

# Clinical Study Protocol

<b>Title</b>	Nabilone for non-motor symptoms in Parkinson's disease: A Randomized Placebo-controlled, double-blind, parallel-group, enriched enrolment randomized withdrawal Study
<b>Short Title</b>	The NMS-Nab study
<b>Protocol Version</b>	1.4
<b>Effective</b>	08 <sup>th</sup> June 2018
<b>Phase</b>	Ila
<b>EudraCT No.</b>	2017-000192-86
<b>Original Date of Issue</b>	December 2016
<b>Investigational Medicinal Product:</b>	Nabilone: Synthetic cannabinoid nabilone, other components: Polyvinylpyrrolidone (Povidone) co-precipitate and corn starch  Placebo: corn starch
<b>Route and Dosage Form</b>	nabilone 0.25 - 1 mg or matching placebo, administered orally once or twice daily

## Confidential Material

The information provided in this clinical investigation plan are strictly confidential and will be available for potential investigators, involved investigators and their study team only, as well as for the medical director of the conducting hospital, health authorities and ethics committees to review, verify or implement the clinical trial. Any publication or disclosure to a third party without prior written consent of the Sponsor is expressly prohibited. By signing the clinical investigation plan, the provisions of it are binding for all parties.

# General Information

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

Statistics will be performed by the Study Team.

## Clinical Study Signature Page, Amendment (1/2)

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

**Short Title:** The NMS-Nab Study

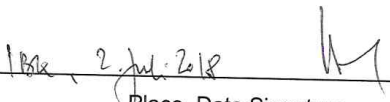
**EudraCT-No.:** 2017-000192-86

**Investigational Medicinal Product:** Nabilone:  
Synthetic cannabinoid nabilone, other components: Povidone pregelatinized starch, yellow iron oxide (E 172) titanium dioxide (E 171), gelatin and Placebo

### Declaration of the Sponsor

The present Clinical Investigation Plan was subject to critical review. Its content is consistent with the current risk/benefit evaluation of the IMP as well as with moral, ethical and scientific principles of Good Clinical Practice, the latest version of the Declaration of Helsinki, the local laws and regulations as well as applicable regulatory requirements.

With the signature below the person confirms to have read this Clinical Investigation Plan and to agree that it contains all information required for study performance. Furthermore, the person agrees to conduct the study as set in this Clinical Investigation Plan and to adhere to the Sponsor's SOPs, if provided and as far as agreed. It has been understood that all documentation previously not published will be kept confidential. Furthermore the person agrees to take all necessary measures to ensure safety and confidentiality of the patient's identities.

O.Univ.-Prof. Dr. Werner Poewe Medical University of Innsbruck Head of the Department of Neurology	 Place, Date Signature
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## Clinical Study Signature Page (2/2)

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Prof. Dr. Seppi Klaus Medical University of Innsbruck Principal Investigator	 IBK, 17. MAR 2017 Place, Date, Signature
Dr. Marina Peball Medical University of Innsbruck Author of the Study Protocol	 IBK, 17. MAR 2017 Place, Date, Signature

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<p>O.Univ.-Prof. Dr. Werner Poewe Medical University of Innsbruck Head of the Department of Neurology</p>	<p> 15/12/2017 Place, Date Signature</p>
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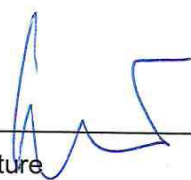
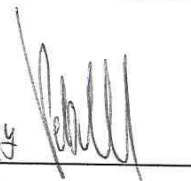
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Prof. Dr. Seppi Klaus Medical University of Innsbruck Principal Investigator	ISK 15.12.2017  Place, Date, Signature
Dr. Marina Peball Medical University of Innsbruck Author of the Study Protocol	INNSBRUCK, 14 - 12 - 2017  Place, Date, Signature

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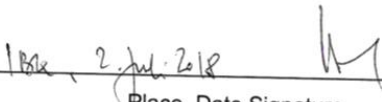
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O.Univ.-Prof. Dr. Werner Poewe Medical University of Innsbruck Head of the Department of Neurology	 Place, Date Signature
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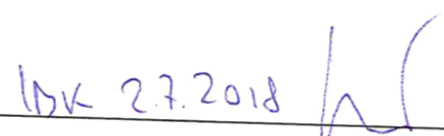
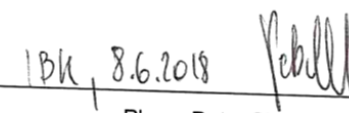
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Prof. Dr. Seppi Klaus Medical University of Innsbruck Principal Investigator	 Place, Date, Signature
Dr. Marina Peball Medical University of Innsbruck Author of the Study Protocol	 Place, Date, Signature



## Study Site and Members of the Study Team

<b>Study Site</b>	<p>Medical University Innsbruck  Department of Neurology  Anichstraße 35  6020 Innsbruck  Austria</p>
<b>Members of the Study Team</b>	<p>Dr. Atbin Djamshidian-Tehrani  Medical University Innsbruck  Department of Neurology  Anichstraße 35  6020 Innsbruck  Austria</p> <p>Dr. Marina Peball  Medical University Innsbruck  Department of Neurology  Anichstraße 35  6020 Innsbruck  Austria</p> <p>Dr. Mario Werkmann  Medical University Innsbruck  Department of Neurology  Anichstraße 35  6020 Innsbruck  Austria</p> <p>Dr. Beatrice Heim  Medical University Innsbruck  Department of Neurology  Anichstraße 35  6020 Innsbruck  Austria</p> <p>Dr. Roberto De Marzi  Medical University Innsbruck  Department of Neurology  Anichstraße 35  6020 Innsbruck  Austria</p> <p>Dr. Sweta Bajaj  Medical University Innsbruck  Department of Neurology  Anichstraße 35  6020 Innsbruck  Austria</p> <p>Dr. Philipp Ellmerer</p>

	<p>Medical University Innsbruck Department of Neurology Anichstraße 35 6020 Innsbruck Austria</p> <p>Dr. Federico Carbone Medical University Innsbruck Department of Neurology Anichstraße 35 6020 Innsbruck Austria</p> <p>Dora Valent, M.Sc. Medical University Innsbruck Department of Neurology Anichstraße 35 6020 Innsbruck Austria</p> <p>Katarzyna Wachowicz, PhD. Medical University Innsbruck Department of Neurology Anichstraße 35 6020 Innsbruck Austria</p> <p>Richard Menegotto Medical University Innsbruck Department of Neurology Anichstraße 35 6020 Innsbruck Austria</p>
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## Additional involved Persons and Institutions

<p><b>Laboratory</b></p>	<p>Laboratory of the Hospital Innsbruck (ZIMCL)  Head: Univ. Prof. Dr. Andrea Griesmacher  Anichstraße 35  6020 Innsbruck  Austria</p> <p><b>Contactperson:</b>  Anna Kirchmayr  E-Mail: <a href="mailto:anna.kirchmayr@tirol-kliniken.at">anna.kirchmayr@tirol-kliniken.at</a>  Tel.: 0043-512 504-24081  Fax: 043-512 504-24088</p>
<p><b>Datamanagement and Monitoring</b></p>	<p><b>OE Clinical Trial Center (OE CTC)</b>  Medical University of Innsbruck  Head: Mag.(FH) Sabine Embacher-Aichhorn  Anichstraße 29-31  6020 Innsbruck  Austria</p> <p><b>Contactperson:</b>  Mag.a (FH) Sabine Embacher-Aichhorn  Tel.: 0043-512 9003-70085  Fax: 0043-512 9003-73086  eMail: <a href="mailto:sabine.embacher@i-med.ac.at">sabine.embacher@i-med.ac.at</a></p>
<p><b>ECG Evaluation</b></p>	<p><b>Cardiologic Outpatient Department</b>  Head: Univ. Prof. Dr. Weiss Günter  Anichstraße 35  6020 Innsbruck  Austria</p> <p><b>Contactperson:</b>  Stefanie Feiss  E-Mail: <a href="mailto:Lki.me.kardio-ambulanz@tirol-kliniken.at">Lki.me.kardio-ambulanz@tirol-kliniken.at</a>  Tel.: 0043-50 504-23268  Fax: 043-50 504-23264</p>

# Protocol Synopsis

<b>Protocol Number:</b>	Version 1.4
<b>Eudract Number:</b>	2017-000192-86
<b>Study Title:</b>	Nabilone for non-motor symptoms in Parkinson's disease: A Randomized Placebo-controlled, double-blind, parallel-group, enriched enrolment randomized withdrawal Study
<b>Number of Centers:</b>	One clinical site (Medical University of Innsbruck)
<b>Clinical Phase:</b>	Ila
<b>Treatment Duration:</b>	Planned start: June 2017 Time of Recruitment: 6 months Titration phase: 2-28 days, 1 – 2 weeks on stable nabilone dose, 4 weeks (+ 2 days) in double-blind parallel-group, enriched enrolment randomized withdrawal phase, dose tapering (individual) and Safety follow-up two weeks after discontinuation from study drug Planned end of the trial: December 2019 (LPLV)
<b>Study Population / Indication:</b>	Subjects with Parkinson's disease (PD)
<b>Study Objective:</b>	To test the clinical effect of nabilone on non-motor symptoms (NMS) in subjects with PD
<b>Study Design:</b>	Placebo-controlled, double-blind, parallel-group, enriched enrolment randomized withdrawal study, in which a screening period is followed by an open-label nabilone dose optimization lasting up to 28 days and at least 1 week on a stable OL nabilone dose. (Part 1)  Eligible subjects, who have signed the informed consent form at the screening visit, will receive open-label nabilone starting with a dosage of 0.25 mg at the evening. During dose titration and optimization, nabilone will be titrated in 0.25 mg increments (increase by 0.25 mg/ every one to four days) 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). During

	<p>titration phase regular two-daily phone calls with the study center will be performed. Dose tapering will be performed according to the investigator's decision. This open-label titration phase will last up to 28 days and will end with a visit on-site (V – 1). Patients should be on a stable nabilone dose for at least 1 week afterwards until Baseline Visit (V 0).</p> <p>During optimization, doses will be adjusted upward in 0.25 mg one to four-daily increments until the patient</p> <ul style="list-style-type: none"> <li>• has reached a rating of “1” (i.e. very much improved) or “2” (i.e. much improved) on the 7-point Clinical Global Impression of Improvement (CGI-I; i.e. a 7 point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline with the following ratings: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse) [i.e. criterion 1]; or</li> <li>• experiences intolerable side effects believed to be related to study medication [i.e. criterion 2]; or</li> <li>• reaches the maximum permitted dosage of 1 mg twice daily [i.e. criterion 3].</li> </ul> <p>Patients who meet</p> <ul style="list-style-type: none"> <li>• criterion 1 will enter into the 1 weeks OL treatment period at that dose.</li> <li>• criterion 2 will proceed to the 1 week OL treatment period at the previous lower dose, providing they will meet the definition of a responder at that dose.</li> <li>• criterion 3 and were a responder will enter the study at 1 mg twice daily.</li> </ul> <p>Patients are discontinued after dose optimization phase</p> <ul style="list-style-type: none"> <li>• if they meet criterion 2 but did not meet the responder definition at the previous dose,</li> <li>• if they meet criterion 2 at the initial dose of 0.25 mg once daily,</li> <li>• or if they meet criterion 3 but did not meet the definition of a responder.</li> </ul> <p>Responders are then randomized in a 1:1 ratio at Baseline Visit to receive either nabilone or matching placebo for 4 weeks + 2 days (Part 2). During the first week of the double-blind withdrawal phase regular phone calls will be held every other day.</p> <p>After 4 weeks of the placebo-controlled, double-blind, randomized withdrawal phase, patients will be invited to the clinic for a Termination Visit (V 1). Following this, nabilone will be tapered in</p>
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	<p>all patients in 0.25 mg two-daily decrements. During this period the patients will receive phone calls every other day. A Safety Telephone Call and a Safety Follow-Up Visit will be executed 5 days <math>\pm</math> 2 days and 2 weeks + 2 days after the last intake of study drug.</p>
<b>Assessments:</b>	<p>Subjects will be evaluated at the clinic site by the investigator at the screening visit, at weeks -1 (end of optimization phase, start of open label nabilone at a fixed dose ranging between 0.25 mg once daily up to 1 mg twice daily), 0 (V 0, baseline of randomized withdrawal phase), 4 (termination visit/ V 1). A Safety Phone Call and a Safety Follow-Up Visit will be performed 5 days <math>\pm</math> 2 days and 2 weeks + 2 days after the end of the last intake of nabilone, respectively.</p> <p>Study visits will include the following assessments:</p> <ul style="list-style-type: none"> <li>• Movement Disorder Society (MDS)-sponsored new version of the UPDRS (MDS-UPDRS) (all visits including screening)</li> <li>• Non-Motor Symptoms Scale (NMSS) (all visits except for V -1)</li> <li>• Hospital Anxiety and Depression Scale (HADS) (all visits except for V -1)</li> <li>• 39-Item Parkinson's Disease Questionnaire (PDQ-39) (all visits except for V -1)</li> <li>• Montreal Cognitive Assessment Scale (MoCA) (all visits except for V -1)</li> <li>• Epworth Sleepiness Scale (ESS) (all visits except for V -1)</li> <li>• Visual Analog Scale (VAS) of Pain (all visits except for V -1)</li> <li>• King's Parkinson's disease pain scale (KPPS) (all visits except for V -1)</li> <li>• Fatigue Severity Scale (FSS) (all visits except for V -1)</li> <li>• Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale (QUIP-RS) (all visits except for V -1)</li> <li>• Columbia Suicide Severity Rating scale (C-SSRS) (all visits)</li> <li>• CGI-I (V -1, V 0, V 1, and Safety Follow-Up Visit only)</li> <li>• Vital signs (all visits including screening)</li> <li>• Concomitant medications (all visits including screening)</li> <li>• Adverse Events (all visits including screening)</li> <li>• Physical examination (screening, V 0, V 1, and Safety Follow-Up Visit only)</li> <li>• Local ECG and Clinical Laboratory tests ((pre-)screening and V 1 only)</li> <li>• Measurement of Eye-Movements with a Tobii TX300 Eye-Tracker (Screening Visit, Termination Visit)</li> </ul>

	<p>Subjects will undergo two-daily phone visits during the titration phase, the first week of the parallel-group, enriched enrolment randomized withdrawal study, and the tapering phase. These will include the following:</p> <ul style="list-style-type: none"> <li>• Concomitant medications use</li> <li>• Adverse Events</li> <li>• CGI-I</li> <li>• Hallucination item (1.2) of Movement Disorders Society – Unified Parkinson’s Disease Rating Scale (MDS-UPDRS)</li> <li>• Orthostatic hypotension (OH) item (1.12) of Movement Disorders Society – Unified Parkinson’s Disease Rating Scale (MDS-UPDRS)</li> <li>• Day-time sleepiness item (1.8) of Movement Disorders Society – Unified Parkinson’s Disease Rating Scale (MDS-UPDRS)</li> <li>• Columbia Suicide Severity Rating scale (C-SSRS)</li> </ul> <p><u>Concomitant medications:</u></p> <p>Anti-parkinsonian treatment:</p> <p>All anti-parkinsonian medications will be permitted during the study. However, no changes to medications or dosage will be allowed during this trial.</p>
<b>Number of subjects:</b>	48 Patients are planned to be included
<b>Inclusion/ Exclusion criteria:</b>	<p>Subjects must meet all inclusion criteria in order to be eligible for the study:</p> <p><i>Inclusion criteria:</i></p> <ol style="list-style-type: none"> <li>1. age <math>\geq 30</math> years</li> <li>2. diagnosis of PD (de novo or on stable medication without disturbing motor fluctuations or dyskinesia)</li> <li>3. NMS with a score of <math>\geq 4</math> on MDS-UPDRS Part 1. One of the following domains have to be affected with a score <math>\geq 2</math>: 1.4 (anxious mood) or 1.9 (pain)</li> <li>4. On a stable regimen of anti-parkinson medications for at least 30 days prior to screening and willing to continue the same doses and regimens during study participation</li> <li>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</li> <li>6. Signed a current IRB-approved informed consent form</li> <li>7. Acceptable method of contraception</li> </ol> <p>Any of the following conditions will exclude the subject from</p>

	<p>entering the study:</p> <p><i>Exclusion criteria:</i></p> <ol style="list-style-type: none"> <li>1. Previous participation in any study with nabilone</li> <li>2. current use of cannabinoids or use within 30 days prior to screening</li> <li>3. current or recent (within 30 days prior to screening) participation in another study with an investigational medicinal product</li> <li>4. atypical or secondary parkinsonism</li> <li>5. presence of motor complications if, based on the investigator's judgment, not adequately controlled (i.e. a score <math>\geq 2</math> on one of the items of the MDS-UPDRS Part IV at screening)</li> <li>6. Hoehn and Yahr stage ON &gt; 3</li> <li>7. Evidence of disturbing impulse control disorder</li> <li>8. History of neurosurgical intervention for PD</li> <li>9. Presence of clinically significant symptomatic orthostatic hypotension at screening (MDS-UPDRS 1.12 &gt; 2)</li> <li>10. Use of prohibited medication listed in 7.4.2</li> <li>11. Laboratory values clinically significant out-of-range at screening or within 4 weeks prior to screening</li> <li>12. Known or diagnosed sinus tachycardia in ECG evaluation at screening or within 4 weeks prior to screening</li> <li>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 &gt; 2)</li> <li>14. recent suicidal attempt within the past five years or suicidal ideation within the past 6 months</li> <li>15. presence of dementia (MDS-UPDRS 1.1 &gt; 2, MMSE of &lt; 24 at screening)</li> <li>16. clinically significant or unstable medical or surgical condition that may preclude safe and complete study participation (based on the investigator's judgment).</li> <li>17. moderate or severe hepatic or renal impairment.</li> <li>18. History of chronic alcohol or drug abuse within the last 2 years</li> <li>19. women of child-bearing potential who do not practice an acceptable method of birth control [*Acceptable methods of birth control for women and men in this study are: surgical sterilization (e.g. tubal ligation for females), intrauterine devices that release hormones (hormone spiral), oral hormonal contraceptive, contraceptive patch, dermal hormonal contraception, vaginal hormonal contraception (NuvaRing®), implants that release progesterone (Implanon®), long-acting injectable contraceptive, partner's vasectomy, a double-protection method, postmenopausal (&gt; 2 year absence of vaginal bleeding).]</li> <li>20. Pregnant women, or women planning to become pregnant during the course of the study, or nursing women.</li> <li>21. Known hypersensitivity to any components of the IMP</li> </ol>
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	<p>or excipients</p> <p>22. Patient is legally incapacitated or persons held in an institution by legal or official order</p> <p>23. Persons with any kind of dependency on the investigator or employed by the Sponsor or investigator</p>
<b>Route and Dosage Form:</b>	nabilone 0.25 – 1 mg or matching placebo, administered orally once or twice daily
<b>Endpoints</b>	<p><b>Primary efficacy endpoint:</b></p> <ul style="list-style-type: none"> <li>• Change from baseline to Week 4/Termination Visit in the MDS-UPDRS Part I (non-motor Experiences of daily living; nmEDL)</li> </ul> <p><b>Key Secondary efficacy endpoints:</b></p> <ul style="list-style-type: none"> <li>• Change from baseline to Week 4/Termination visit in the following assessments:</li> <li>• NMSS</li> <li>• total MDS-UPDRS (i.e. Part II + III + IV)</li> <li>• different domains of NMSS and MDS-UPDRS Part I</li> <li>• HADS</li> <li>• PDQ-39</li> <li>• MoCA</li> <li>• ESS, FSS</li> <li>• VAS of Pain</li> <li>• KPPS</li> <li>• QUIP-RS</li> <li>• CGI-I scale at termination visit</li> </ul> <p><b>Safety and tolerability endpoints:</b></p> <p>Safety and tolerability will be evaluated with reference to the following:</p> <ul style="list-style-type: none"> <li>• Tolerability</li> <li>• Number of subjects (%) who discontinue the study</li> <li>• Number of subjects (%) who discontinue the study due to AE</li> <li>• Safety Measures</li> <li>• Adverse Events (AE)</li> <li>• Clinical and laboratory assessments</li> <li>• Vital signs</li> <li>• ECG</li> <li>• Subjects compliance, prior and concomitant medication use</li> <li>• Hallucination item (1.2) of Movement Disorders Society – Unified Parkinson’s Disease Rating Scale (MDS-UPDRS)</li> <li>• Orthostatic hypotension (OH) item (1.12) of Movement Disorders Society – Unified Parkinson’s Disease Rating Scale (MDS-UPDRS)</li> <li>• Day-time sleepiness item (1.8) of Movement</li> </ul>

	<p>Disorders Society – Unified Parkinson’s Disease Rating Scale (MDS-UPDRS)</p> <ul style="list-style-type: none"> <li>• C-SSRS</li> </ul> <p><b>Exploratory endpoints:</b></p> <ul style="list-style-type: none"> <li>• Change in reaction time, attention span, and concentrativeness as measured by the Eye-tracking examination</li> </ul>
<p><b>Statistical Considerations:</b></p>	<p><b>Sample size calculation</b></p> <p>A total of 38 patients (19 patients per group) will provide 80% power at two-sided 5% significance level to detect a statistically significant difference in the change from baseline to Week 4/Termination visit in MDS-UPDRS Part I score between nabilone and placebo assuming a true difference of 2.5 points. This sample size calculation assumes a standard deviation of the change from randomization to week 4 to be 2.4 points. (46) With a drop- out quote of 25 % we will include 48 patients in the trial.</p> <p>The sample size calculation was performed with the Program nQuery Advisor (Version 7).</p> <p>Importantly, although a sample size calculation is provided, this is an exploratory study evaluating different NMS domains. Therefore, corrections for multiple comparisons are not planned.</p> <p><b>Endpoints</b></p> <p>Results of the changes of all clinical scales in this trial will be shown in a descriptive way by median and interquartile range (quartile 1, quartile 3), separately for the nabilone and placebo of the clinical trial. Mean and standard deviation for the descriptive analysis of the two study arms will also be provided. P-values for the change of the results will be given.</p> <p>The primary and key secondary efficacy criteria refer to the double-blind placebo-controlled enriched enrolment randomized withdrawal phase of the study. The primary efficacy criterion will be measured as the change of the MDS-UPDRS Part I between baseline and week 4. The key secondary efficacy criteria will be measured as the change in the other assessments between baseline and week 4. Because an interpolation of data will not be performed in case of a drop-out, the primary analysis is a per-</p>



	<p>protocol analysis. All statistical tests will be performed with a two-sided alpha risk of 0.05.</p> <p>For the study's primary efficacy and key secondary efficacy analyses, mean changes from randomization to 4-week follow-up in the nabilone and placebo groups will be analyzed separately for the two groups by Wilcoxon matched-pairs test and then compared by Mann-Whitney U Test. <b>(49)</b> The data set for this analysis will include patients with measurements for the score at V0 and V1.</p> <p>Additionally, a sensitivity analysis will be performed for a primary efficacy or key secondary efficacy variable, if mean value of an efficacy variable should be different at randomization at a 2-sided 10% level (using Mann-Whitney U tests). To estimate the treatment effect, we will then compare mean change from randomization to 4 weeks-follow-up in both treatment groups using analysis of covariance, with value at randomization as covariate and treatment group as main effect.</p> <p>Moreover, sensitivity to treatment will be assessed using effect sizes of the different outcome variables when using nabilone to treat non-motor symptoms in Parkinson's disease.</p> <p>For CGI-I analyses, distributions of aggregated ratings (amelioration, aggravation) in the nabilone and placebo groups at 4-week's- Termination Visit will be compared by Fisher exact test. <b>(49)</b></p> <p>The primary safety analysis will be performed with the safety data set. Distributions of AEs, SAEs, and SUSARs in the nabilone and placebo groups at week 4 will be compared by Fisher exact test.</p> <p>Additionally, a safety analysis will be 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 and provided separately for the nabilone and placebo group.</p> <p>This will be a descriptive analysis reporting overall number, frequencies, and percentage of AEs, SAEs, and SUSARs in patients taking nabilone, patients withdrawn from the study, and patients withdrawn due to an AE.</p> <p>Separate summaries of AEs in regard of severity and relationship</p>
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	<p>to the study drug, separate summaries of AEs leading to withdrawal from the study and separate summaries for SAEs will be provided.</p> <p>For the Eye-tracking analyses, mean changes from Screening Visit to the Termination Visit in the nabilone and placebo groups will be analyzed separately for the two groups by Wilcoxon matched-pairs test and then compared by Mann-Whitney U Test.</p>
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## List of Abbreviations

2-AG	2-arachidonoyl glycerol
ADR	Adverse Drug Reaction
AE	An adverse event is “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment”. (47)
AMG	“Arzneimittelgesetz” = Medicines Act in Austria
Anandamide	Arachidonoyl ethanolamide
BID	“bis in die” (Latin), twice daily
CA	competent authority
cAMP	cyclic adenosine monophosphate
CB1 receptor	cannabinoid 1 receptor
CB2 receptor	cannabinoid 2 receptor
CBD	Cannabidiol
CGI-I	Clinical Global Impression – Global Improvement
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating scale
Directive 2001/20/EC	Directive 2001/20 der European Commission
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
DSUR	Development Safety Update Report
ECG	electrocardiogram
ECS	endocannabinoid system
ESS	Epworth Sleepiness Scale
ET	Early Termination Visit
EU	European Union
EudraCT	European Clinical Trials Database
FAAH	fatty acid amide hydrolysis
FSS	Fatigue Severity Scale
GCP	Good Clinical Practice
GPR55	GTP-binding protein-coupled receptor 55
HADS	Hospital Anxiety and Depression Scale
HEENT examination	Examination of the head, eyes, ears, nose, throat
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation

IEC/IRB	Independent ethics committee/ Institutional review board
IMP	Investigational medicinal product
IND	Investigational New Drug
ISF	Investigator Site File
KPPS	King's Parkinson's disease pain scale
LD/CD Treatment	Levodopa / Carbidopa Treatment
LID	Levodopa-induced Dyskinesia
LPLV	Last Patient Last Visit
MDS	Movement Disorder Society
mg	Milligramme
mm	Millimetre
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment Scale
MS	Motor symptoms
NMS	Non-motor symptoms
NMSS	Non-Motor Symptoms Scale
OFF state	the phase with no response to medication and significant motor symptoms
OH	orthostatic hypotension
OL	open-label
ON state	period when the patient notices a benefit on MS from standard oral LD/CD treatment
PD	Parkinson's disease
PDQ-39	39-Item Parkinson's Disease Questionnaire
PPAR	peroxisome proliferator-activated receptor
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease– Rating Scale
RBD	REM Sleep Behavior Disorder
RCT	randomized controlled trials
REM	rapid eye movement
RNA	Ribonucleic acid
SAE	“A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect”. (47)
SOP	Standard Operating Procedures
SUSARs	A SUSAR is an event that is believed to be causal to the to the

administration of the study drug and is severe and unexpected.

TMF	Trial Master File
TC	Telephone Call
TC – S	Safety Telephone Call
TRPV1	transient receptor potential vanilloid type 1 cation channel
UPDRS	Unified Parkinson Disease Rating Scale
V	Visit
V – S	Safety Follow-Up Visit
VAS of Pain	Visual Analog Scale of Pain
$\Delta^9$ -THC	$\Delta^9$ – tetrahydrocannabinol



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# 1 Background and Rationale

## 1.1 The endocannabinoid system

The endocannabinoid system (ECS) has become a center of attention for its (neuro)modulatory effects in the last 25 years and has become a potential target of drug therapy for a variety of illnesses. The ECS plays an important role in many physiological body functions and influences mood, motor control, cognition, eating behavior, and nociception. Therefore, indications like neuropathic pain, anorexia, and spasticity associated with multiple sclerosis or spinal trauma, as well as chemotherapy-induced emesis can now be treated with cannabinoids like nabilone, dronabinol, sativex, and epidiolex. [12,31,32]

The two main cannabis species *sativa* and *indica* have been the ancestors of almost all strains that exist today and from which more than 60 pharmacologically active components derive. The main psychoactive compound of *Cannabis sativa* is  $\Delta^9$  – tetrahydrocannabinol ( $\Delta^9$ -THC), which has a stronger euphoric potential than isolated components of *Cannabis indica* that have more sedative, analgesic, and antiemetic effects. [1,12]

The ECS summarizes endogenous cannabinoids (endocannabinoids), cannabinoid receptors and their synthesis, and degradation enzymes.

Endocannabinoids are endogenous lipids and ligands to cannabinoid receptors. Arachidonoyl ethanolamide (anandamide) and 2-arachidonoyl glycerol (2-AG) have been the first discovered and therefore best known endogenous cannabinoids out of a large group of molecules binding to the endocannabinoid receptors. Endocannabinoids are not stored in vesicles like other neurotransmitters. They show a release on-demand into the extracellular space mainly through retrograde signaling after postsynaptic activation with the duty to decrease presynaptic neurotransmission. After their local and short-lasting task is fulfilled endocannabinoids are taken up by surrounding cells and degraded mainly by fatty acid amide hydrolysis (FAAH) for anandamide and by monoacylglycerol lipase for 2-AG. [2,12,32]

The endocannabinoid receptors, named CB1 and CB2, are G-protein coupled, seven-transmembrane domain receptors of the Gi and Go classes. Both are activated mainly by cannabinoids and their synthetic analogues, eicosanoids or aminoalkylindoles as well as by a large number of synthesized agonists, inverse agonists, antagonists and allosteric modulators. [1] Activation of these receptors inhibits adenylate cyclases and subsequently increases the intracellular amount of cyclic adenosine monophosphate (cAMP), resulting in alteration of the level of activity in voltage- dependent calcium channels and potassium channels and an activation of several mitogen-activated protein kinases. [3]

The CB1 cannabinoid receptor is referred to as the „brain cannabinoid receptor“ due to its numerous occurrence in all brain structures. Particularly, the Cortex, Basal Ganglia, Hippocampus and Cerebellum present with a high density of CB1 receptor. Combining all its effects, the CB1 receptor aids in the control of cell survival, differentiation and proliferation, and several cell functions. Through retrograde activation the duration of synaptic activation, synaptic plasticity, and neurotransmitter release is influenced. [1,4,32]

Moreover, non-neuronal cells of the brain, astrocytes in particular, express the CB1 receptor in a large amount and its activation through glutamate release leads to an activation of presynaptic metabotropic glutamate receptor. [5]

The occurrence of the CB1 receptor is not limited to the brain, but also appears in the peripheral nervous system and other mammal tissues and organs, where it aids in maintaining homeostasis. [1]

The CB2 receptor is of little homology to the CB1 receptor but shows similar ways of activation through Gi/o. It is expressed mostly in cells and organs playing a role in the body's immune system where its activation reduces the liberation of pro-inflammatory response (cytokines, lymphoangiogenic factors). [6] CB2 receptors are also expressed in the gastrointestinal tract and in microglia and vascular cells of the brain as well as in the dorsal vagal motor nucleus, the nucleus ambiguus and the spinal trigeminal nucleus. CB2 receptor activation may contribute to affective behavior but its concrete role in the brain is not defined yet. In the gastrointestinal tract effects on food intake, gastrointestinal motility, gastric secretion and gastroprotection, cell proliferation, and intestinal inflammatory processes are discussed. [7]

In 2003 the U.S. Health and Human Services granted U.S. Patent 6630507 which describes the use of components extracted from Cannabis sativa as useful in neuroprotective disorders like PD, Alzheimer's disease, and HIV- induced dementia. [33] Neuroprotective potential of cannabinoids is believed to be due to receptor- induced but also – independent mechanisms and specific effects of several endocannabinoids and synthetic agents, like THC, CBD, cannabitol, CP55,940, and AM404 (an anandamide analog). [12] In preclinical experiments, cannabinoids have the ability to counteract reactive oxygen species and strengthen endogenous antioxidants and thereby prevent oxidative stress on neuronal cells by reducing microglial and proinflammatory activation through agonistic action of the CB2 receptor system as well as by reducing glutamatergic excitotoxicity. [34, 12]

Moreover, there exist other receptors where several endocannabinoids like anandamide can bind to under certain circumstances, like the transient receptor potential vanilloid type 1 (TRPV1) cation channel, the peroxisome proliferator-activated receptor (PPAR), the

abnormal-CBD receptor and the GTP-binding protein-coupled receptor (GPR)55 that possibly influence the clinic of movement disorders. [1,12]

**Nabilone** is an analogue of dronabinol (THC), the psychoactive component of cannabis, but it is not derived from the cannabis plant in contrast to dronabinol. 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. In Austria, nabilone is licensed for the use as an antiemetic for chemotherapy-induced nausea and vomiting not responding to conventional antiemetic treatment. The FDA approved nabilone for treating anorexia and weight loss in patients with AIDS. Nabilone is widely used as an adjunct therapy for chronic pain management, although it is only officially approved for this use in Mexico.

Nabilone is a racemate consisting of the (S,S) and the (R,R) isomers ("trans") with an average weight of 372.5408 Dalton. After oral administration 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.

The chemical formula of nabilone is:  $C_{24}H_{36}O_3$ .

## 1.2 Non-motor symptoms in Parkinson's Disease

Parkinson's Disease (PD) is a neurodegenerative disorder that occurs with a prevalence of 1,6/1000 in both males and females equally in all geographical areas. It is less common in Asia than in Europe, Africa, North America, South America, or Australia and its prevalence is increasing with age (1% in 60 years old people, 3% at the age of 80 years). The mean age of onset is 55 years (17 – 80 years).

Although PD is generally considered a paradigmatic movement disorder, it has long been recognized that the neuropathology underlying PD involves many brain areas that are not directly involved in motor control. [14,15] It is therefore not surprising that a majority, if not all, PD patients suffer from non-motor symptoms adding to the overall burden of parkinsonian morbidity. [16,17,18] In this trial, male and female PD patients without disturbing motor fluctuations or dyskinesia over the age of 30 years suffering from non-motor symptoms (measured on the basis of UPDRS Part I, including at least anxiety or pain) will be included.

Non-motor symptoms in PD involve a multitude of functions including disorders of sleep-wake cycle regulation, cognitive dysfunction, disorders of mood and affect, autonomic dysfunction as well as sensory symptoms and pain. They become increasingly prevalent and obvious over the course of the illness and are a major determinant of quality of life, progression of overall disability, and of nursing home placement in PD. [19]

Common non-motor symptoms in late stage PD include hallucinations, dementia, and autonomic dysfunction including urinary incontinence, constipation, and symptomatic



orthostatic hypotension. In PD patients who have had 20 years of disease duration, dementia occurs in 83%, hallucinosis in 74%, symptomatic OH in 48%, constipation requiring daily laxatives in 40% and urinary incontinence in 71%. [18]

Moreover, certain non-motor symptoms such as constipation, olfactory loss, anxiety, depression, and RBD may antedate the onset of classical motor symptoms by years or even decades. [20,21,22,23,24,25,26]

Unlike most motor features of PD, NMS often have limited treatment options or response. [13] Although common, there is a paucity of research concerning the diagnosis and treatment of non-motor symptoms in PD. Indeed, non-motor symptoms in PD are frequently missed or undeclared during routine consultations and well-performed large-scale RCTs for the treatment of the different non-motor symptoms in PD are lacking. [27,28]

However, a variety of treatments are available, and for some patients, these treatments can effectively control or improve disability from non-motor symptoms, such as psychiatric symptoms, sleep disorders, autonomic dysfunction, and fatigue (see Table 1).

Table 1: Drug classes for non-motor symptoms in PD

<b>NON-MOTOR SYMPTOMS</b>	<b>DRUG CLASS (NAME)</b>
<b>Disorders of sleep and wakefulness</b>	
REM Sleep behavioural disorder	Benzodiazepine (Clonazepam), hormones (Melatonin)
<b>Autonomic dysfunction</b>	
Constipation	Osmotic laxative (Polyethylene Glycol), Chloride channel activator (Lubiprostone)
Gastrointestinal motility	Peripheral dopamine antagonist (Domperidone)
Orthostatic hypotension	Peripheral dopamine antagonist (Domperidone), mineralcorticoid (Fludrocortisone), vasopressor (Midodrine), acetylcholinesterase inhibitor (Pyridostigmine), Norepinephrine prodrug (Droxidopa)
Sialorrhoea	Anticholinergic (Atropine drops, Glycopyrrrolate), Neurotoxin (Botulinum toxin A, Botulinum toxin B)
<b>Cognitive impairment</b>	
Dementia	Acetylcholinesterase inhibitor (Rivastigmine)
<b>Psychiatric symptoms</b>	
Depression	Dopamine agonist (Pramipexole), serotonin reuptake inhibitor / serotonin and norepinephrine reuptake inhibitor (Citalopram, Escitalopram, Fluoxetine, Paroxetine, Sertraline, Venlafaxine extended release), Tricyclic antidepressant (Desipramine, Nortriptyline)
Psychosis	Atypical antipsychotic (Clozapine, Quetiapine), Acetylcholinesterase inhibitor (Rivastigmine)
<b>Other</b>	Fatigue (Stimulant Methylphenidate, Modafinil)

### **1.3 Preclinical Research in Parkinson's disease**

The endocannabinoid system (ECS) functions as a regulator of dopamine release and uptake. Inversely, changes of dopamine levels in the brain can alter the ECS. [9,10] To date the hypothesis is that endocannabinoids are a compensational mechanism to the loss of dopamine in patients with PD. [1,12] A reduction of CB1 receptors has been shown in post mortem analyses of the caudate nucleus, anterior dorsal putamen and external segment of the globus pallidus in comparison to normal levels to the rest of the brain. This might be related to an overactive endocannabinoid system with increased CB1 receptor activity, messenger RNA levels and levels of endocannabinoids in the basal ganglia which has been described in animal models. It is believed that these findings play a role in motor symptoms of patients with PD and can be influenced by Levodopa therapy. [1,11,30] Moreover, neuroprotective properties of cannabinoids in preclinical experiments are gaining more and more attention for clinicians dealing with patients with movement disorders. These effects are mainly due to antioxidant mechanisms, microglial inhibition and modulation of cell-cell interaction of glia cells and neuronal cells in the basal ganglia. [1,11,30]

Indeed, activated microglia have been found in lesions of neurodegeneration in the substantia nigra of deceased patients with PD in comparison to healthy person. Moreover, a decrease of microglial activation is the reason why CB2 receptor agonists have shown to reduce inflammation and degeneration of dopaminergic neurons in PD. [1,11,30] Interestingly, Barrero et. al discovered that polymorphisms in the cannabinoid receptor gene influence depressive mood in patients with PD. [35]

### **1.4 Therapeutic potential of Cannabinoids in Parkinson's Disease**

The endocannabinoid system takes part in building emotions, motor control, attention and concentration, the sensation of pain, and eating. [12,31,32]

Evidence of effects of cannabinoids on symptoms in PD from clinical trials is scarce. Most of these trials are either small-sized with less than 20 patients included [12,40,42] or uncontrolled [12,36,37,38,39].

Improvement of motor and non-motor symptoms in PD after intake of cannabinoids has been described in several uncontrolled observational studies with ameliorated rest tremor, bradykinesia, rigidity, and Levodopa-induced Dyskinesia (LID) as well as improved pain, psychosis, symptoms of RBD, and sleep-quality. These effects could not be reproduced by randomized controlled trial (RCTs), which were small-sized and used different cannabinoids.

Thus, while a randomized, double-blind, placebo-controlled crossover trial in 7 PD patients suggested improvement of Levodopa-induced Dyskinesia (LID) with the synthetic cannabinoid nabilone (0.03mg/kg nabilone per day) [42], another randomized, double-blind, placebo-controlled crossover trial in 19 PD patients found no effects on LID with an oral cannabis extract (40). Interestingly the same study did not show any effects on QoL (40), while another parallel-group randomized controlled trial (RCT) [43] in 21 PD patients treated with placebo, cannabidiol (CBD) 75 mg/day or CBD 300 mg/day reported improved QoL in patients using CBD 300 mg/day and placebo. The same study showed no difference in the mean total UPDRS scores of patients with placebo and CBD in different dose regimens. Overall, there is no conclusive evidence from RCT on the symptomatic treatment of motor symptoms in PD. [12,40, 43, 42]

Cannabinoids were well tolerated in all of these trials. No serious adverse events were recorded. The most common side effects from the RCTs have been the feeling of dizziness in up to 10% of patients, mild hypotension in up to 90% of patients, deterioration or new-onset change of perception (hallucinations, the feeling to be detached, confusion), and somnolence in up to 47% of patients. [40,42, 43] In one RCT two patients withdrew from the study due to vertigo and postural hypotension resulting from receiving nabilone but this was not consistent with other RCTs which included a greater sample size and documented no withdrawals due to side effects of cannabinoids.

Due to the overall impact of NMS in PD and based on the influence of the endocannabinoid system on NMS in broad manner in PD, we decided to perform a proof of concept study to test nabilone for the treatment of NMS in PD.

We hypothesize that because of the described effects of the endocannabinoid system, nabilone will improve non-motor symptoms in patients with PD. This therapy should be well tolerated by contrast to some of the drug classes used in standard medical care and can therefore be an ethically justified additional treatment option for symptoms not concerning motor control of PD. If the treatment shows to be effective, the use of nabilone in health care practice can be supported by the data from this study.

## **2 Objectives and Endpoints**

### **2.1 Objectives**

#### **2.1.1 Primary Efficacy Objective**

The primary efficacy objective of this study is to demonstrate the efficacy of nabilone concerning non-motor symptoms of patients with Parkinson's disease, based on the change from baseline to Week 4/Termination visit in the MDS-UPDRS Part I.

#### **2.1.2 Key Secondary Efficacy Objectives**

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

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

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

#### **2.1.3 Safety Objectives**

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

##### **1. Tolerability**

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

##### **2. Safety Measures**

- Adverse Events (AE), Serious Adverse Events (SAEs)
- Clinical and laboratory assessments

- Vital signs including performance of active orthostatism (measurement of heart rate and blood pressure after 10 minutes of quiet rest in the supine position and at 1, 2, 3, 5, and 10 minutes of active standing)
- ECG
- Patient's 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 Movement Disorders Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS)
- Day-time sleepiness item (1.8) of Movement Disorders Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS)
- Columbia Suicide Severity Rating scale (C-SSRS)

### **2.1.4 Exploratory Objective**

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

- Change of the reaction time, attention span, and concentrativeness between Screening and Termination Visit as measured by the Eye-tracking examination.

## **2.2 Efficacy Endpoints**

### **2.2.1 Primary Efficacy Endpoint**

The primary efficacy endpoint will be measured as the change of the MDS-UPDRS Part I between baseline and week 4.

### **2.2.2 Key Secondary Efficacy Endpoints**

The change in the other assessments listed above between baseline and week 4 will be the key secondary efficacy criteria, as well as the CGI-I at Termination Visit.

### **2.2.3 Safety Endpoints**

The safety and tolerability of nabilone will be evaluated in this study using the measures described in 2.1.3. between Baseline and Week 4.

### **2.2.4 Exploratory Endpoints**

The change of the reaction time, attention span, and concentrativeness between Screening and Termination Visit as measured by the Eye-tracking examination will be an exploratory endpoint. Because of potential of habituation of the Eye-tracking measurements, we will only these measures at Screening and Termination Visit.

## 3 Study Design

### 3.1 Study Description

This is a mono-centric Phase IIa, placebo-controlled, double-blind, parallel-group, enriched enrolment randomized withdrawal study in patients with Parkinson's disease includes a screening period, followed by an open-label nabilone dose optimization period (Phase 1) and a placebo-controlled, double-blind, parallel-group randomized withdrawal phase (Phase 2).

After providing written informed consent, patients will undergo screening evaluations. Patients must meet all inclusion criteria and none of the exclusion criteria. Eligible subjects, who have signed the informed consent form, will receive open-label nabilone starting with a dosage of 0.25 mg in the evening after the Screening Visit. During dose titration period, nabilone will be titrated in 0.25 mg increments one- to four-daily until a maximum dosage of 1 mg twice daily. Dose tapering will be performed according to the investigator's decision. The dose increments will be hold as follows:

1. 0.25mg 0-0-1;
2. 0.25mg 1-0-1;
3. 0.25mg 1-0-2;
4. 0.25mg 2-0-2;
5. 0.25mg 2-0-3;
6. 0.25mg 3-0-3;
7. 0.25mg 3-0-4;
8. 0.25mg 4-0-4.

Regular **phone calls** with the study center will be performed every other day during titration phase. These will include the following:

1. Concomitant medications use, 2. Adverse Events, 3. CGI-I, 4. Hallucination item (1.2), Orthostatic hypotension (OH) item (1.12), Day-time sleepiness item (1.8) of MDS-UPDRS 5. C-SSRS

The open-label titration phase will last up to 28 days and ends with an on-site visit (V -1).

Afterwards, patients should be on a stable nabilone dosage for at least 1 week before randomization.

Dose adjustments during titration phase will be performed until the patient:

1. has much (CGI-I Rating Scale: 2) or very much (CGI-I Rating Scale: 1) improved NMS on the 7-point Clinical Global Impression of Improvement Scale.
2. experiences intolerable side effects believed to be related to the study medication or;
3. reaches the maximum permitted dosage of 1 mg twice daily.

Criterion 1 defines responders. Patients who meet this criterion will enter into the 4-weeks treatment period at the last prescribed dose. Patients who meet criterion 2 will proceed to the 4-weeks treatment period at the previous lower dose, providing they will meet the definition of a responder at that dose. Patients who meet criterion 3 and were responder will enter the study at 1 mg twice daily.

Patients are discontinued after dose optimization phase if they meet criteria number 2 but did not meet the responder definition at the previous dose, if they meet criteria 2 at the initial dose of 0.25 mg once daily, or if they meet criteria 3 but did not meet the definition of a responder.

After at least 1-week of stable nabilone dosage, responders are randomized in a 1:1 ratio at the Baseline Visit to receive either nabilone at the dosage reached during the titration phase or matching placebo for 4 weeks + 2 days (Part 2). During the first week of the double-blind placebo-controlled parallel-group enriched enrolment randomized withdrawal phase regular phone calls will be held every other day. During the open-label treatment period, dose adjustments can be performed if CGI-I deteriorates. In this case, patient will re-enter the titration phase of the trial.

After having finished the parallel-group, enriched enrolment randomized withdrawal study, a termination visit will be held and nabilone will be tapered in the patients in 0.25 mg two-daily decrements. Phone calls will be held every other day during dose tapering phase. The patients will be asked for the use of concomitant medications, AEs, CGI-I, the items 1.2, 1.8, and 1.12 of MDS-UPDRS Part I, and the C-SSRS. A phone call for safety issues will be held after 5 days  $\pm$  2 days and a Safety Follow- Up Visit will be scheduled after 2 weeks + 2 days of discontinuation from study drug. (see 5.4)

### **3.1.1 Study end:**

- 1) After having finished the parallel-group, enriched enrolment randomized withdrawal study, patients will be down-titrated from the study medication in 0.25 mg decrements every other day. During tapering two-daily phone calls will be held, asking for concomitant medications, AEs, CGI-I, the items 1.2, 1.8, and 1.12 of MDS-UPDRS Part I, and the C-SSRS. A safety call will be performed 5 days  $\pm$  2 days after having stopped study medication and a safety follow-up visit will be done 2 weeks + 2 days after having stopped study medication. (see 5.4)

- 2) If the trial is stopped on behalf of the Sponsor or a regulatory authority or if patients withdraw from study medication due to personal or medical reasons during the course of the study, the patients will be advised to come to the hospital as soon as possible for an Early Termination Visit (see 5.5). A Safety Follow-Up Visit should be performed 2 weeks + 2 days after the last intake of study medication (if the Early Termination Visit occurs not longer than 5 days after the discontinuation of the study medication). (for reasons for discontinuation and withdrawal see 4.3, for ET and Safety Follow-Up Visit see 5.4)

### 3.1.2 Visits

Subjects will be evaluated in the study center by the investigator at the screening visit, at the end of the open-label titration phase (i.e. V -1 / weeks -1), at the end of the open-label 7-day + 7 days treatment period (i.e. V 0 / week 0; baseline of randomized withdrawal phase), and at the termination visit (V 1 / week 4). A Safety Telephone Call (TC – S) and Safety Follow-Up Visit (V - S) will be performed 5 days  $\pm$  2 days and 2 weeks + 2 days after the last intake of study drug.

The following scales or questionnaires will be performed during all study visits:

1. Movement Disorder Society (MDS) - sponsored new version of the UPDRS (MDS-UPDRS) (all visits including screening)
2. Non-Motor Symptoms Scale (NMSS) (all visits except for V -1)
3. Hospital Anxiety and Depression Scale (HADS) (all visits except for V -1)
4. 39-Item Parkinson's Disease Questionnaire (PDQ-39) (all visits except for V -1)
5. Montreal Cognitive Assessment Scale (MoCA) (all visits except for V -1)
6. Epworth Sleepiness Scale (ESS) (all visits except for V -1)
7. Visual Analog Scale (VAS) of Pain (all visits except for V -1)
8. King's Parkinson's disease pain scale (KPPS) (all visits except for V -1)
9. Fatigue Severity Scale (FSS) (all visits except for V -1)
10. Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale (QUIP-RS) (all visits except for V -1)
11. Columbia Suicide Severity Rating scale (C-SSRS) (all visits)
12. CGI-I (V -1, V 0, V 1, and Safety Follow-Up Visit only)
13. Vital signs (all visits including screening)
14. Concomitant medications (all visits including screening)
15. Adverse Events (all visits including screening)
16. Physical examination (screening, V 0, V 1, and Safety Follow-Up Visit only)
17. Local ECG and Clinical Laboratory tests ((pre-)screening and V 1 only)



## 18. Measurement of Eye-Movements with a Tobii TX300 Eye-Tracker (screening, termination visit)

### 3.1.3 Study Duration Per Patient

Recruitment will start after the ethical committee and regulatory authorities approve the study and all necessary documents are available and filed. Recruitment phase will last to the point when 48 patients are included in the trial.

The study will begin with the screening visit. If patient is eligible for the study, patients will then enter in the open-label dose titration phase. This optimization phase will last from 2 up to 28 days for each patient and will include phone calls every other day and a visit at the end of the titration phase (week -1). Before entering the double-blinded withdrawal phase, patients have to stay for a minimum of one week on a stable dose of nabilone. After this week, the baseline visit of the double-blinded withdrawal phase will be performed. The double-blinded withdrawal phase will end with the termination visit.

The total anticipated study duration for an individual patient starting from screening visit will be a minimum of 53 days / 7 weeks + 4 days (including safety follow-up visit) and a maximum of 104 days / 14 weeks + 6 days. The end of the study is defined as the date of the last visit of the last patient in the study (LPLV).

### 3.1.4 Planned Number of Patients

A total of 38 patients will provide 80% power at a 2-sided 5% significance level to detect a statistically significant difference in the change from randomization to Week 4 in MDS-UPDRS Part I score between nabilone and placebo if the true difference is 2.5 points. In the absence of previous data, we empirically chose as clinically meaningful a 2.5 units change from randomization to the visit at 4 weeks (in Phase 2). This sample size calculation assumes a standard deviation of the change from randomization to week 4 to be 2.4 points. (46) Assuming a drop-out rate of 25%, we will include around 48 patients with Parkinson's disease in this trial.

Importantly, although a sample size calculation is provided, this is an exploratory study evaluating different NMS domains. Therefore, corrections for multiple comparisons are not planned.

### 3.1.5 Anticipated Regions and Countries

This study will be held at one clinical site (Medical University of Innsbruck).

## 3.2 Schedule of Events

Table 2: Nabilone for non-motor symptoms in Parkinson's Disease

STUDY PERIOD	Screening	Dose Titration Period		Randomized Withdrawal Period			Dose Tapering		Safety Follow-Up	Early Termination
STUDY WEEK, STUDY VISIT	Week 0, Screening Visit	Telephone calls	Week -1, Visit -1	Week 0, Baseline Visite 0	Phone calls	Week 4, Termination Visit, Visite 1	Telephone calls	Safety Follow-Up Phone Call	Safety Follow-Up Visit V - S	Early Termination Visit ET
Visit Descriptor	SCR		V - 1	V 0		V 1			V - S	ET
Visit window (days)	Day 0	Every other day	2 – 28 days	7 days + 7 days	Every other day in the first week	4 weeks + 2 days	Every other day until IMP Stopp	5 days ± 2 days after IMP Stopp	2 weeks + 2 days after IMP Stopp	As soon as possible after the last intake of IMP
Written Informed consent	X									
Randomization				X						
Vital signs <sup>1</sup>	X		X	X		X			X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X
Physical and Neurol. Exam	X			X		X			X	X
12-lead ECG	X (Or within 4 weeks prior to SCR)					X				X
Clin.Lab. Test <sup>2</sup> , Urinalysis	X (Or within 4 weeks prior to SCR)					X				X
MDS-UPDRS	X	Partly (Part I)	X	X	Partly (Part I)	X	Partly (Part I)	Partly (Part I)	Partly (Part I)	X
NMSS	X			X		X				X
HADS	X			X		X				X
PDQ-39	X			X		X				X
MoCA	X			X		X				X
ESS	X			X		X				X
VAS for Pain	X			X		X				X
KPPS	X			X		X				X
FSS	X			X		X				X
CGI-I		X	X	X	X	X	X	X		X
MMSE (Inclusion Criterion)	X									
C-SSRS	X	X	X	X	X	X	X	X	X	X
QUIP-RS	X			X		X				X
Eye-tracking	X					X				X
Dispense IMP	X		X	X		X				
Drug Accountability			X	X		X			X	X

<sup>1</sup>Vital Signs include height (only at Screening Visit), weight, temperature, pulse rate and blood pressure after at least 10 minutes of rest and at 1,3,5, and 10 minutes of active standing.

<sup>2</sup>Clinical Laboratory Test includes haematology and chemistry. Urinalysis and a urine pregnancy test for women of child-bearing potential will be performed.

### 3.3 Schematic Diagram

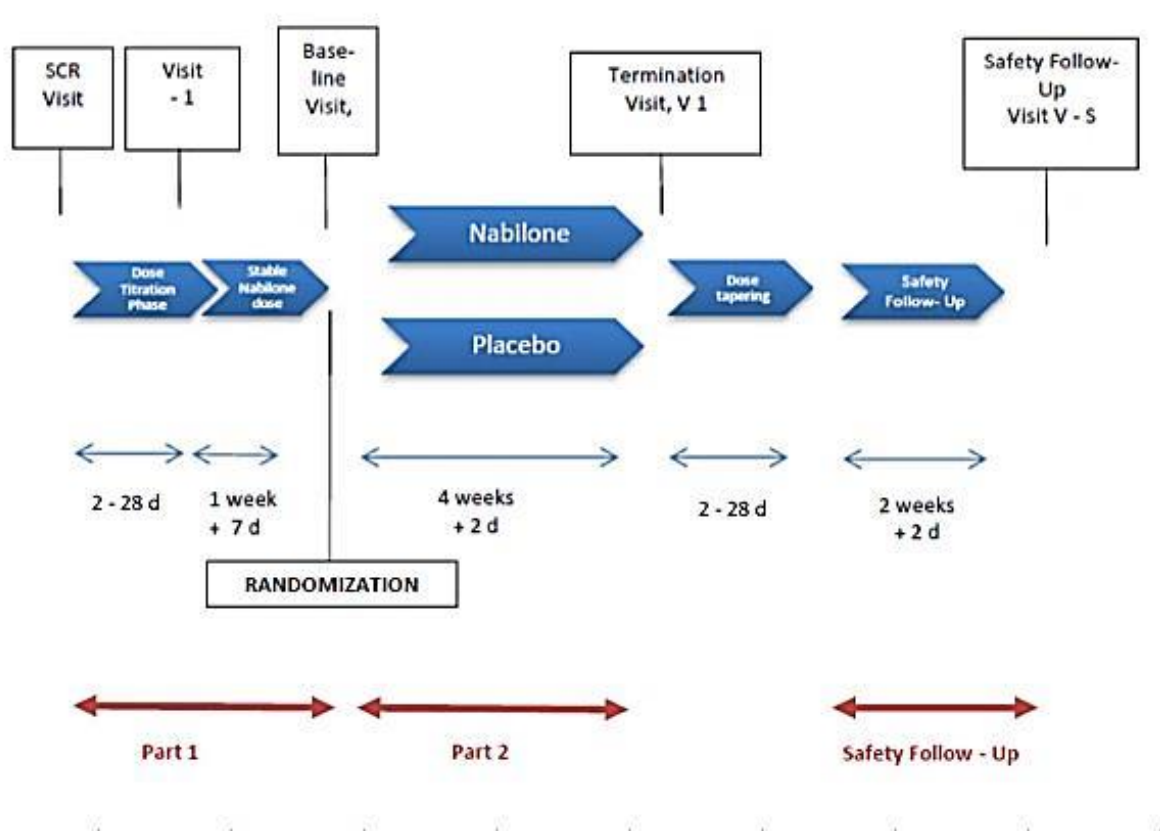


Figure 1: Schematic Diagram for participants

## 4 Study Population and Withdrawal of Patients

### 4.1 Inclusion Criteria

In order to be eligible for the study subjects must meet all inclusion criteria:

1. Age  $\geq 30$  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  $\geq 4$  on MDS-UPDRS Part 1. One of the following domains have to be affected with a score  $\geq 2$ : 1.4 (anxious mood) or 1.9 (pain)
4. On a stable regimen of anti-parkinson 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.

\*Acceptable methods of birth control for women and men in this study are:

surgical sterilization (e.g. tubal ligation for females), intrauterine devices that release hormones (hormone spiral), oral hormonal contraceptive, contraceptive patch, dermal hormonal contraception, vaginal hormonal contraception (NuvaRing®), implants that release progesterone (Implanon®), long-acting injectable contraceptive, partner's vasectomy, a double-protection method, postmenopausal (> 2 year absence of vaginal bleeding).

This means that the following are not regarded as safe: condom plus spermicide, simple barrier methods (vaginal pessaries, condom, female condoms), copper spirals, the rhythm method, basal temperature method, and the withdrawal method (coitus interruptus).

The regulations for contraception are derived from Guideline ICH E8 Chapter 3.2.2.1

Selection of subjects together with ICH M3 Note 4.

### 4.2 Exclusion Criteria

Patients with any of the following characteristics will be excluded from entering the study:

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  $\geq 2$  on one of the items of the MDS-UPDRS Part IV at screening)

6. Hoehn and Yahr 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 listed in 7.4.2
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 (See: acceptable methods of birth control at 4.1.)
20. Pregnant women or women planning to become pregnant during the course of 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

### 4.3 Discontinuation of the Study, Premature Termination

**Subjects** have the right to withdraw fully or partially from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Withdrawal of full consent for a study means that the subject does not wish to receive further investigational treatment and does not wish or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the subject's study data, but no further information will be collected unless a separate consent has been given.

Withdrawal of partial consent means that the subject does not wish to take the protocol-specified product any longer but is still willing to collaborate in providing further data by continuing on study.

**The investigator** has the 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 should be documented. Patients should be discontinued if they experience intolerable side effects

believed to be related to the study drug and they will be terminated if they did not meet the responder criterion at the previous dose or the maximum permitted dose.

If patient discontinues study participation for reasons unrelated to an adverse event, no additional patient will be enrolled to replace that subject.

The **Sponsor** has the right to discontinue this trial at any time. The Sponsor will notify the investigator if the sponsor decides to stop the clinical trial.

The Sponsor has the right to terminate the trial prematurely at any time.

This might be if there are any relevant medical or ethical concerns, or if completing the trial is no longer practicable. If such action is taken, the reasons for terminating the trial must be documented in detail. All trial subjects still under treatment at the time of termination must undergo a final examination (Early Termination Visit as soon as possible and Safety Follow-Up Visit 2 weeks + 2 days after the ET (if the ET is performed after 5 days after the last intake of study drug)) which must be documented. The principal investigator must be informed without delay if any investigator has ethical concerns about continuation of the trial. In case of discontinuation of the trial the IEC and competent regulatory authority must be informed within 15 days of early termination.

#### **4.3.1 Potential Criteria for Withdrawal from Study**

The investigator should inform the Medical Monitor if any of the following events occur that may lead to a discontinuation of the participation in the study:

1. Noncompliance of the patient with the study procedures or medications.
2. The patient doesn't have a stable PD or changes his/her medication or receives neurosurgical intervention for PD.
3. The patient presents with one or more clinically significant laboratory values that are not within normal limits or clinically significant abnormal findings on physical examination, or experiences AEs that are intolerable (as determined by the patient) or that endanger the safety of the patient based on the investigator's judgement.

#### **4.3.2 Definite Criteria for Withdrawal from Study**

A definite withdrawal from the study must be operated if any of the following events occur:

1. The patient withdraws his/ her consent willingly.
2. Patient develops a psychiatric, medical or surgical condition that would interfere with his/ her participation.
3. Patient shows abnormal laboratory values concerning hepatic and renal function as described in the exclusion criteria.
4. Pregnancy of the patient during the study, as confirmed by a positive pregnancy test.
5. Withdrawal of the patient is requested by the Sponsor or a regulatory agency.
6. The Sponsor or a regulatory agency discontinues the study. Reasons for discontinuation may include, but are not limited to the following:
  - Patient enrolment is unsatisfactory
  - Administrative Reasons
7. The Sponsor terminates the study prematurely. Premature termination of the trial will be considered if:
  - The risk-benefit balance for the trial subject changes markedly.

- It is no longer ethical to continue treatment with the IMP.
  - The Sponsor considers that the trial must be discontinued for safety reasons.
  - An interim analysis or results of other research show that one of the trial treatments is superior or inferior to another.
  - It is no longer practicable to complete the trial.
8. Patient has performed an active suicide since the last visit or reports any suicidal behavior. In this case he/she should be referred to a hospital for Mental Health immediately.

Should the trial be discontinued or should a subject request or decide to withdraw from the study, all efforts will be made to complete and report the observations as thoroughly as possible up to the end of withdrawal.

Thus, if a discontinuation of or a withdrawal from the study occurs, all observations, evaluations as well as lab results and other test results should be documented. Moreover, a short description of the primary reason(s) for removing the patient must be recorded in the source documents and provided to the Sponsor.

In case of a discontinuation of or a withdrawal from the study every effort should be made for attendance of an Early Termination (ET) Visit, which will be scheduled as soon as possible, followed by a Safety Follow-Up Visit after 2 weeks + 2 days of the ET (if the ET is performed after 5 days after the last intake of study drug) (see 5.4 and 5.5). Patients will not be followed for any reason after consent has been withdrawn, unless a separate consent has been given for further data collection.

In case the withdrawal was due to an AE the patient should be followed up until he/she has recovered/ it has resolved, has reached a stable state, the investigator determines that it is no longer clinically significant, or the patient is lost to follow up. (see 8)

## **4.4 Further treatment after end of treatment**

After the end of the study treatment, alternative methods for the therapy of disturbing non-motor symptoms in PD can be prescribed to the patients as seen in Table 1: Drug classes for non-motor symptoms in PD, keeping in mind the patient's tolerance. If the patient has shown benefit from the therapy with nabilone, a cannabinoid therapy could be prescribed on behalf of the investigator's decision.

## **4.5 Closure of the Study**

The clinical trial shall be deemed to end when the last patient absolved the planned last visit according to protocol. The completion of the study will be reported to the ethics committee as well as to the relevant authorities.

## 5 Study Procedures (by Visits)

An overview of the study procedures, including the time of events and assessments performed, may be found in 3.2 and 3.3. Details of scales used to evaluate efficacy and safety can be found in Section 6.1 and 6.2 and in the applicable appendices. A detailed description of study procedures by visit will be provided in this section.

Eligible subjects who meet all inclusion criteria and none of the exclusion criteria at the Screening visit will be titrated to the optimal dose as described above which could last up to 28 days (Part 1). During this phase regular phone calls will be held every other day. After reaching the optimal dose, the patients will stay on a stable nabilone dose for at least one week and will then visit the outpatient clinic for the Baseline visit. At Baseline, the participants will be randomized using a randomization list provided by the Statistics Department of the Medical University of Innsbruck and will begin Part 2 of the study. The first dose of IMP will be taken at home after the Baseline Visit. The participants will be evaluated after 4 weeks of double-blind placebo-controlled parallel-group enriched enrolment randomized withdrawal phase (termination visit). However, during the first week of the double-blind placebo-controlled parallel-group enriched enrolment randomized withdrawal phase regular phone calls will be held every other day. A Safety Phone call will take place 5 days  $\pm$  2 days and a Safety Follow-Up visit will be performed 2 weeks + 2 days after the last intake of study medication. At visits after intake of medication, the patients will be requested to return the IMP kits (including all used, unused, and partially used medication) dispensed to them at the previous visit and to take their IMP in the morning before every visit. Furthermore, the patients should take their concomitant medication at home and at the clinic, if permitted, as normally scheduled. Safety evaluations will be performed as scheduled in the schedule of events table with examination of vital signs, AE, concomitant medication, the items 1.2, 1.8, and 1.12 of MDS-UPDRS Part I, and the C-SSRS operated at every visit and AE and concomitant medication, the items 1.2, 1.8, and 1.12 of MDS-UPDRS Part I, and the C-SSRS at every phone call. In the event of Early Termination, patients will be asked to complete an Early Termination Visit as soon as possible and to return for a Safety Follow-Up Visit 2 weeks + 2 days after their last dose of IMP.

Please refer to the Schedule of Events table and the Schematic diagram (in 3.2 for specific timing of assessments and Section 5.1, 5.2, 5.4, and 6 for a detailed description of timing and aim of study procedures and scales.



## 5.1 Screening Period

### 5.1.1 Recruitment and Informed Consent Process

Patients will be seen in the outpatient's department on-site or at the neurologic wards. For interested patients a member of the qualified research team will explain the study purpose, goals, and requirements in an understandable way and an IRB/IEC-approved informed consent form will be handed to the patients considering participation for information.

Relevant contact from the site including phone numbers will be given to the patient. Thus the patient can read, ask questions, and consult his/her family members if requested

It is the responsibility of the principal investigator, or a subinvestigator delegated by the principal investigator to obtain written informed consent from each subject prior to participation in the trial, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. The person taking consent must be GCP trained, suitably qualified and experienced, and have been delegated this duty by the PI on the delegation log.

The investigator or designee will explain the patients are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason.

No clinical trial procedures will be conducted prior to taking consent from the participant.

Consent will not denote enrolment into trial.

If all questions are clarified and the patient has been given ample time to think about his/her participation, the informed consent will be obtained in accordance with ICH GCP by signing the informed consent form at a visit on-site before any trial-related procedures are completed. The signature from the investigator who conducted the informed consent discussion and the patient as well as the date will be provided and documented in the source documents. For patients who consent to participate in the study a copy of the signed ICF and other information available will be provided to them prior to participation. The original signed and dated ICF will be maintained at the investigator's site.

Any patient who is unable to demonstrate understanding of the information contained in the ICF won't be allowed to participate in the study. The ICF and any other information provided to patients will be revised whenever important new information (e.g. safety information resulting in significant changes in the risk/benefit assessment) becomes available that is relevant to the consent and continued participation of a patient in the study. The revised ICF and information must receive IRB/IEC-approval prior to its use, and a copy of the IRB/IEC's approval will be provided to the Sponsor. The patient will be informed of any new information via the revised ICF or information material by the investigator and his/her willingness to further participate in the study will be questioned. A signed and dated new ICF will be

obtained and stored, and a copy will be given to the patient. This will as well be recorded in the source documents.

After providing and documenting consent on the IRB/IEC-approved written ICF, patients will be assigned their patient screening number and proceed to the Screening Visit.

### **5.1.2 Screening Visit**

All subjects must provide written informed consent before any study-specific assessments or procedures are performed.

The following assessments will be performed during the Screening Visit and used to determine whether a patient is eligible for the study or not. Screening data will be reviewed prior to the baseline visit.

#### **Screening Assessments:**

1. Obtain written informed consent (see Section 5.1.1), sign and date, and provide a copy to the patient.
2. Obtain demographics (see: 6.2.2) and medical history including any co-existing pre-treatment AEs and allergies.
3. Obtain neurological and PD history, including questions for disturbing (i.e. treatment required) impulse control disorders.
4. Obtain complete medication history including anti-PD medications, record the start date and stop date (if applicable), as well as the indication
5. Perform assessment of Vital signs: obtain weight, height, and temperature, obtain and record serial BP and pulse measurements after at least 10 minutes of supine rest and again after 1, 3, 5, and 10 minutes of active standing
6. Perform brief physical and neurological examination (see: 6.2.2)
7. Obtain 12-lead ECG and review (if not performed within 4 weeks prior to Screening)
8. Withdraw blood for the following laboratory measurements and record the time and date: haematology, chemistry (if not performed within 4 weeks prior to Screening)
9. Urine sample for urinalysis, including pregnancy test (for women of childbearing potential only)
10. Administer the MDS-UPDRS Part I, II, III, and IV (record if patient is in ON or OFF state), and the Modified Hoehn and Yahr stage (document for entry criteria).
11. Administer the following assessments:
  - a. MMSE
  - b. NMSS
  - c. HADS
  - d. PDQ-39
  - e. MoCA

- f. ESS
- g. FSS
- h. VAS for Pain
- i. KPPS
- j. C-SSRS
- k. QUIP-RS
- l. Eye-tracking

## 12. Review inclusion and exclusion criteria for eligibility

If the patient does not meet eligibility criteria at the time of screening, e.g., if a laboratory result disqualifies the patient from participating in the study, the patient is considered a screen failure. Record the primary reason for screen failure in the source documents. Screen failures maybe eligible for rescreening to acceptable parameters. This will need to be discussed with the Sponsor or designee.

Screening does not necessarily constitute enrolment of the subject.

Pseudonymized information on the patient including date of screening visit, demographics, medical history, and neurological history (including Parkinson's disease, UPDRS scores, modified Hoehn and Yahr staging, current treatment, and concomitant medications) will be reviewed for preliminary eligibility of the patient. If eligible, dose titration phase will begin.

13. Dispense the IMP kits assigned by the Sponsor to the patient so that he/she has enough until the Week - 1 Visit.
14. Record the dates the patient is instructed to take the study drug on the packaging of it. Record the following information in the source documents: patient number, assigned IMP kit number, date, and time the study drug was dispensed.
15. Instruct the patient to bring his/her used, unused, and partially used IMP kits to the next visit and schedule this visit.
16. Review the dosing instructions for the study drug with the patient and answer any questions. The patient will be instructed to take one tablet of the study drug by mouth two times daily starting in the evening after the Baseline Visit. The evening dose should be approximately 12 hours after the morning dose. Document that the patient understood the dosing instructions.

### 5.1.3 Dose Titration Phase

For patients who remain eligible, proceed with starting nabilone with a dosage of 0.25 mg in the evening and titrate in in one- to four-daily increments at a maximum dosage of 1 mg

twice daily. Dose tapering will be performed according to the investigator's decision. Dose increments will be held as follows:

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.

Regular **phone calls** with the study center will be performed every other day during titration phase. These will include questions for concomitant medication, AEs, and the assessment of the CGI-I. Moreover, the items 1.2, 1.8, and 1.12 of MDS UPDRS Part I, and the C-SSRS will be assessed. The duration of the open-label titration phase can range from 2 days up to 28 days.

Dose adjustments during titration phase will be performed until the patient:

1. Criterion 1: has much (CGI-I Rating Scale: 2) or very much (CGI-I Rating Scale: 1) improved NMS on the 7-point Clinical Global Impression of Improvement Scale.

This criterion defines responders. Patients who meet this criterion will enter into the 4-weeks treatment period at the last prescribed dose.

2. Criterion 2: experiences intolerable side effects believed to be related to the study medication.

Patients who meet criteria 2 will proceed to the 4-weeks treatment period at the previous lower dose, assuming they will meet the definition of a responder at that dose.

3. Criterion 3: reaches the maximum permitted dosage of 1 mg twice daily.

Patients who meet criteria 3 and were a responder will enter the study at 1 mg twice daily.

Patients are discontinued if they meet criteria number 2 but did not meet the responder definition at the previous dose, if they meet criteria 2 at the initial dose of 0.25 mg once daily, or if they meet criteria 3 but did not meet the definition of a responder.

#### **5.1.4 Visit -1 (week – 1)**

Patients will have an on-site visit at the clinic after they meet the responder criterion at their “optimal dose”. The following assessments should be performed at this visit:

1. Perform assessment of Vital signs: obtain weight and temperature, obtain and record serial BP and pulse measurements after at least 10 minutes of supine rest and again after 1, 3, 5, and 10 minutes of active standing
2. Ask for AE occurring since the last visit.
3. Interview on concomitant medication use since the last visit.
4. Administer the MDS-UPDRS Part I, II, and IV (record if patient is in ON or OFF state), and the Modified Hoehn and Yahr stage (document with date and time).

5. Administer the following assessments:
  - a. CGI-I
6. Collect all used, unused, and partially used study drug and record it in the source documents and Drug Accountability Section.
7. Schedule the Baseline Visit, which must occur after at least 1 week of stable nabilone dosage (1 week + 7 days) from the date of the Visit -1.
8. Instruct the patient to bring their medication to the baseline visit (including concomitant medication so that they are able to maintain their regular treatment schedule)
9. Dispense the IMP kits assigned by the Sponsor to the patient so that he/she has enough until the Baseline Visit.
10. Record the dates the patient is instructed to take the study drug on the packaging of it. Record the following information in the source documents: patient number, assigned IMP kit number, date, and time the study drug was dispensed.
11. Review the dosing instructions for the study drug with the patient, answer any questions, and remind the patient to return all used, unused, and partially used study drugs at the next visit. The patient will be instructed to take one tablet of the study drug by mouth two times daily starting in the evening after the Baseline Visit. The evening dose should be approximately 12 hours after the morning dose. Document that the patient understood the dosing instructions.

## **5.2 Baseline Visit / V 0 and Randomization to Study Drug**

Randomization will occur at Baseline (Visit 0), after the patient's eligibility for the study has been confirmed and all pre-dosing Baseline procedures have been performed. Baseline Visit will take place 1 – 2 weeks after V -1.

### **5.2.1 Baseline Visit / V 0 (week 0)**

At the beginning of the Baseline Visit the patient's medical history and co-existing pre-treatment AEs since the last assessment will be reviewed and continued eligibility for the study will be confirmed. The following assessments should be performed and documented with date and time at this visit:

1. Perform assessment of Vital signs: obtain weight, temperature, obtain and record serial BP and pulse measurements after at least 10 minutes of supine rest and again after 1, 3, 5, and 10 minutes of active standing
2. Ask for AE occurring since the last visit.
3. Interview on concomitant medication use since the last visit.

4. Perform physical and neurological examination
5. Administer the MDS-UPDRS Part I, II, III, and IV (record if patient is in ON or OFF state), and the Modified Hoehn and Yahr stage
6. Administer the following assessments:
  - a. NMSS
  - b. HADS
  - c. PDQ-39
  - d. MoCA
  - e. ESS
  - f. FSS
  - g. VAS for Pain
  - h. KPPS
  - i. CGI-I
  - j. C-SSRS
  - k. QUIP-RS
7. Collect all used, unused, and partially used study drug and record it in the source documents and Drug Accountability Section.
8. Schedule the Termination Visit / V 1, which must occur after 4 weeks + 2 days from the date of the Visit 0.
9. Instruct the patient to bring their medication to the baseline visit (including concomitant medication so that they are able to maintain their regular treatment schedule)

### **5.2.2 Randomization**

If the Sponsor confirms the patient to be eligible and after one week of stable nabilone dosage, responders are randomized in a 1:1 ratio to receive either nabilone at the dosage reached during the titration phase or matching placebo for 4 weeks.

During the randomized withdrawal phase of the trial, dose adjustments can be performed if CGI-I deteriorates. In this case, patient will re-enter the titration phase of the trial.

For randomization a randomization list provided by the Statistics Department of the Medical University of Innsbruck will be used to randomize the patients to the placebo or nabilone group. Information about the blinded medication kits to be used will be provided by the Sponsor or its designee to the investigator according to the randomization and the scheduled visits. (For further details see: 7.2)

10. Dispense the double-blind IMP kit assigned by the Sponsor to the patient for this study visit.
11. Record the dates the patient is instructed to take the study drug on the packaging

of it. Record the following information in the source documents: patient number, assigned IMP kit number, date, and time the study drug was dispensed.

12. Review the dosing instructions for the study drug with the patient, answer any questions, and remind the patient to return all used, unused, and partially used study drugs at the next visit. The patient will be instructed to take one tablet of the study drug by mouth two times daily starting in the evening after the Baseline Visit. The evening dose should be approximately 12 hours after the morning dose. Document that the patient understood the dosing instructions.
13. Instruct the patient to inform the investigator if an AE or a change of concomitant Medication occurs during this period, if the patient runs out of IMP kit (e.g. due to damage), or if the patient's condition worsens, and provide relevant contact details.

The patient will leave the clinic with enough IMP for the next 4 weeks + 2 days and begin to take the assigned IMP (placebo or nabilone) in the evening after the baseline visit.

During the first week of placebo-controlled, double-blind, parallel-group, enriched enrolment randomized withdrawal phase of the trial, the patients will receive **phone calls** every other day to ask for AEs, Concomitant Medication use, CGI-I, the items 1.2, 1.8, and 1.12 of MDS-UPDRS Part I, and the C-SSRS.

### **5.3 Termination Visit / V 1 (week 4)**

After 4 weeks of placebo-controlled, double-blind, parallel-group, enriched enrolment randomized withdrawal phase, the patient will return to the clinic to perform his/her termination Visit / V1. The time and date of the last dose of study drug will be documented. The following assessments should be performed and documented with date and time at this visit:

1. Perform assessment of Vital signs: obtain weight, temperature, obtain and record serial BP and pulse measurements after at least 10 minutes of supine rest and again after 1, 3, 5, and 10 minutes of active standing
2. Ask for AE occurring since the last visit.
3. Interview on concomitant medication use since the last visit.
4. Perform physical and neurological examination
5. Obtain 12-lead ECG and review
6. Obtain blood samples to perform the following laboratory measurements:  
haematology, chemistry, pregnancy test (for women of childbearing potential only)
7. Urine sample for urinalysis, including pregnancy test (for women of childbearing potential only)
8. Administer the MDS-UPDRS Part I, II, III, and IV (record if patient is in ON or OFF

state), and the Modified Hoehn and Yahr stage

9. Administer the following assessments:

- a. NMSS
- b. HADS
- c. PDQ-39
- d. MoCA
- e. ESS
- f. FSS
- g. VAS for Pain
- h. KPPS
- i. CGI-I
- j. C-SSRS
- k. QUIP-RS
- l. Eye-tracking

10. Collect all used, unused, and partially used study drug and record it in the source documents and Drug Accountability Section.

Nabilone will then be down-titrated in 0.25 mg decrements every other day until it is discontinued. During dose tapering phone calls will be held every other day to receive information on AEs, Concomitant Medication use, CGI-I, the items 1.2, 1.8, and 1.12 of MDS-UPDRS Part I, and the C-SSRS will be executed. A phone call for safety issues will be held after 5 days  $\pm$  2 days and a Safety Follow- Up Visit will be scheduled after 2 weeks + 2 days of discontinuation from study drug. (see 5.4)

The Safety Follow- Up Visit should therefore be scheduled with the patient and he/she should be reminded on the telephone calls. Relevant contact to the site should be updated if necessary if there are any questions or adverse events occurring until the Safety Telephone Call or Follow-Up Visit.

## **5.4 Safety Telephone Call (TC – S) and Safety Follow-Up Visit (V – S)**

The **Safety Telephone Call** will be held after 5 days  $\pm$  2 days after stopping the study drug and will include the assessment of AE, concomitant medication, and the CGI-I.

Questions for the following items and assessment of the following scale will be performed:

- Hallucination item (1.2) of Movement Disorders Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS)



- Orthostatic hypotension (OH) item (1.12) of Movement Disorders Society – Unified Parkinson’s Disease Rating Scale (MDS-UPDRS)
- Day-time sleepiness item (1.8) of Movement Disorders Society – Unified Parkinson’s Disease Rating Scale (MDS-UPDRS)
- C-SSRS

Documentation in the source document will include the time and date of the call as well as the results of the assessments.

The **Safety Follow-Up Visit** will take place 2 weeks + 2 days after the withdrawal from study drug and will include the following assessments (documented with date and time in the source documents):

1. Perform assessment of Vital signs: obtain weight, temperature, obtain and record serial BP and pulse measurements after at least 10 minutes of supine rest and again after 1, 3, 5, and 10 minutes of active standing
2. Ask for AE occurring since the discontinuation of the study drug.
3. Interview on concomitant medication use since the last intake of study medication.
4. Perform physical and neurological examination
5. Administer the MDS-UPDRS Part I and C-SSRS
6. Collect all used, unused, and partially used study drug and record it in the source documents and Drug Accountability Section.

## 5.5 Early Termination Visit

If the patient has discontinued IMP, an early termination visit should be performed as soon as possible after the last dose of study drug and the Sponsor should be informed. The date of the last intake of study drug should be documented and a reason for withdrawal of the study drug if available. This visit will include the following assessments (documented with date and time in the source documents):

1. Perform assessment of Vital signs: obtain weight, temperature, obtain and record serial BP and pulse measurements after at least 10 minutes of supine rest and again after 1, 3, 5, and 10 minutes of active standing
2. Ask for AE occurring since the discontinuation of the study drug.
3. Interview on concomitant medication use since the last intake of study medication.
4. Perform physical and neurological examination
5. Obtain 12-lead ECG and review
6. Obtain blood samples to perform the following laboratory measurements:  
haematology, chemistry, pregnancy test (for women of childbearing potential only)

7. Urine sample for urinalysis, including pregnancy test (for women of childbearing potential only)
8. Administer the MDS-UPDRS Part I, II, III, and IV (record if patient is in ON or OFF state), and the Modified Hoehn and Yahr stage
9. Administer the following assessments:
  - a. NMSS
  - b. HADS
  - c. PDQ-39
  - d. MoCA
  - e. ESS
  - f. FSS
  - g. VAS for Pain
  - h. KPPS
  - i. CGI-I
  - j. C-SSRS
  - k. QUIP-RS
  - l. Eye-tracking
10. Collect all used, unused and partially used study drug kits and document in the source documents and Drug Accountability Section.

A Safety Follow-Up Visit should be performed 2 weeks + 2 days after the last intake of study medication (if the Early Termination Visit occurs not longer than 5 days after the discontinuation of the study medication).

## **5.6 Unscheduled Visit / USV**

An Unscheduled Visit is defined as any additional visit performed at any time between the Screening Visit and the Safety Follow-Up Visit. This visits can be held at the investigator's discretion. An USV should at least contain questions and assessments for:

1. AE occurring since the last visit.
2. Concomitant medication use since the last visit.
3. CGI – I
4. C-SSRS
5. Obtain and record the date and approximate time when the patient took the most recent dose of IMP. Collect all used, unused, and partially used study drug kits dispensed at the previous visit and document in the source documents and Drug Accountability Section. Assess compliance. Document any missed doses, lost tablets, and number of tablets taken

The reason for the Unscheduled Visit should be provided and recorded in the source documents.

Additional assessments can be performed if necessary by the means of the investigator including a neurological and physical exam, laboratory tests and urinalysis, a pregnancy test, a 12-lead ECG, and the clinical scores used in the trial.

In consultation with the Medical Monitor, discuss any other appropriate diagnostic tests required to evaluate AEs.

## **5.7 Telephone calls**

Telephone calls will be performed according to the study protocol during dose titration phase(s), the first week of placebo-controlled, double-blind, parallel-group, enriched enrolment randomized withdrawal phase, and during dose tapering as summarized in 3.2 (Schedule of Events). Telephone calls will be held every other day (1) during dose titration phase until optimal dose will be reached, (2) during the first week of the placebo-controlled, double-blind, parallel-group, enriched enrolment randomized withdrawal phase, and (3) during dose tapering until IMP is stopped. A Safety Telephone Call will be held 5 days  $\pm$  2 days after discontinuation of study medication. During these telephone calls patients will be asked for any AEs, SAEs, and the CGI-I. Moreover, the hallucination item (1.2), the day-time sleepiness item (1.8), the OH item (1.12) of the MDS-UPDRS, and the C-SSRS will be applied.

If the site is not able to reach a patient (or study partner) via telephone on the scheduled day and all attempts have been made and there is no other possibility to reach the patient and no reasonable explanation, the site is allowed to stop trying to connect to the patient. At least 3 attempts have to be made. Attempts have to be documented as well as the decision to discontinue trying. The site has to attempt to reach the patient on the consecutive working day again.

If a telephone call is scheduled on a Saturday, the patient should be reached on Friday. If a telephone call should be held on Sunday, the call will be scheduled on Monday. On bank holiday, the patient should be called the day before or after the day off.

The patients will be provided with an emergency phone number available 24 hours to contact a member of the study team in case of emergencies.

## 6 Description of Assessments: Efficacy and Safety Variables

### 6.1 Assessments of Efficacy

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

Currently, the **MDS-UPDRS Scale** is the most common used scale in evaluation motor symptoms in patients with PD. The Movement Disorder Society (MDS)-sponsored new version of the UPDRS was published in 2003 with respect to the Task Force for Rating Scales' proposed criticism of the original UPDRS concerning issues of weakness and ambiguities. (44) 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 behaviors 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 will administer the UPDRS subscales in accordance with requirements for background and experience in research settings. Trainings will be documented by providing a Certificate of Rater Approval. The UPDRS Scale will first be measured before the patient receives nabilone and in subsequent visits after the patient's morning dose of nabilone. It will be documented if the patient is in an ON state (i.e. period when the patient notices a benefit on MS from standard oral LD/CD treatment) or in an OFF state (i.e. the phase with no response to medication and significant motor symptoms).

The key secondary efficacy criteria will be measured as the change in the other clinical scales and questionnaires regarding motor symptoms and different domains of non-motor

symptoms in Parkinson's Disease between baseline and week 4. Therefore, the total MDS-UPDRS Part I, II, III, and IV (total UPDRS: 50 items, Part I: 0 to 52 points, Part II: 0 – 52 points, Part III: 0 – 132 points plus Hoehn and Yahr Scale 0 - 5 points, Part IV: 0-24 points), the Non Motor Symptoms Scale (4 domains, 15 items, points from 0 – 12x15 with the latter being severely impaired daily or always), the Hospital Anxiety and Depression Scale (14 items, values from 0 – 42 points), the Parkinson's Disease Questionnaire – 39 (8 domains, 39 items), the Montreal Cognitive Assessment (8 items, score ranges from 0 – 30 points), the Epworth Sleepiness Scale (8 items, ranges from 0 – 24 points), the Fatigue Severity Scale (9 items, 9 – 63 points), the Visual Analog Scale of Pain, the King's Parkinson's Disease Pain Scale (7 domains, 14 items, 0 – 168 points), and the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale (7 domains, 0 – 122 points) will be performed. The result of the Clinical Global Impression – Global Improvement scale (ratings from 1 to 7) at Visit V 1 will be used as a key secondary efficacy criterion. All presented scales are measured in points given above.

The **Non-Motor Symptoms Scale (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 orthostatic hypotension, 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 **Hospital Anxiety and Depression Scale** 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.

### **Parkinson's Disease Questionnaire-39**

The PDQ-39 is the most widely used PD specific measure of health status and functional capacity. Its thirty-nine 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.

### **Montreal Cognitive Assessment Scale**

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.

### **Epworth Sleepiness Scale (ESS)**

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

### **Visual Analog Scale (VAS) of Pain**

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

### **King's Parkinson's disease pain scale (KPPS)**

Chaudhuri et al. initially published the KPPS to be a reliable and valid scale to rate different types of pain in PD in 2015. (45) Its aim is to evaluate the global and bedside burden of pain and to characterize various phenotypes of pain in Parkinson Disease (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>

### **Fatigue Severity Scale (FSS)**

To evaluate the level and severity of fatigue of patients during the past week the FSS will be 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.

### **Clinical Global Impression - Improvement (CGI-I)**

The CGI-I is used by the investigator to rate the patient's total improvement based on a 1 to 7 point weighted scale at which one point means "very much improved" and seven points indicate a status of being "very much worse". If the scale has not been assessed, a zero score will be given. The rater should evaluate the improvement of the patient to his clinical judgment, whether or not the improvement is believed to be due to drug therapy.

### **Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale (QUIP-RS)**

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 behavior. The 3 domains of related disorders are medication use, punning, 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.

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## **6.2 Safety Assessments**

**Tolerability** will be described through the:

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

**Safety Measures** include the following:

- Adverse Events (AE), Serious Adverse Events (SAEs), Suspected Unexpected Serious Adverse Reactions (SUSARs)
- Clinical and laboratory assessment
- Vital signs including performance of active orthostatism (measurement of heart rate and blood pressure after 10 minutes of quiet rest in the supine position and at 1, 2, 3, 5, and 10 minutes of active standing)
- ECG
- Patient's 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 Movement Disorders Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS)
- Day-time sleepiness item (1.8) of Movement Disorders Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS)
- Columbia Suicide Severity Rating Scale (C-SSRS)

### **6.2.1 Adverse Events, Serious Adverse Events, Adverse Drug**

#### **Reaction, Suspected unexpected serious adverse reactions**

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

### **6.2.2 Description of other safety measures**

#### **Demographics**

At the Screening Visit, the patient will be 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 will be held at the Screening Visit, Baseline Visit, V 1, the Safety Follow-up Visit, and an Early Termination Visit (if applicable) of the patient and documented in the patient's record.

All physical examinations will be performed by trained medical personnel only, prior to IMP administration on dosing days. Any abnormal findings will be recorded as AEs.

Physical examination must at least include assessment of the vigilance and orientation, general condition, nutritional condition, HEENT (head, eyes, ears, nose and throat), respiratory system, heart, abdomen, extremities, and visible skin and mucous membrane.

Patients should be questioned for defecation and the act of urination.

Neurological examination should include standard neurological assessment of vigilance, orientation, mental status (e.g. consciousness), meningism, cranial nerves, the motor system and sensory system of both upper and lower extremities, reflexes (including pathological reflexes), cerebellar signs, gait, tandem gait, and postural stability, as well as special tests for parkinsonism (e.g. finger tapping, toe tapping, facial expression, ...).

## **Laboratory assessments and Urinalysis**

All laboratory assessments will be made at the central laboratory of the Medical University of Innsbruck to ensure the patient's safety and for early detection of changes in the course of the clinical trial. All members of the study team that are authorized by the principal investigator will be allowed to obtain blood samples. In total 8.2 ml of blood will be withdrawn in 2 tubes at one visit. After withdrawal of blood, it will be sent to the central laboratory and processed via standard methods. Time and Date of Collection of Blood will be provided in the patient's records.

The results will be displayed in the clinical information system, printed, reviewed by the principal investigator or authorized medical personnel, signed, dated and filed in the patient's chart. An interpretation by the principal investigator or authorized medical personnel (clinically significant (c.s.) or non-clinically significant (n.c.s)) will be provided.

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

If an abnormal laboratory measurement or result at urinalysis will be detected, further measures and care will be performed to ensure the patient's safety. The abnormal finding

will be recorded and reported as an AE, SAE, or SUSAR if clinically significant. In the case of a serious adverse event or SUSAR, further participation of the patient in the trial will be discussed with the Medical Monitor.

Laboratory assessments will include standard hematology, chemistry, and urinalysis as outline in the schedule of events table and will be performed using standard kits of outpatient's department. The following laboratory parameters will be measured:

Haematology: Leucocytes, Erythrocytes, Haematocrit, Haemoglobin, MCH, MCV, MCHC, Platelets

Chemistry: AST, ALT, Troponin-I, CK-MB, Creatinine, GGT, Electrolytes, Total conjugated and unconjugated bilirubin

Urinalysis: Leucocytes, Nitrite, Protein, Glucose, pH, Ketones, Urobilinogene, Bilirubin, Blood, Haemoglobin, Urine pregnancy test (females of childbearing potential, only)

(RBC: red blood cell, WBC: white blood cell, MCV: mean corpuscular volume, MCH: mean corpuscular haemoglobin, MCHC: mean corpuscular haemoglobin concentration, ALP: alkaline phosphatase, ALT: alanine transaminase, AST: aspartate transaminase, BUN: blood urea nitrogen, CK-MB: creatine phosphokinase-MB, GGT: gamma-glutamyl transpeptidase, LDH: lactate dehydrogenase, pH: reverse logarithmic representation of relative hydrogen proton (H<sup>+</sup>) concentration)

### **Vital signs**

Vital signs including the evaluation of weight, height (only at Screening Visit), temperature, and active orthostatism will be performed at all visits during the course of the study. The latter will be 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 should be 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 BP cuff (sphygmomanometer) with digital advert will be used. Patients with symptomatic orthostatic hypotension will be excluded from the study.

### **Concomitant medications**

The patients will be asked for concomitant medication on every visit and telephone call and will be assessed in regard to permitted and prohibited concomitant medication.

### **Twelve-lead Electrocardiogram (ECG)**

For ECG analysis the patient will be sent to the cardiologic outpatient's department of the

Medical University of Innsbruck at Screening (if not performed within 4 weeks prior to SCR), Visit V 1 and Early Termination Visit (if applicable) at which an ECG is required. The ECG will be reviewed by a cardiologist and displayed in the information system of the clinic. Members of the study team will print it, the investigator or a designee will review it, and the copy will be filed in the patient's records. If an abnormal ECG will be detected, necessary procedures to ensure the safety of the patient will be performed and an AE, SAE, or SUSAR will be recorded and reported as described in 6.2. A standard 12-lead ECG will be performed in a supine position after at least 10 minutes of resting to minimize variability at the study visits outlined in the Schedule of Events table. ECGs for each patient should be obtained from the same machine whenever possible. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to any scheduled vital signs measurements and blood draws.

For safety monitoring purposes, the investigator or designee must review, sign, and date all ECG tracings.

The 12-lead ECG includes standard PR, QRS, QT, and QTc (heart-rate corrected QT) intervals as read by the machine. Fridericia's correction (QTcF) must be used for correction of the QT interval. The recorded ECG will be used to determine eligibility at the Screening visit and to supervise the heart rhythm through the course of the study. Tachycardia is defined as a pulse rate above 100 bpm and by its characteristic changes in ECG waves. A QTcF interval under 430 ms for males and under a value of 450 ms for females is considered to be normal. Values above 450 ms for male patients and above 470 ms for female participants display a prolonged QTcF interval (FDA).

### **Patient's Compliance**

The patient's compliance will be 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**

### **Orthostatic hypotension (OH) item (1.12) of MDS-UPDRS**

These items are part of the UPDRS Part I (Mental Activity, Behaviour, and Mood) 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 are assessed to detect potential side effects that may occur due to drug treatment. They will be assessed at every clinical visit and during all phone calls and documented in the source documents.

### **Columbia Suicide Severity Scale (C-SSRS)**

The C-SSRS was initially designed for suicidal assessment in one study, but has shown overall successful prediction of suicidal behaviour in adolescences and adults. It is the only screening tool to assess the full range of suicidal ideation and behaviour including criteria for the next steps (e.g. referral to a mental health professional). Suicidality in this study with this scale will be assessed by trained study personnel only (Posner et. al, 2011) on 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 will be used and for all other visits and phone calls the version "Since the last visit" will be administered.

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## **6.3 Assessment of exploratory endpoint**

- Eye-tracking Examination (reaction time, attention span, concentrativeness)

### **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 will measure the reaction time using prosaccade and antisaccade tasks. Moreover, we will assess attention spans and the concentrativeness using a customized saccade task and a test involving task-switching. The examination will be performed at the Screening Visit and the Termination Visit (Week 4). Examinations will take place in a quiet room by trained personnel only.

## 7 Study Treatments

### 7.1 Details of Study Treatment

#### 7.1.1 Name and Description of Investigational Medicinal Product (IMP) and Comparator

##### **Nabilone:**

Nabilone is a synthetic cannabinoid derivative. Canemes 0.25 mg capsules are an oral dosage form in white hard gelatine capsules. Each capsule contains 0.25 mg Nabilone as the active ingredient, in the form of a polyvinylpyrrolidone (Povidone) co-precipitate and corn starch. Each PE bottle contains 28 capsules for a treatment period of approximately 1 month.

Synthetic cannabinoid nabilone
Other components: Polyvinylpyrrolidone (Povidone) co-precipitate and corn starch
Administration form: capsules
Mode of administration: oral
Dose: 0.25 – 2 mg per day
Manufactured in 0.25 mg dosage strength
Bottles of 28 capsules each
For clinical trial use only, Usage as described in the protocol
Stored at room temperature, Store pharmaceutical material out of the reach and sight of children
<b>Sponsor:</b> Medical University of Innsbruck, Austria Represented by O.Univ.-Prof. Dr. Werner Poewe

##### **Placebo: Matching Placebo capsules**

Placebo capsules to be used in the double-blind treatment phase are visually and physically indistinguishable from the active drug product and contain no active ingredient. They consist of corn starch.

#### 7.1.2 Dosing Instructions

During titration phases nabilone will be started with a dosage of 0.25 mg in the evening orally and titrated by 0.25 mg increments every one- to four- daily. Dose adjustments should be performed as follows:

First dose to be implemented: 0.25 mg orally in the evening once a day (0-0-1)

Increase in one to four-day- steps, according to the investigator's decision:

2. 0.25 mg by mouth BID (1-0-1),
3. 0.25 mg 1-0-2 orally,
4. 0.25 mg 2-0-2 orally,
5. 0.25 mg 2-0-3 by mouth,
6. 0.25 mg 3-0-3 orally,

7. 0.25 mg 3-0-4 p.o.,
8. 0.25 mg 4-0-4 orally

A maximum of 1 mg twice a day should not be exceeded. Between morning dose and evening dose a time interval of 12 h should be met. Preferably, tablets should be taken at the same time each day. In case a participant misses a dose, he/she will be instructed to take their next dose of nabilone at the normally scheduled time.

The increment of dosage should take place until the patient has much (CGI- I Rating Scale: 2) or very much (CGI-I Rating Scale: 1) improved, reached a maximum dose of 1 mg BID or experiences intolerable adverse events that are believed to be related to the study drug.

In the double- blinded withdrawal phase of the study, the participants will receive nabilone 0.25 mg – 1 mg BID or matching placebo, administered orally once or twice daily. During this phase the fixed dosage of the study drug should not be changed. If the patient deteriorates in his CGI-I, dose adjustments can be made and the patients restart again at titration phase.

### **7.1.3 Packaging and Labelling**

The IMP supplies for this study will be packaged according to current GMP guidelines and applicable national laws and regulations. For titration phase, IMP will be packaged in an open-label fashion and for the randomized withdrawal phase IMP will be packaged in a double- blind fashion. Packaging, labelling and distribution of IMP will be performed by the company Kwizda.

### **7.1.4 Handling and Storage Requirements**

The investigators will be responsible for ensuring the correct storage and sufficient stocks of the IMP and comparative drug at the trial centers. The investigator bears the responsibility for the proper storage in a secure location at the site which means in a lockable cabinet with restricted access to the investigator(s) and authorized site staff. Personnel having access to the IMP will be listed on the Authorization and Delegation log in the Investigator Site File (ISF). The investigators will ensure that the IMP is only used according to this protocol and will only be dispensed to participants of the study. Dispensing will be performed by authorized members of the study team. The investigator will be responsible for the Drug Accountability log. Drug accountability will be recorded in the patient's record as well. Drug accountability will be noted by a monitor during site visits and at the completion of the trial. Unused study drug from all sites will be sent to the company Kwizda for destruction after completion of the trial (LPLV).

## **7.2 Randomization and Blinding, Subject's Compliance**

### **7.2.1 Randomization and Numbering of Patients**

Responders according to the criteria, (see: Inclusion criteria 4.1.) are randomized in a 1:1 ratio to receive either nabilone or matching placebo for 4 weeks.

For randomization a generated list provided by the Statistics Department of the Medical University of Innsbruck will be used to distribute the patients to the placebo or nabilone group. The list will be kept at the Sponsor's premises.

Each patient will receive a unique number at the Screening visit to be identified throughout his/her participation in the study (in ascending order, starting with number 001 for the first patient). This number will be used in all communications between the investigator and the Sponsor for the specific patient.

A patient only enters the trial, if he meets all inclusion and none of the exclusion criteria during the screening visit. After assuring eligibility of the patient, the Sponsor or its designee will use the randomization list to assign the participant to a treatment group and the medication to be used will be determined. The allocated kit number to the specific participant for each visit and information about the blinded medication kits to be used will be given to the investigator by the Sponsor or its designees according to the randomization and the scheduled visits.

Therefore, the Sponsor or a designee needs to be provided with the randomization list and information on the medication that has been sent to the site.

In case of a drop-out, no replacement will be recruited and the screening number will be assigned as before in an ascending order.

### **7.2.2 Procedures for Maintaining and Breaking the Treatment Blinding**

#### **Maintaining the Treatment Blinding:**

All members of the study team on-site will be blinded to the treatment group of the patients in the four weeks of randomized, double-blinded, parallel-group, enriched-enrolment randomized withdrawal phase of the trial. Treatment Blinding will be maintained by receiving nabilone or placebo labelled and packed in an equal looking fashion so that the study team cannot distinguish between the two treatment groups. Randomization will be performed according to a randomization list no member of the study team will see before the end of the trial. The Sponsor will have separate documentation concerning the randomization which will be kept in the Trial Master File and stored at a locked cabinet of the Sponsor. No data

collected in the study should offer evidence of a participant's assignment to a particular study arm.

The patients will receive a screening number at the Screening Visit and will be randomized according to the randomization list. No patient will be informed about the assigned treatment group. Assignment will be documented by the Sponsor or its designee in the Trial Master File which will be stored securely at the Sponsor's premises.

### **Emergency Envelopes**

Emergency envelopes containing the patient's name, number in the trial, the assigned treatment group, the dosage, and the start and presumably end of the intake of study medication will be provided in case of need. These emergency envelopes will be provided by the Sponsor or its designee and will be stored on-site separately from study documentation in a locked cabinet. In case of an emergency, a member of the study team is allowed to open the emergency envelope on behalf of the principal investigator. Authorized members will be displayed in the Delegation Log. Opening the emergency envelopes has to be documented in the patient's records and the Sponsor or its designee has to be informed.

### **Unblinding**

All patients are allowed to be unblinded after the end of the trial (official closure of the study) by providing the documentation to the authorized investigators on-site. Authorization will be shown in the Delegation Log. The documentation will be provided by the Sponsor's or its designee. No patient is allowed to be unblinded before the end of the trial, except for emergencies. Premature treatment unblinding will be performed via the emergency envelopes by a member of the study team after consultation with the principal investigator in case of an "emergency". An emergency can be any event that is serious and related to the treatment in the investigator's discretion or an event for which knowledge of the treatment group is crucial (i.e. pregnancy).

## **7.3 Drug Accountability and Treatment Compliance**

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



(LPLV).

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

### **7.3.1 Procedures for Monitoring Patient Compliance**

In outpatient treatment procedures for the verification and documentation of the compliance will be as follows:

- The patients only receive the amount of medication units at each visit that will be needed until the next visit.
- The Investigator takes back the empty containers or non-used units.

The patient must return all used, unused, and partially used study drug supplies at the planned visits in the study course. Drug accountability must be done in the presence of the participant. Thus discrepancies between the dosing regime and the patient's compliance can be clarified directly. Drug Accountability must be recorded in the source documents and the Drug Accountability Log in the Investigator Site File.

The end of treatment for the patient should be documented at the Termination visit (week 4). In case of persistent noncompliance of a patient (<80% to >120% of the assigned dose), the Sponsor or its designee will be informed to decide together with the investigator whether the patient should be discontinued or not.

## **7.4 Prior and Concomitant Medications/Treatments**

### **7.4.1 Allowed Anti-PD Medications/Treatments**

All Anti-PD Medications are allowed in this study preconditioned the patient has a stable Parkinson's disease and that the regimens of Anti-Parkinson's medications, other current prescribed/non-prescribed medications or dietary supplements are stable for at least 30 days prior to screening and will be continued on the same doses and regimens.

The addition of any new anti-PD medication or other prescribed / non-prescribed drugs are prohibited during the study as well as changes to frequency or intervals between doses.

Participants will be 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 will be recorded in source documents.

### **7.4.2 Prohibited Concomitant Medications/Treatments**

Nabilone has an addictive and CNS depressing effect if taken together with diazepam, Na-Secobarbital, alcohol and codeine.

Interactions between nabilone and the following medications have been observed. Therefore, these the intake of these drugs during the course of the clinical trial is prohibited for participants of this study.

- amphetamine, cocaine, other sympathomimetics
- atropine, scopolamine, antihistaminics, other anticholinergic substances
- amitriptyline, amoxapine, desipramine, other tricyclic antidepressive drugs
- 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
- antipyridines
- theophylline
- naltrexone

## **7.5 Concomitant Non-Pharmacologic Therapies**

All non-pharmacological therapies (physical therapy, exercise, yoga, ...) the patient performs to improve his/her parkinson symptoms can be continued during participation in the study. During the trial, however, such non-pharmacological therapies should not be started. All non-pharmacological therapies will be documented in the source documents at the Screening Visit. The concomitant non-pharmacological therapies should be kept on the same levels during the study.

## 8 Adverse Events

### 8.1 Summary of known and possible Adverse Events of the IMP

Generally, nabilone is well tolerated.

**Common adverse reactions (>1/100 to <1/10) observed in patients are:**

- Somnolence
- Vertigo
- Euphoria
- Ataxia
- impaired vision
- difficulties to concentrate
- sleep disturbances
- dysphoria
- headache
- hypotension
- nausea
- dry mouth

Controlled trials with patients taking nabilone showed that at least one side effect occurred per subject. Most patients develop a tolerance in regard of adverse events concerning the CNS and therefore relaxation, somnolence and euphoria reside after some weeks. This effect is reversible.

**In therapeutic doses nabilone is a potential addictive drug.** The potential to cause mental addiction is unknown and no patient has shown withdrawal symptoms in clinical trials. In conjunction with psychological stress, an **overdose phenomenon** of nabilone can appear at therapeutic doses. Symptoms due to overdosing nabilone have been described as enhanced psychomimetic and psychological side effects of the drug. In clinical trials a normalization of the mental state of the patient was reached after 72 hours of withdrawal of the drug without additional therapy. One should monitor vital signs due to the possible occurrence of hypertension, hypotonia, and tachycardia.

No cases of patients taking doses above a level of 10mg daily have been described in clinical trials so far. Hereby, one would expect symptoms like hallucinations, anxiety, respiratory depression, and coma.

**No adaption of dose needs to be done in the elderly.** Nabilone should not be used in patients under the age of 18 years because it has not been studied in separate trials. The primary route of elimination of nabilone is biliary. Thus **it should not be used in patients with severe impairment of liver function.** No data in patients with impaired renal function have been collected, which is why it should be used with caution in these patients.

**Nabilone should not be used during pregnancy or lactation** because of the lack of data in this cohort. In experiments with animals, no reproductive toxicity has been described. No studies on carcinogenesis have been performed.

**Minor risks of nabilone (>1/10.000 to <1/1.000) include:**

- Confusion
- Disorientation
- Hallucination
- Psychosis
- Depression
- difficulties in coordination
- tremor
- loss of appetite
- anxiety
- depersonalisation
- tachycardia
- abdominal pain

The IMP can cause alterations of physical and mental capabilities which are essential for tasks requiring high attention e.g. driving or operating machines. The study medication can be detected in the body after withdrawal (total half-life 35 hours) which could lead to misinterpretation in case of a control through regulatory authorities e.g. police.

## **8.2 Definition of an Adverse Event (AE)**

An adverse event is “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment”. (47)

An AE can therefore be any unfavourable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease which is considered to be clinically relevant by the physician and is temporally associated with the use of a medicinal

(investigational) product, whether or not related to the study drug.

Adverse events include:

- Worsening or increase in frequency or intensity of a pre-existing disease or medical condition in an unexpected manner
- Abnormal laboratory tests (clinically significant)

Adverse events do not include:

- Pre-planned interventions/hospitalizations
- Medical or surgical procedures, e.g. surgery, endoscopy, tooth extraction, transfusion. However, the event leading to the procedure is an AE. If this event is serious, the procedure must be described in the SAE narrative.
- Pre-existing disease or medical condition that does not worsen.
- Overdose of either study drug or concomitant medication without any signs or symptoms.

In order to ensure complete safety data collection, all AEs occurring during the study (i.e., after the signing of the ICF), including any post-treatment periods required by the protocol, must be recorded in source documents even if no investigational product was taken but specific study procedures were conducted. This includes all AEs not present prior to the Screening Visit and all AEs that occurred or worsened after the Screening Visit. Events that occur prior to giving informed consent are captured as medical history.

Signs or symptoms of the disease for which the investigational product is being studied should be recorded as an AE if their frequency or intensity increases in a clinically significant manner or their nature changes unexpectedly as compared to the clinical course known to the investigator from the patient's history, or the natural course of the disease.

### **8.3 Definition of a Serious Adverse Events (SAEs)**

“A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect”. (47)

An adverse event is therefore considered serious by the definition by the International Conference on Harmonization (ICH) guidelines if it can be characterized by at least one of the following criteria:

- Results in death

- is life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it had been more severe.
- requires inpatient hospitalization or prolongs an existing hospitalization
- causes persistent or significant disability or incapacity (i.e. a substantial disruption of a person's ability to conduct normal life functions)
- or is a congenital anomaly/birth defect (including that occurring in a fetus)
- or requires medical or surgical intervention to prevent one of the above mentioned outcomes. (i.e. the development of drug dependency or drug abuse)

Inpatient hospitalization is defined as an overnight stay in a hospital unit and/or emergency room that includes at least one night (midnight to 06:00 AM).

The following is not considered as a SAE and should be reported as an AE only:

- Treatment of an emergency or outpatient basis for an event not fulfilling the definition of seriousness given above and not resulting in hospitalization

The following reasons for hospitalization are not considered as AEs or SAEs:

- Standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g. hospitalization for coronary angiography in a subject with stable angina pectoris
- Elective treatment of a pre-existing disease or medical condition that did not worsen, e.g. hospitalization for chemotherapy for cancer, elective hip replacement for arthritis
- Hospitalization for cosmetic elective surgery, social and/or convenience reasons

A change in vital signs, diagnostic tests (e.g., an electrocardiogram), or laboratory test results may be an SAE if the change meets one of the above criteria.

## **8.4 Adverse Drug Reaction (ADR) & Unexpected Adverse Drug Reaction**

An ADR is any noxious and unintended response to an IMP related to any dose with at least a reasonably possible causal relationship with the IMP.

Unexpected ADR means the nature or severity of which is not consistent with the applicable product information available for the IMP. Expected ADRs are listed in the appropriate reference documents (e.g. Investigator's Brochure).

## **8.5 Suspected Unexpected Serious Adverse Reactions (SUSARs)**

A SUSAR is an event that is believed to be at least possible related to the administration of the study drug and is severe and unexpected. It therefore may illustrate a side effect of the drug. For clinical studies in which an IMP is used, the FDA defines an “unexpected” AE as an AE that has never been seen before, or is not consistent with the information about the drug’s risks in the relevant source documents (e.g. Investigator’s Brochure).

## **8.6 Pregnancy**

In the event a patient becomes pregnant after the first intake of any IMP, the investigator and the Sponsor should be informed immediately. The patient should be withdrawn from the study as soon as pregnancy is known, and should immediately stop the intake of the IMP. If a pregnancy should be confirmed after informed consent has been obtained but prior to the initiation of the study drug, the patient must be excluded from the trial. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications (including spontaneous abortions) and elective terminations must be reported as an AE or SAE. Any SAE occurring in association with a pregnancy brought to the investigator’s attention after the subject has completed the study and considered by the investigator as possibly related to the IMP, must be promptly reported to the Sponsor.

The participant should return for an Early Termination visit as soon as possible and should be followed by via a Safety Follow-Up Visit 14 days + 2 days after discontinuation of the study drug (if the ET is performed after 5 days after the last intake of study drug). The investigator must inform the patient of currently known potential risks for pregnancy outcome and available treatment alternatives.

In case the partner of a male patient enrolled in the clinical study becomes pregnant, the Sponsor must be informed immediately by the investigator or designee and a decision of the further procedure will be made.

The pregnancy will be documented in the source documents including the progression of the pregnancy and the eventual date of birth (if applicable) as well as the health of the mother and of the child. The health of the child must be followed for 30 days after birth for any significant medical issues.

A pregnancy becomes an SAE in the following circumstances: miscarriage, abortion, or anomaly/birth defect of the child. Those SAEs must be reported to the Sponsor as described below.

As the consent for the study does not cover the consent for the follow-up of the pregnancy, a separate consent has to be obtained.

## 8.7 Overdose of Investigational Medicinal Product

If the patient has taken a dose beyond that prescribed in the protocol (including section on overdose) should be recorded in the source documents and in the Drug Accountability.

These events are only considered to be AEs or SAE if there are associated clinical signs and symptoms or if the act of taking the excess medicine itself is an AE or SAE (e.g., suicide attempt). Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or AE.

## 8.8 Grading of Severity of Adverse Events

The term “serious” in SAE refers to the outcome of a patient’s event that poses a threat to his/her life or functioning rather than to its intensity, which is described by the term “severity”. In the latter, the event itself may be of relatively minor medical significance (such as a severe headache).

Intensity of all adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 on a five-point scale (grade 1 to 5) and reported in detail in the patient’s records and CRF.

Adverse events not listed in the CTCAE version 4.03 should be graded as follows:

Table 4: CTC grading of Adverse Events

CTC grade	Equivalent to	Definition
Grade 1	mild	Discomfort noticed but no disruption of normal daily activity
Grade 2	moderate	Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall wellbeing or symptoms of the patient.
Grade 3	severe	Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall wellbeing or symptoms; delaying the onset of treatment is not putting the survival of the patient at direct risk.
Grade 4	life-threatening / disabling	An immediate threat to life or leading to a permanent mental or physical condition that prevents work or performing normal daily activities; treatment or medical intervention is required in order to maintain survival.
Grade 5	death	AE resulting in death



## 8.9 Causality

The assessment of relationship of adverse events to the administration of IMP is a clinical decision based on all available information and considering all relevant factors such as (but not limited to) the underlying indication, coexisting diseases, concomitant medication, etc. at the time of the completion of the patient's record and case report form of this visit.

The term "related" refers to the ability of the study drug to cause the AE implicating a relationship in time and that the event would not have happened without the effort of the study drug.

The question: "Is there a reasonable possibility that the study drug caused the event?", should be asked. Answer **YES** (possibly, probably or definitely related) if one or more of the following criteria apply:

- The event follows a reasonable temporal sequence from administration of study drug
- The event could not be reasonably attributed to the known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient
- The event follows a known pattern of response to study drug
- The event disappears or decreases on cessation or reduction in dose of the study drug. (It should be noted that in some situations an AE will not disappear or decrease in intensity upon discontinuation of study drug despite other clear indications of relatedness).

Otherwise answer **NO** (not related).

Moreover, the relationship between the AE and the study drug can be described stepwise:

- definitely related: an AE that follows a temporal relationship with implementing the study drug and a known response pattern to it and cannot be otherwise explained by the patient's medical condition or concomitant medication
- probably related: meets all criteria mentioned above and has to improve after de-challenging the patient with the study drug.
- possibly related: an AE that has a temporal relationship between administration of the study drug and its occurrence and is a known response pattern to the IMP but could also be explained by the patient's medical history or treatment.
- Unrelated: an AE without a relationship in time to study drug treatment and which is most likely explained by the patient's medical condition or therapies.

## 8.10 Recording, Reporting, and Follow-Up Procedures

## **8.10.1 Procedures for Recording, Reporting, and Follow-Ups of Adverse Events**

### **Recording and Reporting of Adverse Events**

The patient will be given the opportunity to report AEs spontaneously at every on-site visit and telephone call. Moreover, the rater will propose an open-ended, non-leading question to the participant to detect AEs.

Documentation needs to be done in the patient's medical record and in a special section for adverse events in the CRF where the following details must be entered:

- Type of adverse event (diagnosis or syndrome; if not known signs or symptoms)
- Start (date)
- End (date)
- Severity (mild, moderate, severe, life-threatening/disabling, death)
- Serious (no / yes)
- Unexpected (no / yes)
- Outcome (resolved, ongoing, ongoing – improved, ongoing – worsening)
- Action taken (none, study medication dose reduced, study medication interrupted, study medication discontinued, medication therapy, surgical procedure, hospitalization, other)
- Relation to study drug (possibly, probably or definitely related or not related)

The investigator should use syndromes or diagnosis of standard medical terminology to record adverse events, whenever possible.

The Sponsor should be informed immediately by the investigator on-site, if an AE is thought to be at least probably related to the study drug treatment to discuss whether or not the administration of the IMP should be stopped.

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events
- Pregnancies

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e. no more than 24 hours after becoming aware of the information).

New significant information includes the following:

- New signs or symptoms or a change in the diagnosis.
- Significant new diagnostic test results.
- Change in causality based on new information.
- Change in the event's outcome, including recovery.
- Additional narrative information on the clinical course of the event.

Investigators must also comply with local requirements for reporting SAEs to the local health authority and IRB/EC.

### **Follow Up of Adverse Events**

An AE will be followed until the patient has recovered/ it has resolved, has reached a stable state, the investigator determines that it is no longer clinically significant, or the patient is lost to follow up. The end of an AE should be documented in the CRF and the patient's record. If an AE is still ongoing at the end of the study for a patient, follow up will be provided until resolution/stable level is achieved, or until it no longer is clinically significant by the judgement in the investigator, or until the patient is lost to follow up. In the latter the investigator has to take all possible actions in the discretion of his judgement to contact the patient and document a loss of follow-up in the source documents.

In case of withdrawal from the study due to an AE, an Early Termination (ET) Visit will be scheduled as soon as possible followed by a Safety Follow-Up Visit after 2 weeks + 2 days of the ET (if the ET is performed after 5 days after the last intake of study drug).

## **8.10.2 Recording, Reporting, and Follow-Up Procedures for Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions**

### **Reporting and Recording of Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions**

Investigators will seek information on SAEs and SUSARs at each patient contact throughout the trial. As for all AEs, whether reported by the patient or noted by study personnel, SAEs and SUSARs will be recorded in the patient's medical record and on the Adverse Event Section of the CRF.

In the event of a **serious adverse event**, the investigator has to use all supportive measures for best patient treatment. An SAE form must be completed by the investigator and reported no more than 24 hours after receiving notice of the event.

The site must provide the Sponsor with a detailed description containing at least the symptoms and course of events, the actions taken, the medication given and if the dose of the study drug was changed. The following details should be available with the initial report:

- Patient number
- Patient: date of birth, ethnic origin
- Name of investigator and investigating site
- Period of administration
- The suspected investigational medicinal product (IMP)
- The adverse event assessed as serious
- Concomitant disease and medication
- Relevant medical history
- Short description of the event and outcome
- Description
  - Onset and if applicable, end
  - Therapeutic intervention
  - Causal relationship to each of the study drugs (for definition see: 8.2.1.)
  - Hospitalization or prolongation of hospitalization
  - Death, life-threatening, persistent or significant disability or incapacity

This insight from the investigator is very important for the Sponsor to assess the safety of the IMP and in determining whether the SAE requires reporting to the regulatory authorities in an expedited manner.

In case of a new development of the event, the initial report should be followed by the follow-up report, indicating the outcome of the SAE.

A copy of the reports will be provided to AOP Orphan Pharmaceuticals for safety records.

**SUSARs** need to be reported and followed up in the same manner as SAEs. The Sponsor decides if the event needs to be classified as a SUSAR in discussion with the investigator. Therefore, detailed information about the event and the subsequent actions should be made available within 24 hours by the investigator and any relevant updates should be reported within 24 hours. SUSARs will be reported to the required regulatory authorities, investigators/institutions, and ethical committees in compliance with all reporting requirements according to local regulations and good clinical practice by the Sponsor and/or its designees.

After informed consent has been obtained but prior to initiation of the study drug, only SAEs considered to be related to a protocol-mandated intervention should be reported (e.g. SAEs related to invasive procedures such as withdrawal of blood).

### **Follow Up of Serious Adverse Events and SUSARs**

For SAEs, SUSARs and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g. from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

An SAE and SUSAR will be followed until it has resolved, has reached a stable state, the investigator determines that it is no longer clinically significant, or the patient is lost to follow up.

If an SAE or SUSAR of a participant is still ongoing at the end of the study, follow up will be provided until resolution/ a stable level is achieved, or until the SAE or SUSAR is no longer clinically significant by the judgement in the investigator, or until the patient is lost to follow up. In the latter the investigator has to take all possible actions in the discretion of his judgement to contact the patient. A loss of follow-up should be documented in the source documents.

In case the IMP was withdrawn due to an SAE or SUSAR, patients will be advised to come to the hospital as soon as possible for an Early Termination Visit (see 5.5). A Safety Follow-Up Visit should be performed 2 weeks + 2 days after the last intake of study medication (if the Early Termination Visit occurs not longer than 5 days after the discontinuation of the study medication). (see 5.4) The patient should be followed up until he/she has recovered/ it has resolved, has reached a stable state, the investigator determines that it is no longer clinically significant, or the patient is lost to follow up.

## **8.11 Review and Annual report on Adverse Events, Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions**

Data from this study will be reviewed periodically by the Sponsor or a designee to detect any safety concern(s) related to the study drug as early as possible so that the investigators, regulatory authorities, and IRB/IEC will be informed appropriately and as early as possible. SAEs will be reviewed ongoing and reconciliations will be performed in collaboration with the Sponsor of the study.

If necessary, additional safety measurements can be implemented during the course of the

study after approval by the local IRB/IEC and regulatory authorities.

Once per year, the Sponsor or principal investigator will supply a report on the safety of trial subjects with all available relevant information concerning patient safety during the reference period to the competent supreme federal authority where the trial is being conducted. This report will also be supplied to the responsible ethics committee.

The annual safety report will be compiled according to the corresponding ICH guideline E2F „Development Safety Update Report – DSUR“.

The data lock point for the patient data to be included and analyzed is the day of the overall approval of the clinical trial.

The Sponsor or principal investigator will supply the report within 60 days of one year after the reference date (data-lock point).

## 9 Documentation

The accomplishments of the study in agreement with the GCP-guidelines and the investigational plan as well as the accuracy of all data documented in the CRF are the responsibility of the Investigator. All collected data of this study have to be recorded on the CRF and/or the patient's record by appropriate authorized persons. This also includes data of patients who dropped-out of the study. It has to be assured that all persons authorized for CRF entries can be identified. A list with signatures and identification codes of the persons must be archived in the ISF and TMF. Moreover, logs according to ICH E6 (e.g. Signature/Delegation/Screening/Drug Accountability log) will be implemented and maintained by the investigator.

The investigator records the participation of a patient on a special identification list of patients (Screening Log). This list gives the possibility for a later identification of the patients and contains the patient number, full name, date of birth and the date of the enrolment into the study. The identification list of patients remains in the study center after the closure of the study. Additionally, the participation of the patient in this clinical study has to be recorded in the patient's medical record.

Each patient will receive a unique patient identification number. Data will be documented using this code for each patient that will also be used for communication with the Sponsor and other authorities. Only the Investigator and his/her designees will be able to connect the number and the patient's name. Data collection must be completed for each subject which has signed an ICF and was administered study drug.

Patient's data will be stored on-site in a locker to which only the investigator and his/her designees have access. Personal patient information (such as name, date of birth etc.) is stored separately from the research data.

For all work involving data collections of human information, electronic or otherwise, the study centre will adhere to the law as laid down in the European Regulation (EU) 2016/679 (Regulation (EU) of the European parliament and of the council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)) as well as national data protection law. These concern the protection of individuals with regard to the processing of personal data and on the free movement of such data. Adequate measures to ensure data protection, confidentiality will be duly taken into account by the Investigators and all parties involved in the study.

## **9.1 Data Recording (Case Report Form, CRF and Patient's Record)**

In this study, a Case Report Form (CRF) will be used for direct entry of the assessments of the scales used and for the telephone calls. Demographic data, medical history, neurological and PD history, medication history (including anti-parkinson's disease medication), adverse events (including SAEs, SUSARs, ADRs), concomitant medication, the assessments of Vital Signs, and the neurological and physical examination will be provided at the Screening Visit in the CRF. The patient's record will be used to document the date and identification of the visit, the investigator(s) conducting the visit, the process of Informed Consent (the description of the process of informed consent, the person conducting Informed Consent, the date, time, and version of ICF), the time and date of all the assessment of the clinical scales, the time and date of blood samples and urinalysis, the time and date of ECG analysis, protocol deviations (including actions), and the Drug Accountability (for returned and assigned kits). The results of blood samples, urinalysis and ECG will be kept in the patient's file.

The CRFs and the patient's records are established to implement the Clinical Study Protocol, to facilitate subject observation and to record subject and IMP data during the clinical investigation according to the trial's protocol. In this study, they exist as printed or written documents and are direct-entry CRFs.

In the patient's record and the CRFs, the following data should be documented:

- the date and identification of the investigation, including the version number of the Clinical Study Protocol;
- identification of the subject, date of enrolment, demographic data (at the Screening Visit);
- identification of the IMP by lot number and kit number (if applicable);
- medical diagnosis for which the subject is to be treated with the IMP to be investigated together with any concomitant illness (at the Screening Visit);
- subject compliance information for concurrent procedures measures and for any emergency;
- relevant previous medication and/or procedures (at the Screening Visit only);
- subject baseline characteristics (at the Screening Visit only);
- concomitant medication and/or procedures;
- compliance with the inclusion/exclusion criteria;
- dated clinical and non-clinical findings according to the Clinical Study Protocol;
- procedural data;



- subject assessment during the use of the IMP and follow-up with dates;
- reported adverse events and adverse effects with dates;
- date of the end of follow-up;
- signature(s) of the clinical investigator(s) at the completion of follow-up

Therefore, the CRF and the medical record of the patient will be a source document in this study.

Only the use of ballpens is allowed for the entry in paper-based records. Corrections have to be made in a way, that the previous entries remain readable (the use of any instrument of correction is not allowed). Corrections have to be signed and dated by the authorised person, who made the corrections. Data, which are not available or were not collected, have to be clearly identifiable as such (NA). The reasons should be documented, if necessary.

The investigator assures, that all data of patients are recorded immediately, readable, completed, and correct in the patient's chart and in the CRFs.

After the end of the study (end of the study defined as the last visit of the last patient) and after the verification regarding the plausibility and completeness by the Monitor, all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file. Source data will be stored for 30 years (for medical records and other original data) after the end of the study (i.e. last visit of the last patient) according to local and national regulations. It is the responsibility of the investigator to inform the Sponsor before study related documents will be destroyed.

Monitors, auditors, and other authorized agents of the Sponsor or its designee, the EC/IRB approving the research, local law regulatory agents and appropriate authorities in conducting investigations for which the person's medical history is necessary will be granted access to the study subject's original medical records without violating the confidentiality of the subject to the extent permitted by the law and regulations. In any presentation of the results of this study or in publications, the subject's identity will remain confidential.

## **9.2 Trial Folders**

The trial folders should serve as gapless documentation. Individually or together they should allow the evaluation of the trial implementation as well as quality of data.

### **9.2.1 Trial Master File (TMF)**

The paper-based TMF, established at the beginning of the trial and secured in a safe place, contains all essential documents that demonstrate that the trial is conducted in accordance with regulatory requirements and ICH GCP. All documents will be maintained and updated

as appropriate throughout the trial. Previous versions of the documents must be retained in the TMF and will be clearly labelled as outdated. Previous versions will be relocated in a section for outdated documents. The TMF is archived at the end of the study for 15 years.

### **9.2.2 Investigator Site File (ISF)**

The paper-based ISF, established at the beginning of the trial will be secured in a safe place (the file is provided to the site at the site initiation visit). It contains all essential documents maintained by the PI. All documents will be maintained and updated as appropriate throughout the trial. Previous versions of the documents must be retained in the ISF and will be clearly labelled as superseded-previous versions will be relocated in a section for outdated documents. Within each monitoring visit, the ISF will be checked for actuality and completeness in accordance to the formalities. After completion or discontinuation of the study this ISF has to be kept for 15 years.

## **9.3 Data Storage**

### **9.3.1 Storage duties of the Sponsor**

The Sponsor has to keep all study-relevant documents of the clinical study after completion or discontinuation of the study for a minimum of 15 years.

### **9.3.2 Storage duties of the investigator**

The Investigators have to keep all records and documents, which are related with the study or the allocation of investigational medicinal products (e.g. data entry form, consent form, list of the allocations of investigational medicinal products and further relevant documents), for a minimum of 15 years. Medical records and other source data (e.g. paper-based CRF) have to be kept for 30 years.

## **10 Data Management**

Data are administered and processed by members of the study team with the support of the software Microsoft Word, Excel, and IBM SPSS Statistics.

The evaluation of the data takes place by the programmed range-, validity- and consistence checks. In addition to that a manual/visual evaluation of the plausibility in accordance with the requirements of the GCP is performed. Queries may occur, which will be forwarded to the investigator by the Monitor of the study. By means of the queries the investigator has to evaluate and respond to the accrued discrepancies. After the record of all entries and clarification of all queries, the data based will be closed at the completion of the study. This performance has to be documented.

## **11 Protocol Deviations**

All deviations to the study protocol have to be documented in the patient's record with the explanation for variance. Deviations have to be announced to the Sponsor, who is responsible for their evaluation, within 24 hours after receipt of knowledge. The report should include the patient's study code, sex, year of birth, a brief description of the event, the cause of it (if applicable), the time, the date, the duration of the event, and the corrective and preventive measurements performed. Protocol Deviations will be reported to the Sponsor to decide if the patient will be discontinued in the study or not.

The Sponsor can terminate a trial during the course of it, whenever a reason for concern appears. The Sponsor or the investigator can discontinue a patient's participation in the trial on their behalf (for criteria see 4.3). Reasons for termination of a trial or of a study participant have to be documented in the patient's record or other source documents. In case of a security termination, the test person has to be further monitored. Deviations have to be analyzed whether changes of the clinical investigation plan or the closure of the study are necessary. If necessary, the ethics committee or the responsible authorities have to be informed.

In case of a withdrawal from the study, the data will be included in the analysis up to the time of discontinuation.

## 12 Statistical Analysis

### 12.1 Determination of Sample Size

This is a phase 2 randomized clinical trial that uses an enriched enrolment randomized withdrawal design to evaluate the effects of continuous nabilone therapy versus withdrawal to placebo in patients with PD suffering from NMS. This design has the advantage that the patient population enrolled is enriched by including only responders. (48) Moreover, exposure of patients to placebo during the withdrawal phase may be shorter than in a randomized treatment phase.

The power calculation refers to the primary endpoint of the study, i.e. change of MDS-UPDRS Part I score from randomization to Week 4 during the placebo-controlled, double-blind, parallel-group randomized withdrawal phase (i.e. phase 2 of the study). A total of 38 patients (19 in each group) will have 80% power to detect a probability of 0,231 that an observation in Group 1 is less than an observation in Group 2 using a Wilcoxon (Mann-Whitney) rank-sum test with a 0,050 two-sided significance level. With this, a statistically significant difference in the change from randomization to Week 4 in MDS-UPDRS Part I score between nabilone and placebo will be detected if the true difference is 2.5 points. In the absence of previous data, we empirically chose as clinically meaningful a 2.5 units change from randomization to the visit at 4 weeks (in phase 2) This sample size calculation assumes a standard deviation of the change from randomization to week 4 to be 2.4 points. (46) Assuming a drop-out rate of 25%, we plan to include around 48 patients with Parkinson's disease in this trial. The sample size calculation was performed with the Program nQuery Advisor (Version 7).

Importantly, although a sample size calculation is provided, this is an exploratory study evaluating different NMS domains. Therefore, corrections for multiple comparisons are not planned.

### 12.2 Study Populations: Datasets or Populations analyzed

The primary analysis will be performed including all randomized subjects with scoring of MDS-UPDRS Part I at randomization and 4-week follow-up. The subjects will be grouped according to the randomized treatment group (nabilone or placebo) and all summaries and efficacy analysis will be based on the set. In case of a drop-out, no interpolation can be performed. Therefore, the primary analysis is a per-protocol analysis.

Safety and tolerability summaries will be based on a safety set which will include all patients receiving at least one dose of study medication during the randomized trial phase. The subjects will again be grouped by their assigned treatment group during the study. The safety set will be used for summaries of safety and tolerability. Additionally, summaries of baseline and demographic data will be produced out of the safety set.

## **12.3 Background and Demographic Characteristics**

All baseline and demographic summaries will be produced for the data of patients gained at the Screening Visit. The data will be given for participants being randomized in V 0.

The number and characteristics of patients in every safety set, the number and characteristics of patients assigned to a specific treatment group, the number of AEs, SAEs and SUSARs with description, the number of subjects with premature discontinuation from the study/or the study drug along with reasons for discontinuation will be provided. Furthermore, the number of screened subjects, the number of screening failures and reasons why they have been excluded will be given.

A consort diagram will be provided.

## **12.4 Efficacy Variables and Analysis**

This is a phase II randomized clinical trial that uses an enriched enrolment randomized withdrawal design to evaluate the effects of continuous nabilone therapy versus withdrawal to placebo in patients with PD suffering from NMS followed by an open-label treatment phase. The primary and key secondary efficacy criteria refer to the randomized, double-blind, placebo-controlled enriched enrolment randomized withdrawal phase of the study. Data analysis will be performed using IBM SPSS Statistics Software and Microsoft Excel.

Results of the changes of all clinical scales in this trial will be shown in a descriptive way by median and interquartile range (quartile 1, quartile 3), separately for the nabilone and placebo of the clinical trial. Mean and standard deviation for the descriptive analysis of the two study arms will also be provided. P-values for the change of the results will be given.

The primary efficacy criterion will be measured as the change of the MDS-UPDRS Part I between baseline (i.e. randomization) and week 4. The key secondary efficacy criteria will be measured as the change in the other clinical scales and questionnaires between baseline and week 4, except for the CGI-I measures, which will be singularly evaluated at week 4.

Because an interpolation of data will not be performed in case of a drop-out, the primary analysis is a per-protocol analysis.

For the study's primary efficacy and key secondary efficacy analyses, mean changes from randomization to 4-week follow-up in the nabilone and placebo groups will be analyzed separately for the two groups by Wilcoxon matched-pairs test and then compared by Mann-Whitney U test. (49)

For all analyses, statistical significance will be set at the 2-sided 5% level. Additionally, a sensitivity analysis will be performed for a primary efficacy or key secondary efficacy variable, if mean value of an efficacy variable should be different at randomization at a 2-sided 10% level (using Mann-Whitney U tests). To estimate the treatment effect, we will then compare mean change from randomization to 4 weeks-follow-up in both treatment groups using analysis of covariance, with value at randomization as covariate and treatment group as main effect.

Moreover, sensitivity to treatment will be assessed using effect sizes of the different outcome variables when using nabilone to treat non-motor symptoms in Parkinson's disease.

For CGI analyses, distributions of aggregated ratings (amelioration, aggravation) in the nabilone and placebo groups at 4-week's- Termination Visit will be compared by Fisher exact test. (49)

All other analyses on the exploratory efficacy criteria will be performed with paired Wilcoxon signed-rank tests separately for the two treatment groups and compared by Mann-Whitney U tests. (49)

## **12.5 Safety Analysis**

The primary safety analysis will be performed with the safety data set. Distributions of AEs, SAEs, and SUSARs in the nabilone and placebo groups at week 4 will be compared by Fisher exact test. Additionally, a safety analysis will be performed on all events as well as the hallucination item, orthostatic hypotension item and day-time sleepiness item of Part I of MDS-UPDRS occurring through the overall study. This will be a descriptive analysis reporting overall number and frequencies of the item's points score, AEs, SAEs, and SUSARs in patients taking nabilone or placebo. Data will be presented separately for the nabilone and placebo group.

Separate summaries of AEs in regard of severity and relationship to the study drug, separate summaries of AEs leading to withdrawal from the study and separate summaries for SAEs will be provided.

Tolerability measures will be provided in a descriptive analysis and will include the number of patients who discontinued from the study (%) and the number of patients who discontinued from the study due to an AE (%).

Safety measures include vital signs including performance of active orthostatism, a 12-lead ECG, the hallucination item (1.2, 0 – 4 points) of MDS-UPDRS Part I, the orthostatic hypotension item (1.12, 0 – 4 points) of MDS-UPDRS Part I, the Daytime sleepiness item (1.8, 0 – 4 points) of MDS-UPDRS Part I, and the C-SSRS. All patients will therefore be questioned about the occurrence of an AE at each scheduled and unscheduled on-site visit or telephone visit.

Vital signs including performance of active orthostatism will be taken at any scheduled visit on-site. (see 7.2) In the latter the heart rate and blood pressure of the patient will be measured after 10 minutes of quiet resting in a supine position and at 1, 2, 3, 5, and 10 minutes - time points of active standing.

Clinical examination, ECG, and laboratory assessment including urinalysis and urine pregnancy test for women of childbearing potential will be executed at the Screening Visit (laboratory assessment and ECG if not performed within 4 weeks prior to Screening), the Baseline Visit (clinical examination only), the Termination Visit, an Early Termination Visit (if applicable), and the Safety Follow-Up Visit (except for ECG, laboratory testing and urinalysis).

For the Eye-tracking analyses, mean changes from Screening Visit to the Termination Visit in the nabilone and placebo groups will be analyzed separately for the two groups by Wilcoxon matched-pairs test and then compared by Mann-Whitney U Test.

## **12.6 Handling of Missing Data**

After withdrawal of study drug treatment, all patients will perform an ET visit. All withdrawals from the study or the study drug will be included in the safety analysis up to the time of discontinuation regardless of the duration of their participation. In case of a drop-out, no interpolation can be performed. Therefore, the primary analysis is a per-protocol analysis.

## **13 Quality Management**

Training, monitoring and audits are performed for quality assurance reasons within this clinical study. Monitoring and auditing procedures developed or endorsed by the Sponsor will comply with ICH-GCP guidelines and local legal requirements to ensure acceptability of the study data and patient's safety.

### **13.1 Qualifications**

The Sponsor is responsible for selecting the investigator and Institution. Each investigator should be qualified by training and experience and should have adequate resources. Each individual involved in conducting a trial should be qualified by education, training and experience to perform his or her respective task(s) (see ICH GCP E6).

To meet those objectives, every member of the study team must be GCP-trained. A Certificate of MDS-UPDRS Training, a C-SSRS Training Certificate, and experience in using the other scales (e.g. MMSE) must be provided by every investigator in the trial who intends to use these scales. The members of the study team must be trained on the trial's protocol and the completion of the source data entry (CRF and patient's record) by the principal investigator. This process has to be documented in the ISF. Authorization of a member of the study team to perform study related tasks have to be reported in the Delegation Log of the ISF.

### **13.2 Monitoring**

A study monitor will perform source document verification at regular intervals in accordance with GCP and ICH guidelines. The objectives of the monitoring procedures are to ensure that the trial subject's safety and rights as a study participant are respected, that accurate, valid and complete data are collected, used, and stored, and that the trial is conducted in accordance to the trial protocol, the principles of GCP and local legislation.

All investigators agree that the monitor regularly visits the trial site. For monitoring, all study-related documents must be given access to the monitor by the investigator for confirmation of data. Moreover, the investigators assure that the Monitor will receive appropriate support in their activities at the trial site, as agreed in separate contracts.

The Informed Consent Form (ICF) includes a statement that the Monitor has the right – while observing the provisions of data protection legislation – to compare CRFs with the trial subject's medical records (doctor's notes, ECGs, laboratory printouts etc.).



A study specific monitoring plan will be established and the study will be monitored with the agreed plan.

All representatives from regulatory authorities and the EC/IRB will be gained access to the study-related documents needed for their investigation. Protection of the patient's personal data will be guaranteed to the extent possible.

### **13.3 Audits and Inspections**

During the course of 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 has to grant direct access to all data and must provide support at all times.

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, CRFs, trial subject's medical records, drug accountability documentation, and trial-related correspondence).

After each external audit an audit-certificate by the Auditor has to be delivered to the investigator. This certificate has to 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. An audit-certificate will be attached to the final report at the end of the study. Additionally, according to the Austrian Medicines Law (AMG) 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.

## **14 Reporting**

### **14.1 Annual Progress Reports**

The Sponsor/investigator will submit a summary of the progress of the trial to the accredited EC and to the competent supreme federal authority (if applicable) once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, data of safety of the trial subjects including serious adverse events/ serious adverse reactions, other problems, protocol deviations and amendments.

The annual safety report will be compiled according to the corresponding ICH guideline E2F „Development Safety Update Report – DSUR“.

The data lock point for the patient data to be included and analyzed is the day of the overall approval of the clinical trial. The Sponsor or principal investigator will supply the report within 60 days of one year after the reference date (data-lock point).

### **14.2 Final Study Report**

The end of the study is defined as the last visit of the last patient of the study (LPLV).

On completion of the study, the EC/IRB, and the regulatory authorities will be notified that the study has ended. Within one year after the end of the study, the investigator/Sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited EC/IRB.

All information regarding this clinical study has to be kept in confidence. The statistical analysis and the integrated final study report will be prepared according to ICH E6 and finalized within 12 months after the last patient's last visit (LPLV) took place. The final study report will be reviewed and signed by the Sponsor, the principal investigator and all further responsible persons. All information in that report is strictly confidential.

The principal investigator will sign the final study report of the clinical trial. This confirms that the report describes implementation and results of the clinical trial by the best of his knowledge.

## **15 Publication**

The results of this study will be published according to the principles of publication policy. There are no arrangements on publication issues with subsidizing parties.

## **16 Amendments**

Amendments must be submitted to the appropriate regulatory authorities and ethical committees. Substantial amendments may be implemented only after approval of both parties has been obtained. Urgent amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving approval. However, approval must be obtained as soon as possible after implementation. Therefore, the Sponsor or its designee must inform the regulatory authority and the EC about the new events, the measures taken and their plan for further action as soon as possible. The procedure should be held as follows: immediate telephone contact, followed by an e-mail or FAX notice, followed by a follow-up letter.

# 17 Ethical and Regulatory Aspects

## Ethical Conduct of the Study

Ethics committee (EC) authorization for this study will be required. The project raises important issues of consent, confidentiality, data security, quality control, and national data protection legislation. To protect the information on each participating individual, protect privacy, and prevent misuse of data, all investigators and all parties involved in this study will adhere to national codes and rules for working with participant's clinical data. Participants will be labeled in a coded fashion with unique identifiers. Data will be held secure and confidential and kept apart from personal identifiers.

The project will be conducted in strict adherence to the Convention for the Protection of Human Rights and Fundamental Freedoms, and EU regulations on ethical issues including Regulation (EU) 2016/679 on the protection of individuals regarding the processing of personal data and the free movement of such data and the Directives 2001/20/EC, and 2005/28/EC relating to implementation of good clinical practice in the conduct of clinical trials.

## Regulatory Requirements

The present study will be conducted in compliance with Good Clinical Practices (ICH-E6: GCP recommended for adaptation on 1st of May 1996 by the ICH Steering Committee), the Declaration of Helsinki in its latest version concerning the conduct, evaluation and documentation of the study, the "Charter of Fundamental Rights" of the European Union (2000/C 364/01), the local laws and regulations and the applicable regulatory requirements.

When conducting a clinical trial on drugs for use in humans in Austria the Medicines Act ("Arzneimittelgesetz", AMG) has to be considered. This Act implemented the European Directives 2001/20/EC and 2005/28/EC into national law. In particular, section III (Clinical Trials) is relevant for the conduction of a clinical trial.

## 17.1 Responsibilities of the Sponsor and the investigator

The Sponsor of this clinical trial will assume responsibility for inducement and organization of the implementing trial according to the AMG. The procedures set out in this study protocol are designed to ensure that the Sponsor and the investigator abide the principles of ICH E6 recommended for adaptation on 1st of May 1996 by the ICH Steering Committee and the Declaration of Helsinki concerning the conduct, evaluation and documentation of the study. The study will also be performed adhering the local legal conditions and requirements. Each investigator has to confirm this by signing the study protocol.

#### Responsibilities of the Sponsor:

- Verification of the understanding of the Investigator's Brochure or the described study medication
- Verification of the understanding of treatment schedule
- Ensuring for enough time and capacity for the implementation of this study
- Correct collection and documentation of data, reporting
- Provision of all data to the Sponsor, monitor or relevant authorities for audits or inspections
- Assurance for the confidential handling of patient's data and information

The principal investigator accepts the responsibility for the implementation of this clinical trial at this study site according to the AMG.

## 17.2 Approval and Consent

### **Independent Ethics Committee or Institutional Review Board**

Before initiation of the study, the conduct of the study will be submitted to our local Ethics Committee (EC) / Institutional Review Board (IRB). Written approval of the study, the protocol, the Informed Consent Form (ICF), all questionnaires, and all other relevant study documentation must be obtained before the first patient will be screened and the study drug is released to the investigator. Any necessary extensions or renewals of EC/IRB approval must be obtained for changes to the study such as amendments to the protocol, the ICF or other study documentation. The written approval of the EC/IRB together with the approved ICF must be filed in the study files.

The investigator will report promptly to the EC/IRB any new information that may adversely affect the safety of the participants or the conduct of the study. The investigator will submit written summaries of the study status to the EC/IRB as required. On completion of the study, the EC/IRB will be notified that the study has ended. End of the study is the time when the last visit of the last patient has been performed (LPLV).

### **Regulatory Authorities**

All relevant study documentation will be submitted to the regulatory authorities according to local/national requirements, for review and approval before initiating the study.

On behalf of the AMG in Austria, the Sponsor of the clinical trial submits the application to the competent ethics committee (EC) and the competent authority (CA). The CA reviews only the justification for and the relevance of the Clinical Trial. The EC acts as the "expert reviewer" for the CA and decides within 35 days, with only one "clockstop" possible to obtain

supplementary information. If the EC vote is negative, the CA issues a legal document (“Bescheid”) prohibiting the clinical trial.

On completion of the study (LPLV), the regulatory authorities will be notified of the end of the study.

### **Informed Consent**

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to GCP.

No subject will undergo any study related examination or activity in the responsibility of the investigator before he/she has given written informed consent to participate in the study.

The investigator or designee explains orally and in writing manner the nature, the duration, the importance, the relevance, the purpose of the study, the consequences, and the action of the drug in such a manner that the patient and a study partner (if applicable) are aware of potential risks, inconveniences, and adverse events of the study and the study drug. It should also be straightened out that the subject is free to choose to take part in the study or to withdraw from participation without consequences for his/her further care. The patient should be given the opportunity to ask for clarification of any points he/she does not understand and, if necessary, ask for more information. At the end of the interview, the subject will be given ample time to consider his/her participation in the study. Subjects and the investigator will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the investigator in the investigator’s site file. A signed and dated copy of the Patient Information and Informed Consent Form will be provided to the patient.

If new information becomes available that may be relevant to the subject’s willingness to continue participation in the study, a new ICF will be approved by the EC/IRB (and regulatory authorities, if required). The study subjects will be informed about this new information and re-consent will be obtained.

### **Risks and Benefits**

**Benefits:** The patients participating in the study will receive specialized care and regular clinical monitoring. The results of this trial will be useful to evaluate the effect of nabilone on non-motor symptoms in PD. Moreover, management of NMS are an important area of unmet need in PD. Due to the overall impact of NMS in PD and based on the influence of the endocannabinoid system on NMS in broad manner in PD, we perform this trial of nabilone in PD patients. Hopefully, a symptomatic improvement of the patient’s clinical condition could be achieved.

**Risks:** Disadvantages of participation could be the additional time spent in the hospital, the withdrawal of blood, currently unknown risks of the study drug therapy, or allergies to components of the IMP the patient is unaware at inclusion in the study.

Patients will receive either nabilone or placebo. Treatment care in the study population will not be affected by the trial because nabilone will be used as an add-on therapy.

Generally, nabilone is well tolerated. Common adverse reactions ( $>1/100$  to  $<1/10$ ) observed in patients are somnolence, vertigo, euphoria, ataxia, impaired vision, difficulties to concentrate, sleep disturbances, dysphoria, a headache, hypotonia, nausea, and a dry mouth. Controlled trials with patients taking nabilone showed that at least one side effect occurred per subject. Most patients develop a tolerance in regard of adverse events concerning the CNS and therefore somnolence and euphoria reside after some weeks. This effect is reversible. The potential to cause mental addiction is unknown and no patient has shown withdrawal symptoms in clinical trials.

Minor risks of nabilone ( $>1/10.000$  to  $<1/1.000$ ) include confusion, disorientation, hallucination, psychosis, depression, difficulties in coordination, tremor, loss of appetite, anxiety, depersonalisation, tachycardia, and abdominal pain.

All AEs will be rapidly detected by close clinical monitoring. In case of an AE the patient should be followed up until he/she has recovered/ it has resolved, has reached a stable state, the investigator determines that it is no longer clinically significant, or the patient is lost to follow up. Study treatment will be stopped in the discretion of the investigator and appropriate measurements, reporting, and visits on-site will be performed.

These controlled risks must be balanced against the prospect of identifying a new therapeutic option for non-motor symptoms in PD.

There are no known risks in relation to the Eye-tracking analysis.

## **17.3 Patient Insurance**

During their participation in the clinical trial the patients will be insured as defined by legal requirements. The Sponsor is providing insurance in order to indemnify (legal and financial coverage) the investigator/trial center against claims arising from the study, except for claims that arise from malpractice and/or negligence. The compensation of the subject in the event of study-related injuries will comply with the applicable regulations.

This insurance covers for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study.

## **17.4 Data Protection and Confidentiality**

All local legal requirements regarding data protection will be adhered to. All study findings and documents will be regarded as confidential. The investigator and members of the research team must not disclose any information without prior written approval from the

Sponsor. The pseudonymity of patients participating must be maintained. Throughout documentation and evaluation, the patients will be identified on CRFs and other documents by an ascending number according to their order of screening. Documents that identify the patient personally (e.g., the signed informed consent, patient identification list, patient's record) must be maintained in confidence by the investigator. The patients will be informed in the ICF that all study findings will be stored in a locked cabinet and on computer and handled in strictest confidence.

## **17.5 Discontinuation of the Study by the Sponsor**

The Sponsor or its representative is authorized to temporary hold or discontinue the study for any reason and at any time decided.

The investigator/Sponsor will notify the accredited EC/IRB of the end of the study (LPLV).

The Sponsor or its representative will notify the EC/IRB immediately of a temporary halt of the study, including the reason of such an action. In case the study is ended prematurely, the Sponsor or its designee will notify the accredited EC/IRB within 15 days, including the reasons for the premature termination.



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