR, screening; V, visit. Higher Score values indicate worse outcome in all scales and questionnaires.
NMSS Domains: Domain 1: Cardiovascular, Domain 2: Sleep/Fatigue, Domain 3: Mood/Apathy, Domain 4: Perceptual problems/Hallucinations, Domain 5: Attention/Memory. Domain 6, Domain 7: Urinary, Domain 8: Sexual dysfunction, Domain 9: Miscellaneous.
For all p-values, significance level was set at p≤0.05. Effect size according to Cohen´s D. Cohen´s D of 0.2, 0.5, and 0.8 were considered 'small', 'medium', and 'large' effect sizes.

Efficacy conclusions

In this open-label study, we examined the long-term efficacy and safety of the synthetic cannabinoid nabilone in PD patients with troublesome NMS. There was no significant change on the different efficacy variables assessing NMS in PD once patients were on nabilone. The patient´s self-rating, however, indicated a long-lasting improvement (CGI-I).

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 (12-15), which is in line with the post-hoc analysis of this study, when efficacy variables where compared with the timepoint before nabilone was started. This confirms the results of the double-blind phase of the preceding NMS-Nab study.

11. Safety Evaluation

Extent of exposure

Duration: (mean ±standard deviation)
Mean duration of titration phase was 27.76 ±14.11 (27.00) days and mean duration from V 1 to V 3 was 180.26 ±8.23 (181.00) days for all included patients. Data of drop-outs was included up to the point of study discontinuation as per protocol. Both drop-outs discontinued between V 1 and V 2. The non-responder was not included in the analyses (ID: 012, female, born 1967, education: 14 years, year of symptom onset: 2016, age of symptom onset: 49 years).

Dose: Cumulative Subject Exposure
The NMS-Nab2 study is an open-label long-term study. According to the World Health Organisation, there is no defined daily dose for nabilone. The cumulative subject exposure was 13487 units, where one unit represents 0.25 mg of nabilone (Table 7).
For daily doses of individual patients, dose ranges, and demographic data: see above (Table 2 and Table 5). Of 21 patients included in the final analysis (dataset defined above), 52.38% are female, and 66.67% of subjects are 65 years of age and older. 100% of subjects are Caucasian. Patient 012 was a non-responder (data see above).

Table 7: Cumulative Subject Exposure

Subject # (ID at screening)	Units*
1	999
2	65
3	500**
4	884
5	626
6	373
7	941***
8	590
9	974
10	679
11	289**
12	164****
13	572**
14	1173
15	191
16	390*****
17	1277***
18	715******
19	1120
20	576**
21	197
22	192
Total	**13487**

*1 unit=1 capsule=0.25 mg nabilone
**patient lost 1 bottle of nabilone, exposure was calculated based on the returned bottles
*** patient lost 2 bottles of nabilone, exposure was calculated based on the returned bottles
****non-responder
*****Patient dropped one bottle with 20 capsules in it. Calculation based on maximal exposure (20 capsules).
****** patient lost 4 bottles of nabilone; exposure was calculated based on the returned bottles.

Drug concentration
Not applicable

Adverse events

Brief summary of adverse events
Between V 1 and V 3, two patients discontinued the trial: one patient due to insomnia with need for an additional medication that was prohibited in combination with nabilone according to the study protocol (brotizolam). The other patient discontinued the therapy without consultation with the study team because of deterioration of a pre-existing mild cognitive impairment (medical history). This did not resolve after IMP discontinuation. (1 patient of 21 = 4.76%)

Common AEs (>1 patient) are given in Table 8 and a full list of AEs and SAEs is given in Table 9 and 10 and the Appendix (PDF-File for individual patient data). Between V 1 and V 3, the most common treatment-related adverse events were concentration difficulties (possibly related n=1, not related n=1). The daily dose of nabilone was slightly reduced in both patients which lead to a resolution of the AEs. Other common AEs included infections, intermittent falls, a transient numbness of the face without clinical correlate, osteopenia/osteoporosis, insomnia, lumbar pain, arthrosis, and a worsening of PD. The latter was leading to hospitalization in one patient. Suicidality according to C-SSRS did not occur in any patient during the study and follow-up period.

Table 8: Safety Analysis of the open-label phase

Most common AEs between V 1 and V 3 (n>1)			
AE	**total (n)**	**Severity of AE (n)**	
		mild	**moderate**
Respiratory tract infection	4	2	2
Concentration difficulties (disturbance in attention)	3	2	1
Intermittent falls	3	2	1
Urinary tract infection	2	2	0
Transient numbness of the face (hypoesthesia)	2	1	1
Osteopenia/Osteoporosis	2	1	1
Insomnia	2	0	2*
Lumbar pain (back pain)	2	0	2
Worsening of PD	2	0	2**
Arthrosis (osteoarthropathy)	2	0	2

*leading to discontinuation in one patient. **1 SAE.
Abbreviations: n, number; AE, adverse event; SAE, serious adverse event; PD, Parkinson´s Disease.

Display of adverse events
See above and Table 9 and 10.

Table 9: Safety Analysis of the titration phase: Full list of AEs and SAEs

Titration phase
AEs (n=13)
Mild Vertigo (n=2): possibly related (n=1), probably related (n=1) Pain (n=2): possibly related (n=1, in both legs), not related (n=1, diffuse) Headache (n=1): possibly related Inner tension (n=1): possibly related Sleep disturbances (maintenance of sleep, n=1): not related

Upper respiratory tract infection (n=1): not related Dry skin (n=1): not related Fall (n=1): not related **Moderate** Frontal sinusitis (n=1): not related Insomnia (n=1): not related
SAEs (n=2)
Moderate: Medication-induced Nausea (n=1): not related, hospitalization Medication-induced Emesis (n=1): not related, hospitalization

Abbreviations: n, number; AE, adverse event; SAE, serious adverse event.

Table 10: Safety Analysis of the open-label phase: Full list of AEs and SAEs

Open-label phase*
AEs (n=39)
Mild Concentration difficulties (n=2): possibly related (n=1), not related (n=1) Intermittent falls (n=2): not related Upper respiratory tract infection (n=2): not related (viral n=1, bacterial n=1) Urinary tract infection (n=2): not related Vertigo (n=1): possibly related Muscle cramps (n=1): not related Hypercholesterinaemia (n=1): not related Osteoporosis (n=1): not related Haematoma right ankle with oedema (n=1): not related Vitamin B12 deficiency (n=1): not related Numbness of the left side of the face (n=1): not related Bursitis right elbow (n=1): not related Skin infection leg (n=1): not related Eczema (n=1): not related **Moderate** Insomnia (n=2): not related (n=1 leading to discontinuation) Lumbar pain (n=2): not related Arthrosis (n=2): not related (polyarthrosis of both hands n=1, gonarthrosis n=1) Respiratory tract infection (n=2): not related (upper respiratory tract, bacterial n=1, bronchitis n=1) Concentration difficulties (n=1): possibly related Transient dysarthria (n=1): possibly related Transient numbness of the face (n=1): possibly related Intermittent falls (n=1): not related Chronic widespread pain of the joints and muscles (n=1): not related Chronic diarrhoea (n=1): not related Autonomous reaction (n=1): not related Nausea (n=1): not related Vertebral fracture (thoracic vertebral body 7) associated with pain (n=1): not related Osteopenia (n=1): not related Worsening of PD (n=1): not related Lipoma left arm and chest (n=1): not related Restless legs syndrome (n=1): not related
SAEs (n=2)
Moderate Worsening of PD (n=1): not related **Severe, Life-threatening**

Adenocarcinoma of the rectum (n=1): not related
Safety Follow-Up phase
AEs (n=7)
Mild Restless legs syndrome (n=1): not related Intermittent panic attacks (n=1): not related **Moderate** Pain (n=3): not related (shoulder and knee n=1, diffuse neuropathic pain n=1, lumbar pain n=1) Suspected borreliosis after bite of a tick (n=1): not related Insomnia (n=1): not related
SAEs (n=1)
Severe: Multiple herniated discs lumbar, degenerative changes in lumbar spine (n=1): not related

*Adverse events that started in the titration phase and continued in the open-label phase were noted here.
Abbreviations: OL, open-label; n, number; AE, adverse event; SAE, serious adverse event; PD, Parkinson´s Disease.

Analysis of adverse events

See above

Listing of adverse events by patient

See attached Excel File. Demographic and baseline values of individual patients at the screening visit are also 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.

Patient 12 was a drop-out and is therefore not included in the safety set for analysis as per protocol. This patient experienced a gastroenteritis during the titration phase which was moderate and unrelated to the study drug.

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No participant died during the study. There was no SUSAR during this trial. There were four SAEs reported during the conduct of this trial, all of which were rated “unrelated to the IMP” by the investigators.

- Patient 002 (male, 72 years of age) was hospitalized due to lumbar pain. An MRI of his lumbar spine revealed a herniated disc in the segment 4/5 (Intervertebral disc protrusion). A surgical decompression was performed. At the time of admission to the hospital, the patient had already discontinued the IMP without consultation with the study team because of deterioration of a pre-existing mild cognitive impairment (medical history). The patient was discontinued from the study shortly after discharge (discharge: 26th November 2018; ET visit performed 30th November 2018).
- Patient 003 (male, 75 years of age) experienced a worsening of PD and was hospitalized for implementation of intrajejunal levodopa treatment (pump system) for symptomatic relief. He continued his previous nabilone dose after discharge (8th March 2019).
- Patient 004 (female, 57 years of age) was diagnosed with adenocarcinoma of the rectum in November 2018. She received surgical treatment as well as combined radiochemotherapy thereafter. The SAE was still ongoing but stable after the patient discontinued the study as per protocol.
- Patient 006 (female, 64 years of age) experienced nausea and vomiting after up-titration of levodopa treatment. She was monitored on the neurologic ward of an external hospital from 19th November 2018 to 21st November 2018, which was during the titration phase of this trial. After discharge she continued with titration of nabilone as per protocol.

Copies of the last SAE Follow-up reports to the regulatory authorities are attached to this report (PDF-Files) for further details (text in german). Unfortunately, the PDF-File for patient 003 contains an error: We wrote “männlich” (= male), but she is female (= ”weiblich”).

Safety Conclusions

Overall, nabilone treatment was well tolerated. The most common treatment-related AE was difficulties with concentration, which was resolved in both patients after decrease of nabilone dose, which is in line with information from the SmPC and other controlled trials using nabilone (16). Most AEs were not related to the IMP and not unsurprising for a long-term follow-up study. Interestingly, dizziness and symptoms of OH were not commonly reported by the 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 (17-19). 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 (20-25). 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, 22, 24, 26). Besides symptomatic treatment, preclinical research revealing neuroprotective properties of cannabinoids gains interest in clinicians dealing with patients with movement disorders (6).

The primary endpoint of this study was the assessment of long-term safety of nabilone treatment in PD patients. Overall, nabilone was well tolerated with most AEs being unrelated to the IMP. There was no significant change on the different efficacy variables assessing NMS in PD once patients were on nabilone. The patient´s self-rating, however, indicated a long-lasting improvement (CGI-I). 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 (12-15), which is in line with the post-hoc analysis of this study, when efficacy variables where compared with the timepoint before nabilone was started. This also confirms the results of the double-blind phase of the preceding NMS-Nab study. This study adds to the limited evidence of safety and efficacy of cannabinoid-based treatment in PD patients.

PRINCIPAL OR COORDINATING INVESTIGATOR(S) SIGNATURE(S)

OR SPONSOR'S RESPONSIBLE MEDICAL OFFICER

STUDY TITLE: Nabilone for non-motor symptoms in Parkinson's disease: An open-label study to evaluate long-term safety and efficacy (NMS-Nab2 Study)

STUDY AUTHOR(S): Prof. Dr. Klaus Seppi, Dr. 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: SEPPI **SIGNATURE(S):**

AFFILIATION: MD Medical University Innsbruck, Department of Neurology

DATE: IBK 25- JAN- 2021

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	Original, Protocol Version 1.0 Approved by the EC: 07th February 2018 Non-prohibition by the regulatory authorities: 13th April 2018 (Substantial) Amendment 1: Primary reason for the amendment: The protocol was adapted to reflect changes in EU data protection regulations. A change in the list of prohibited medication was made. Changes in study team members were added. Protocol Version 1.1 Approved by the EC: 25th August 2018 Non-prohibition by the regulatory authorities: 6th September 2018 (Non-Substantial) Amendment 2: Primary reason for the amendment: Changes in study team members. Protocol Version 1.2 Approved by the EC: 27th December 2018 (Non-Substantial) Amendment 3: Primary reason for the amendment: Changes in study team members. Protocol Version 1.3 Approved by the EC: 27th June 2019
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

Study Site
Medical University Innsbruck
Department of Neurology
Anichstraße 35
6020 Innsbruck Austria

Members of the Study Team
(Affiliation for all: MUI Department of Neurology Anichstraße 35 6020 Innsbruck Austria)

Principal Investigator:
Dr. Klaus Seppi

Subinvestigators:
Dr. Werner Poewe (also representative of the Sponsor)
Dr. Atbin Djamshidian-Tehrani
Dr. Marina Peball

Dr. Mario Werkmann
Dr. Beatrice Heim
Dr. Roberto De Marzi
Dr. Philipp Ellmerer
Dr. Federico Carbone
Dr. Kathrin Marini
Dr. Sabine Spielberger
Dr. Olliver Schorr
Dr. Marina Cassazza

Study coordinators and study nurse:
Dora Valent, M.Sc.
Anja Weber, PhD

Sponsor of the Clinical Trial	Medical University of Innsbruck Represented by: O.Univ.-Prof. Dr. Werner Poewe Department of Neurology Anichstraße 35 6020 Innsbruck Austria E-Mail: mui-sponsor@i-med.ac.at Tel.: 0043-512-504-23850 Fax: 0043-512-504-23852
Coordinating Investigator of the Clinical Trial	Prof. Dr. Seppi Klaus Medical University Innsbruck Department of Neurology Anichstraße 35 6020 Innsbruck Austria E-Mail: Klaus.Seppi@tirol-kliniken.at Tel.: 0043-512-504-81498 Fax: 0043-512-504-25819
Author of the Clinical Investigation Plan	Dr. Marina Peball Medical University Innsbruck Department of Neurology Anichstraße 35 6020 Innsbruck Austria E-Mail: Marina.Peball@i-med.ac.at Tel.: 0043-512-504-82718 Fax: 0043-512-504-25819
Manufacturer of the study medication and placebo	AOP Orphan Pharmaceuticals AG Wilhelminenstraße 91/II 1160 Wien Austria Tel.: 0043-1-503 72 44-37
Responsible Contact Person for Drug Safety	Prof. Dr. Prof. Hans-Guenther Knaus Medical University Innsbruck Department for Medical Genetics, Molecular and Clinical Pharmacology Peter-Mayr Strasse 1 A-6020 Innsbruck, Austria Tel.: 0043-512-9003 70440 / 70441 Fax: +43-512-9003 73440 E-mail: hans.g.knaus@i-med.ac.at

Statistics was performed by the Study Team.

Other involved Persons and Institutions

Monitoring	**Katarzyna Wachowicz, PhD** Medical University of Innsbruck Anichstraße 35 6020 Innsbruck Austria Tel.: 0043-512 504 - 25810 Fax: 0043-512 504 - 25819
Datamanagement	**Neurological Study Centre** Medical University of Innsbruck Anichstraße 35 6020 Innsbruck Austria Contactperson: Members of the Study team Tel.: 0043-512 504 - 25810 Fax: 0043-512 504 - 25819

Publications based on the study

None

Documents submitted with this report

Clinical study protocol, version 1.3, dated 04th June 2019 (PDF-File)

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

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

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

Last SAE Follow-Up reports (regulatory authorities, PDF-File)