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United States

A Phase IIa, Randomized, Double Blind, Placebo Controlled, Single Dose, Safety and Pharmacokinetic/Pharmacodynamic Study of INP103 (POD L-dopa) Administered in the Presence of Decarboxylase Inhibitor to L-dopa Responsive Parkinson's Disease Patients

Short Title: Therapeutic potential for intranasal levodopa in Parkinson's Disease – OFF Reversal (THOR 201)

Protocol Number INP103-201

Development Phase: Phase IIa

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Amendment 04

01 February 2019

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LIST OF ABBREVIATIONS

AE	Adverse Event
AUC	Area Under the Curve
ANCOVA	Analysis of Covariance
BMI	Body Mass Index
cGMP	Current Good Manufacturing Practices
CNS	Clinical Network Services
eCRF	Case Report Forms
C_{max}	Maximum plasma concentration
COMT	Catechol-O-Methyl Transferase
CRO	Contract Research Organization
CSH	Heterogeneous Compound Symmetry
CSR	Clinical Study Report
CTN	Clinical Trial Notification
DA	Dopamine Agonist
DCI	Decarboxylase Inhibitor
EC	Ethics Committee
FSH	Follicle-Stimulating Hormone
H&Y	Hoehn & Yahr
HREC	Human Research Ethics Committee
IB	Investigator Brochure
ICH GCP	International Conference on Harmonisation Note for Guidance on Good Clinical Practice
INP103	Impel's drug-device combination product (L-dopa delivered by the I231 POD Device. Also referred to as POD L-dopa)
ITT	Intention-to-Treat
L-dopa	Levodopa
LLN	Lower Limit of Normal
LS	Least Square
MAOB-I	Monoamine Oxidase B Inhibitor
MDS-UPDRS	Movement Disorder Society Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
MMSE	Mini Mental State Examination
NHMRC	National Health and Medical Research Council
PI	Principal Investigator
PD	Parkinson's Disease
PDyn	Pharmacodynamic
PK	Pharmacokinetic
POD	Precision Olfactory Delivery
PPP	Pharmaceutical Packaging Professionals

SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedures
$t_{½}$	Apparent Terminal Half-Life
TEAE	Treatment-Emergent AE
TGA	Australian Therapeutic Goods Administration
T_{max}	Time to maximum plasma concentration
TOEPH	Heterogeneous Toeplitz Structure
ULN	Upper Limit of Normal
w	Weight
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

PROTOCOL AUTHORISATION

Title: **A Phase IIa, Randomized, Double Blind, Placebo Controlled, Single Dose, Safety and Pharmacokinetic/Pharmacodynamic Study of INP103 (POD L-dopa) Administered in the Presence of Decarboxylase Inhibitor to L-dopa Responsive Parkinson's Disease Patients**

Short Title: **Therapeutic potential for intranasal levodopa in Parkinson's Disease – OFF Reversal (THOR 201)**

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the current Declaration of Helsinki and the guidelines on Good Clinical Practice.

DocuSigned by Stephen Shrewsbury
Stephen Shrewsbury | I approve this document 2/1/2019 1:31:02 PM PST
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01-Feb-2019 | 13:31 PST

Dr Stephen Shrewsbury, Sponsor's Medical Monitor & Chief Medical Officer, Impel NeuroPharma	Date

DECLARATION OF INVESTIGATORS

Title: **A Phase IIa, Randomized, Double Blind, Placebo Controlled, Single Dose, Safety and Pharmacokinetic/Pharmacodynamic Study of INP103 (POD L-dopa) Administered in the Presence of Decarboxylase Inhibitor to L-dopa Responsive Parkinson's Disease Patients**

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All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure(s) (IB), Case Report Forms (eCRFs), and scientific data not in the public domain.

The study will not be commenced without the prior written approval of a properly constituted Human Research Ethics Committee (HREC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the Ethics Committee (EC), except where necessary to avert an immediate hazard to the subjects.

I have read the protocol and agree that the study will be conducted in compliance with the protocol and in accordance with the principles of the current version of the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects), and with the National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research (2007, incorporating all updates as at May 2015). The study will be conducted in accordance with the Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95), as adopted by the Australian Therapeutic Goods Administration (2000).

I acknowledge that I am responsible for the overall study conduct. I agree to personally conduct or supervise the described clinical study. I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study at my site are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout the study.

Investigator Name	Site	Signature	Date

FACILITIES AND PERSONNEL

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STUDY SYNOPSIS

Protocol Title:	A Phase IIa, Randomized, Double Blind, Placebo Controlled, Single Dose, Safety and Pharmacokinetic/ Pharmacodynamic Study of INP103 (POD L-dopa) Administered in the Presence of Decarboxylase Inhibitor to L-dopa Responsive Parkinson's Disease Patients (THOR 201)
Protocol Number:	INP103-201
Sponsor:	Impel NeuroPharma 201 Elliott Ave W, Suite 260 Seattle, Washington 98119 United States
Australian Sponsor:	Clinical Network Services (CNS)
CRO:	Clinical Network Services (CNS)
Study Phase:	Phase IIa
Study Objective(s):	**Primary Objective:** To compare the safety and tolerability of intranasal single doses of INP103 in the presence of decarboxylase inhibitor (DCI) to that of placebo in patients with Parkinson's Disease (PD) during an OFF episode. **Secondary Objectives:** 1. To characterize the pharmacokinetics (PK) of single doses of INP103 2. To explore the effect of single doses of INP103 versus placebo on motor function 3. To explore the PK/PDyn relationship of single doses of INP103 and motor function
Study Design:	This is a Phase IIa randomized, double-blind, placebo controlled, single dose study to compare the safety, tolerability and PK/PDyn of intranasal L-dopa following administration of INP103 in the presence of L-dopa decarboxylase inhibitor (DCI) during an OFF episode. <u>Screening Assessment</u> Subjects will attend two pre-dosing visits: an initial Screening visit up to Day -21 (Visit 1), and a second screening visit (Visit 2), which may be repeated, between Day -20 and Day -1 (the day prior to Visit 3) during which dopaminergic responsiveness will be confirmed (see Screening Procedures below).

Randomization and Dosing

Subjects will be instructed not to take their usual PD medication from 22:00 pm on Day -1 (the day prior to dosing).

Subjects who arrive at the study site on Day 0 (or who were domiciled overnight) and are determined by the investigator to be in an ON state up to the scheduled time of dosing will not be dosed and will be excluded from further study participation.

Subjects will be enrolled into one of four dose treatment cohorts with at least 8 subjects per cohort. All subjects in Cohorts 1, 2 and 3 will receive oral DCI, benserazide hydrochloride, 25 mg at 60 ± 5 minutes before dosing with INP103 or placebo. Subjects in Cohort 4 will receive the DCI as carbidopa at 1/10th the dose of, and with, L-dopa via the POD device. At the discretion of the Sponsor, depending on rate of recruitment, cohort 4 may be over enrolled with a total of up to 12 subjects using the 3:1 randomization scheme. On Day 0 (Visit 3), subjects in each cohort will be randomized to receive treatments as follows:

Cohort	**Treatment (Study Drug)**
1	INP103 35 mg L-dopa (n=6); Placebo (n=2)
2	INP103 70 mg L-dopa (n=6); Placebo (n=2)
3	INP103 140 mg L-dopa (n=6); Placebo (n=2)
4	INP103 70 mg L-dopa/7.0 mg carbidopa (n=6, maximum 9); Placebo (n=2, maximum 3)

Cohorts will be enrolled and dosed in sequence. Escalation to the next higher dose cohort (Cohorts 1 to 2 and 2 to 3) may only commence after review and approval of safety data by a Safety Monitoring Committee (SMC). Interim analysis of data will be conducted upon completion of Cohort 1 and 2 study procedures, at the discretion of the Sponsor, depending on rate of recruitment. In this scenario, Cohort 1 and 2 data will be soft-locked, patients may be unblinded and tables, listings, and figures of collected data will be produced. Unblinding of Cohort 1 and 2 data will not jeopardise blinding of any enrolled Cohort 3 or 4 subjects at the time of the interim analysis.

Follow-up

Subjects will be monitored for 7 days after administration of INP103 or placebo. All subjects will be observed as in-patients for at least 240 minutes post-dosing. Follow-up

	evaluations will occur 7 days after dosing. The SMC will have 7–14 days between dosing of Cohorts 1 and 2 and again between 2 and 3 to review safety data compiled by the site and contract research organization (CRO).
Outcome Measures:	**Primary Endpoints:** Safety and tolerability, including the assessment of physical examinations (including nasal inspection), electrocardiograms (ECGs), vital signs (including supine and standing blood pressure, all other vital signs supine only), clinical laboratory results, and adverse events (AEs; specifically, overall dyskinesia assessments over the immediate 240 minutes following dosing and over 7 days of follow-up. **Secondary Endpoints:** 1. PK profile of L-dopa for 120 minutes following dosing with INP103 ($AUC_{0\text{-}2h}$, C_{max} and T_{max}). 2. Motor function, evaluated as: • Change from baseline to 30 minutes post-dose in MDS-UPDRS Part III score (primary motor function endpoint) • Change from baseline to 15, 30, 45, 60, 90 and 120 minutes post-dose for C1, C2, C3 and change from baseline to 30, 60, 90, 120 minutes for C4, in MDS-UPDRS Part III score • Cumulative proportion of responders by post-dose time point (15, 30, 45, 60, 90 and 120 minutes for C1, C2, C3 and change from baseline to 30, 60, 90, 120 minutes for C4,), where response is defined as an improvement of 30% in MDS-UPDRS Part III score from baseline. • Time to response, where response is defined as an improvement of 30% in MDS-UPDRS Part III score from baseline • Duration of response, where response is defined as an improvement 30% in MDS-UPDRS Part III score from baseline • Area Under the Curve (AUC) of changes in MDS-UPDRS Part III scores from pre-dose at 15, 30, 45, 60, 90 and 120 minutes for C1, C2, C3 and change from baseline to 30, 60, 90, 120 minutes for C4, • Maximum response in MDS-UPDRS Part III scores from pre-dose to 15, 30, 45, 60, 90 and

	120 minutes for C1, C2, C3 and change from baseline to 30, 60, 90, 120 minutes for C4, • Subjective time to ON, as evaluated by the Investigator and by subject self-assessment 3. The PK/PDyn relationship of single doses of INP103 and motor function
Investigational Products and Administration:	INP103 is a drug-device combination product containing a drug component, L-dopa, and device component, the I231 Precision Olfactory Delivery (POD) device. In Cohorts 1, 2, and 3, L-dopa will be administered intranasally in single doses of one (35 mg), two (70 mg) or four (140 mg) puffs of INP103, 60 minutes after oral benserazide hydrochloride 25 mg. In Cohort 4 the INP103 formulation will contain L-dopa:carbidopa in a 10:1 ratio (70 mg L-dopa and 7.0 mg carbidopa (2 capsules)). Dosing will take place once OFF episode is confirmed and will not include predosing with oral benserazide. Placebo is an inert, visually similar product without L-dopa or carbidopa (microcrystalline cellulose).
Planned Subjects:	At least 32 L-dopa responsive PD patients will be enrolled and randomized; 4 cohorts with at least 8 patients per cohort. At the discretion of the Sponsor, depending on rate of recruitment, cohort 4 may be over enrolled with a total of up to 12 subjects using the 3:1 randomization scheme. Subjects will not be replaced once dosed. Randomized subjects who have not been dosed may be replaced. Subjects may only be dosed in ONE cohort.
Subject Selection Criteria:	**Inclusion Criteria:** 1. Adult males and females, 40 to 80 years of age (inclusive) at the time of Screening (Visit 1) 2. Diagnosed with Idiopathic PD (by UK Brain Bank Criteria) with Modified Hoehn & Yahr (H&Y) Stage I-III during an ON period at Visit 1 3. Subjects who are prone to (and recognize) OFF episodes (when their usual PD medication has worn off) 4. Shown to be responsive to L-dopa medication (≥ 30% improvement in MDS-UPDRS Part III Motor Examination score) as assessed during the Screening period (Visit 2)

	5. On a stable dose of L-dopa containing medication for at least 2 weeks prior to Visit 1 (up to 1200 mg/day) with no single dose exceeding 250 mg. All other anti-PD medication (e.g. dopamine agonists [DAs], monoamine oxidase-B inhibitor (MAOB-I) or catechol-O-methyl transferase (COMT) inhibitors ARE allowed if the subject has been on a stable dose for at least 30 days prior to Visit 1. 6. Willing to omit their (usual) PD drugs (e.g. usual regular anti-PD medication including any L-dopa containing medication, DAs and/or COMT inhibitors and any required anti-OFF treatment) from 22:00 pm the evening prior to study dosing until 120 minutes post study treatment dosing. Cohorts 1, 2 and 3 ONLY WILL take oral benserazide 25 mg on arrival at the research site (at 60 ± 5 minutes before dosing with INP103 or placebo). Cohort 4 will omit oral benserazide and subjects may be dosed once OFF episode has been confirmed and all baseline assessments have been completed. 7. If female and of childbearing potential must agree to use adequate contraception (see Section 4.4) during the study 8. Able and willing to attend the necessary visits at the study centre 9. Willing to provide voluntary written informed consent signed prior to entry into the study **Exclusion Criteria:** 1. Severe dyskinesia (defined as per MDS-UPDRS) during a 'normal day' that would significantly interfere with the subject's ability to perform study assessments 2. In receipt of L-dopa containing medication at > 1200 mg/day 3. History of significant psychotic episode(s) within the previous 12 months in the opinion of the Investigator, or currently receiving anti-psychotic medication at a moderate dose (quetiapine >50 mg/day, risperidone >1 mg/day or olanzapine >2.5 mg/day) 4. Mini Mental State Examination (MMSE) ≤ 25 as documented within the previous 36 months or as assessed by Investigator during Screening

	5. History of suicidal ideation or attempted suicide within previous 12 months 6. Narrow-angle glaucoma 7. Presence of skin lesions that, in the opinion of the Investigator, may be cancerous 8. Females who are pregnant, planning a pregnancy or lactating 9. Subjects with any underlying physical condition that, in the opinion of the Investigator, would make it unlikely that the subject will comply with or be able to complete the study requirements 10. Use of any medication likely to interact with benserazide, carbidopa or INP103 (see Appendix 5) 11. Laboratory test abnormalities at Screening (Visit 1) deemed clinically significant by the Investigator. 12. History or presence of alcoholism or drug abuse within the 2 years prior to INP103 or placebo dosing 13. Administration of an investigational product in another trial within 30 days or 5 half-lives (whichever is longer) prior to INP103 or placebo dosing 14. Significant nasal congestion, physical blockage in either nostril, or significantly deviated nasal septum as evaluated by the PI or other suitably trained healthcare professional 15. Subjects who have previously shown hypersensitivity to L-dopa or benserazide (for Cohorts 1, 2 and 3), or L-dopa or carbidopa (for Cohort 4) or any of their excipients

Treatment Groups:	Subjects will receive one of the following treatments: All subjects in Cohorts 1, 2 and 3 will receive oral benserazide hydrochloride (benserazide) 25 mg at 60 ± 5 minutes prior to INP103 or placebo dosing and time recorded. Cohorts 1, 2 and 3 will comprise eight subjects total; six subjects in receipt of INP103 (L-dopa via I231 POD Device) and two subjects placebo (via I231 POD Device). Cohort 4 will NOT receive oral benserazide. Cohort 4 will comprise of eight subjects; six subjects in receipt of INP103 (L-dopa with carbidopa via I231 POD Device) and two subjects placebo (via I231 POD Device). At the discretion of the Sponsor, depending on rate of recruitment, cohort 4 may be over enrolled with a total of up to 12 subjects using the 3:1 randomization scheme. Cohort 1 (INP103 35 mg L-dopa total or placebo as one spray to one nostril): Each subject in this cohort will receive one dose of INP103 or placebo delivered by one actuation of the device. Cohort 2 (INP103 70 mg L-dopa total or placebo as one spray to each nostril): Each subject in this cohort will receive one dose of INP103 or placebo delivered by two actuations of the device. Cohort 3 (INP103 140 mg L-dopa total or placebo as two sprays to each nostril): Each subject in this cohort will receive one dose of INP103 or placebo delivered by four actuations of the device. Cohort 4 (INP103 70 mg L-dopa/7.0 mg carbidopa total or placebo as one spray to each nostril): Each subject in this cohort will receive one dose of INP103 or placebo delivered by two actuations of the device, one to each nostril. At 120 minutes post study dosing, subjects should take their usual anti-OFF medication (e.g. Madopar rapid) if they have not returned to ON, and their usual morning dose of PD medications (e.g. their regular Madopar® or Sinemet® morning dose). Subjects will remain under observation for another 120 minutes before they can be allowed to leave (health status permitting). Escalation to Cohorts 2 and 3 may only commence after review and approval of safety data by a SMC (see Study Design, above) of Cohorts 1 and 2 respectively. There will be no SMC meeting between Cohorts 3 and 4 if there are no safety concerns raised by the SMC meetings occurring after Cohorts 1 and 2, since the dose of L-dopa and DCI in Cohort 4 is less than Cohort 3. However, all usual safety monitoring will remain in place.

Screening Procedures:	Screening assessments must be completed within 3 weeks of randomization into the study and will require two clinic visits to complete. At the first Screening visit (Visit 1, up to Day -21) subjects will be required to sign a consent form, after which the following initial Screening assessments will be conducted: • Review of medication and medical history • Review of inclusion and exclusion criteria • Measurement of height and weight • Recording demographic information • Full physical examination, including full MDS-UPDRS (I to IV). • 12-Lead ECG • Vital signs (blood pressure – both supine and standing; supine only heart rate, respiration rate and oral temperature) • Clinical laboratory testing (non-fasting haematology, serum chemistry and urinalysis) • Serum pregnancy test (in women of childbearing potential only [WOCBP]) • Follicle-Stimulating Hormone (FSH; in postmenopausal women only) The second Screening visit (Visit 2) is required to complete the Screening assessment for dopamine response. Subjects must return to the clinic between Day -20 and Day 0 (Visit 3). Subjects must discontinue their usual anti-PD medication from 22:00 the previous evening (i.e. Day -10 if attending Visit 2 on Day -9) and their usual morning (i.e. Day -9 if attending Visit 2 on Day -9) L-dopa dose (50–250 mg e.g. in Madopar® or Sinemet®) in order to have their OFF state confirmed and characterized. A full MDS-UPDRS (see Appendix 4) will be conducted upon arrival and used as the baseline result, after which the subject will then be allowed to receive their usual L-dopa-containing medication (which may be combined with a decarboxylase inhibitor [DCI], if part of the subject's usual PD treatment). The MDS-UPDRS III (motor examination) only assessment will be repeated at 15, 30, 45, 60, 90 and 120 minutes post-dose thereafter for C1, C2, C3, and at 30, 60, 90, and 120 minutes for C4, and time to ON assessed by physician and by subject self-assessment.

	Subjects showing at least a 30% improvement in MDS-UPDRS Part III score during Visit 2 will be deemed dopamine responsive and will be eligible to be randomized. The Visit 2 assessment may be repeated during the 20 day window for Visit 2 if the subject usually responds well (subjectively) to their usual dopaminergic OFF medication, but does not achieve at least a 30% improvement at their initial Visit 2 assessment.
Randomization Procedure:	At least thirty-two (32) (maximum 36) subjects will be randomized. All subjects in Cohorts 1, 2 and 3 will receive oral benserazide hydrochloride 25 mg 60 ± 5 minutes before study drug. Subjects in Cohort 4 will not receive the oral benserazide and may be dosed once OFF episode has been confirmed and all baseline assessments have been completed. Treatment assignment will be randomized 3:1 in each of 4 dose cohorts of at least eight subjects total per cohort (Cohort 4 may be allowed to enrol 12 subjects depending on rate of enrolment): • INP103 (n=6) (Cohorts 1, 2 and 3) or INP103 with carbidopa (n=6, max 9) (Cohort 4) • Placebo (n=2, or Cohort 4, n=2, max 3)

Study Assessments:	**Clinical:** Medical history, AEs, concomitant medication use, height and weight, physical examination (including nasal inspection), periodic vital signs (blood pressure - both supine and standing; supine only heart rate, respiratory rate and temperature) and 12-lead ECGs. **Laboratory:** • Haematology • Serum chemistry • Urinalysis **Pregnancy test for WOCBP:** A serum β-human chorionic gonadotropin (βHCG) will be performed at Screening (Visit 1) and a urine pregnancy test will be performed in clinic before dosing on Day 0 (Visit 3). **FSH for postmenopausal women:** A serum FSH test will be performed at Screening (Visit 1). **Pharmacokinetics:** Blood sampling for PK parameter calculation **Pharmacodynamics:** • MDS-UPDRS Full • MDS-UPDRS III • Time to ON as assessed by the physician and by subject self-assessment
Safety and Tolerability Assessments:	Specific assessments to evaluate treatment safety include the following: overall dyskinesia assessment, nasal inspection (as part of physical examinations), the frequency and type of AEs, concomitant medications (including any short acting anti-OFF medication, permissible only at/after 120 minutes post dosing on dosing days alongside the subject's delayed usual anti-PD morning dose), clinical laboratory testing, 12-lead ECGs and vital signs (to include supine and standing blood pressure, all other vital signs supine only). All treated subjects will be observed for 240 minutes post dose and will undergo follow-up evaluations (by appropriately trained/qualified staff) at Day 7.
Pharmacokinetic Assessments:	PK blood samples will be collected from an indwelling cannula positioned so that it does not interfere with arm movements within 15 minutes prior to dosing and at 4, 9, 14, 29, 44, 59, 89 and 119 minutes after dosing (with INP103 or placebo).

Pharmacodynamics Assessments:	A full MDS-UPDRS score will be conducted at the start of all visits. MDS-UPDRS III scoring and assessment of time to ON by the physician/subject will occur after usual ON medication taken at Visit 2, and following dosing at Visit 3 as shown in the Study Schedule.
Statistical Analysis:	At least thirty-two (32) subjects are considered sufficient for assessment of safety and tolerability of SADs of INP103. Furthermore, with 8 subjects per cohort, the study has 80% power to detect a difference in improvement of 13 points compared to placebo from pre-dose in MDS-UPDRS Part III scores within each dose level, assuming a standard deviation of 11 points. **Safety Population:** All subjects who receive any amount of INP103 or placebo will be included in the Safety Population. A pooled placebo group (of subjects from each of the five cohorts) will be used for comparisons. The data will be analysed according to the treatment actually received. **PK Population:** All subjects who receive any amount of INP103 or placebo and have sufficient samples collected for non-compartmental analysis of L-dopa will be included in the PK Population. The data will be analysed according to the treatment received. **Intention-to-Treat (ITT) Population:** All randomized subjects who have pre-dose and at least one post-dose assessment of motor function will be included in the ITT Population. A pooled placebo group (of subjects from each of the five cohorts) will be used for comparisons. The data will be analysed according to the randomized treatment group. **Safety and Tolerability:** Continuous safety data will be summarised with descriptive statistics (arithmetic mean, SD, median, minimum, and maximum) by treatment. Categorical safety data will be summarised with frequency counts and percentages by treatment. AEs will be coded using the most current Medical Dictionary for Regulatory Activities (MedDRA®) available at CNS. A by-subject AE data listing, including verbatim term, preferred term, system organ class, treatment, severity, and relationship to INP103 or placebo, will be provided. The number of subjects experiencing treatment emergent AEs (TEAEs) and number of individual TEAEs will be summarized by treatment, system organ class and preferred term. TEAEs will also be summarized by seriousness,

	severity, relationship to INP103 or placebo and the time of onset relative to dosing. Dyskinesia assessment, nasal inspection, laboratory evaluations, vital signs assessments (including supine and standing blood pressure, all other vital signs supine only) and ECG parameters will be summarized by treatment and collection time point. A summary of change-from-baseline at each time-point by treatment will be presented. In addition, the proportion of subjects experiencing orthostatic hypotension or abnormal ECGs will be summarized by treatment group. Proportion of subjects with abnormal physical examination findings will be summarized by treatment group. Prior and concomitant medications will be listed by subject and coded using the most current World Health Organization (WHO) drug dictionary and summarized by therapeutic class (Level 4 for anti-PD medications and Level 2 for other medications) and preferred name. Medical history will be listed by subject. **Pharmacokinetics:** L-dopa concentrations will be summarized with descriptive statistics (arithmetic and geometric mean, SD, median, minimum, and maximum) by treatment group and time point. In addition, PK parameters ($AUC_{0\text{-}0.5h}$, $AUC_{0\text{-}1h}$ $AUC_{0\text{-}2h}$, C_{max}, T_{max}) will be summarized with descriptive statistics by treatment group. **Pharmacodynamics:** Changes from baseline at Visit 3 in MDS-UPDRS Part III scores will be estimated using a Mixed Model for Repeated Measures (MMRM) with treatment group (INP103 35 mg L-dopa, INP103 70 mg L-dopa, INP103 140 mg L-dopa,, INP103 70 mg/7.0 mg L-dopa: carbidopa , or placebo), time point (15, 30, 45, 60, 90 or 120 minutes in C1, C2, C3, and at 30, 60, 90, or 120 minutes in C4) and the interaction between treatment group and time point as fixed factors. The pre-dose score will be included as a covariate. The focus will be in the estimation of changes within each treatment group. The cumulative proportion of responders will be summarized descriptively by treatment group and time point. The endpoint related to time of response and time to ON will be evaluated with Kaplan-Meier methods. The duration of response will be summarized by treatment group. The AUC and individual maximum response from pre-dose to 15, 30, 45, 60, 90 and 120 minutes in C1, C2, C3, and at 30, 60, 90, or 120 minutes in C4 will be analysed with

	an Analysis of Covariance (ANCOVA) model with treatment group as a fixed factor and pre-dose MDS-UPDRS Part III score as a covariate. **Pharmacokinetic/Pharmacodynamics relationship:** The analyses required to investigate the PK/PDyn relationship of INP103 will be defined in the Statistical Analysis Plan (SAP) which will be completed before the database is locked.
Study Duration:	Up to 28 days per subject from Screening (Visit 1) to follow-up (Visit 4)

STUDY SCHEDULE

Table 1: Study Schedule

Visit	**1**	**2**	**3**											**4**
Day	**Up to -21**	**Up to -20 to -1**	**-1**	**0**										**7**
Window	**N/A**	**N/A**	**N/A**			**See Footnotes (and Section 7.4.3)**							**± 10 mins**	**± 2 days[a]**
Time (min)				**Pre-dose**	**0**	**5**	**10**	**15**	**30**	**45**	**60**	**90**	**120**	**240**	
Visit	**Screening**	**Dopamine response**	**Treatment**											**Follow-up**
Domiciled [b]		X	X	X	X	X	X	X	X	X	X	X	X		
Discharged														X	
Informed consent	X														
Medical history	X														
Inclusion/Exclusion Criteria	X			X											
MMSE[m]	X														
Demographics	X														
Confirmation of Eligibility		X		X											
Randomization				X[c]											
Height	X														
Weight	X														
Vital Signs [d]	X			X					X		X		X		X
12-lead ECG [d]	X			X									X[d]		X

Visit	**1**	**2**	**3**											**4**
Day	**Up to -21**	**Up to -20 to -1**	**-1**	**0**										**7**
Window	**N/A**	**N/A**	**N/A**			**See Footnotes (and Section 7.4.3)**							**± 10 mins**	**± 2 days[a]**
Time (min)				**Pre-dose**	**0**	**5**	**10**	**15**	**30**	**45**	**60**	**90**	**120**	**240**	
Visit	**Screening**	**Dopamine response**	**Treatment**												**Follow-up**
Physical Examination [e]	X			X									X[e]		X
Laboratory assessments (haem/serum chemistry)	X			X											X
Urinalysis (dipstick and microscopy if abnormal)	X			X											X
Serum Pregnancy Test (WOCBP only)	X														
Urine Pregnancy Test (WOCBP only)				X											X
FSH (Post-menopausal women only	X														
COHORTS 1, 2 & 3 ONLY: Administration of benserazide 25 mg				X[f]											
INP103/placebo Administration [g]					**X**										
Pre-treatment (INP103/placebo) AEs	X X X X														

Visit	**1**	**2**	**3**											**4**
Day	**Up to -21**	**Up to -20 to -1**	**-1**	**0**										**7**
Window	**N/A**	**N/A**	**N/A**			**See Footnotes (and Section 7.4.3)**							**± 10 mins**	**± 2 days[a]**
Time (min)				**Pre-dose**	**0**	**5**	**10**	**15**	**30**	**45**	**60**	**90**	**120**	**240**	
Visit	**Screening**	**Dopamine response**	**Treatment**											**Follow-up**
AEs					CONTINUOUS									
Rate dyskinesias					X				X		X		X	X	X
Nasal examination				X				X					X		X
Evaluation of ON/OFF (Investigator and self-assessment)		X		X					X	X	X	X	X	X	
Rescue OFF Tx allowed													X		
Usual morning anti-PD medication													X		
MDS-UPDRS Full[h]	X	X[h]		X											X
MDS-UPDRS (III) motor (Cohorts 1 through 3)		X[i]						X[j]	X[j]	X[j]	X[j]	X[j]	X[j]		
MDS-UPDRS (III) motor (Cohort 4)		X[i]							X[j]		X[j]	X[j]	X[j]		
Prior and Concomitant Medications	X			X		CONTINUOUS									
Subject Questionnaire [k]													X		
Light Breakfast Offered		X		X											

Visit	**1**	**2**	**3**											**4**
Day	**Up to -21**	**Up to -20 to -1**	**-1**	**0**										**7**
Window	**N/A**	**N/A**	**N/A**	**See Footnotes (and Section 7.4.3)**									**± 10 mins**	**± 2 days[a]**
Time (min)				**Pre-dose**	**0**	**5**	**10**	**15**	**30**	**45**	**60**	**90**	**120**	**240**	
Visit	**Screening**	**Dopamine response**	**Treatment**											**Follow-up**
PK Blood Collection [1] (Cohorts 1 through 3)				X					X		X	X	X		
PK Blood Collection [1] (Cohort 4) **Collected 1 minute prior to timepoint**				X		X	X	X	X	X	X	X	X		

[a] A +4 day window may be permitted in exceptional circumstances.

[b] Prior to V2 and/or V3, subjects may attend the unit the previous evening and be domiciled overnight to allow early morning confirmation of their OFF state and facilitate scheduling of pre and post dosing procedures. Subjects not attending the unit the previous evening will arrive on Day 0.

[c] Randomization may be performed on the day of dosing (Day 0) or the evening before (Day -1) for subjects being housed overnight prior to dosing.

[d] Subjects should be rested in a recumbent position for ≥ 3 minutes prior to recording of ECGs. Subjects should be supine for at least 3 minutes prior to determination of supine vital signs (including blood pressure), after which they should stand and have only standing blood pressure measured immediately. Staff should be on hand to support subjects if required. ECGs and vital signs should be assessed after UPDRS assessment and PK blood draws. Sites may follow their usual sequence of procedures for recording vital signs and ECG where they occur together. The window allotted for vital signs will be +15 minutes at the 30 and 60 minute post-dose timepoints. The vital signs and ECG collection at 120 minutes may occur up to 180 minutes. Due to variability in assessment length, assessments collected out of window, with the exception of PK samples and UPDRS, will not be considered deviations.

[e] Complete physical examinations (including nasal examination) should be conducted at Screening, Day 0 (pre-dose only) and end of study visits. A directed physical examination will be conducted at 120 minutes post-dose at Visit 3 only and may occur up to 180 minutes.

[f] 60 ±5 minutes pre-INP103 or placebo administration in Cohorts 1, 2 and 3 only.

[g] Subjects will be randomized to INP103 (35, 70 or 140 mg; n=6 to each dose) or placebo (n=2) in each of Cohorts 1, 2 and 3 and to INP103 with carbidopa (70 mg L-dopa/7.0 mg carbidopa; n=6) or placebo (n=2) in Cohorts 4. At the discretion of the Sponsor, depending on rate of recruitment, cohort 4 may be over enrolled with a total of up to 12 subjects using the 3:1 randomization scheme. In Cohort 4, dosing may commence as soon as OFF state has been confirmed and all baseline assessments have been completed and will not include oral benserazide.

[h] Full MDS-UPDRS (Parts I-IV) will be assessed on arrival at clinic for dopaminergic responsiveness assessment at Visit 2 during Screening. Subjects will omit their usual anti PD therapy from 22:00 the previous evening and should arrive at the clinic in an OFF state.

[i] Once a full MDS-UPDRS assessment has been undertaken, subjects will take their usual 'ON' medication and repeat only the MDS-UPDRS Part III (motor) assessment at +15, +30, +45, +60, +90 and +120 minutes for C1, C2, C3, and +30, +60, +90, and +120 for C4. Subjects demonstrating a 30% improvement in MDS-UPDRS Part III (motor assessment) within the 120 min will be deemed dopamine responsive and will be eligible for randomization.

[j] MDS-UPDRS Part III is assessed after PK blood draws and actual time will be recorded (time from dosing to START of assessment).

[k] Subject Questionnaire may be administered from 120 minutes up to 180 minutes to allow other study assessments to occur first.

[l] Baseline PK samples will be taken within 15 minutes prior to dosing. For Cohorts 1-3; the time window for blood sample collection is ± 5 minutes for the samples through 120 minutes. Actual time samples taken will be used for PK analysis. PK blood draws will occur AS SOON AFTER MDS-UPDRS Part III assessments as possible (even if outside of the ± 5 minute window) and time noted. **FOR COHORT 4 ONLY**: PK sample collection will occur 1 minute prior to the timepoint (samples will be collected at 4, 9, 14, 29, 44, 59, 89, and 119 minutes post-dose). For Cohort 4; the window for blood sample collection is up to +1 minute for timepoints 5 minutes up through 30 minutes and ±2 minutes for timepoints 45 minutes through 120. PK blood draws will occur IMMEDIATELY PRIOR TO MDS-UPDRS Part III assessments as possible (even if outside of the time window) and time noted.

[m] Only required if no documented history of an MMSE within 36 months prior to Screening.

[n] A light breakfast should be offered to the patient 30 minutes prior to dosing; see section 4.7.

1. BACKGROUND AND INTRODUCTION

1.1. Introduction

The purpose of this study is to evaluate the INP103 drug-device combination product specifically as it pertains to the intranasal administration of L-dopa (levodopa; L-3,4-dihydroxyphenylalanine) to the upper nasal cavity using the I231 Precision Olfactory Delivery (POD) device. L-dopa is the immediate metabolic precursor to the neurotransmitter dopamine; following crossing of the blood brain barrier, in a healthy brain, exogenous L-dopa is rapidly converted to dopamine. Dopamine itself cannot cross the blood brain barrier. Levodopa is given in combination with a decarboxylase inhibitor (DCI), which is either benserazide (in the brand Madopar®) or carbidopa (in Sinemet®) to ensure the L-dopa is not metabolized in the periphery before it can cross into the brain. INP103 is an experimental nasal L-dopa product. In Cohorts 1, 2, and 3 of this study, the DCI benserazide will be delivered orally 60 minutes before intranasal dosing with INP103. In Cohort 4, the INP103 formulation will contain the DCI, carbidopa, in a w:w ratio of 10:1 (L-dopa:carbidopa, the lowest ratio for oral co-administration) and will not require pre-treatment with an oral DCI. Neither DCI has any pharmacological activity other than to inhibit dopa decarboxylase. Cohort 4 will receive the same dose of L-dopa as in Cohort 2 and lower DCI levels than the orally administered benserazide.

PD is a degenerative disorder of the central nervous system characterised by involuntary muscle movements (dyskinesias, including tremors), rigidity, slowness of movement and potential cognitive impairment. Motor symptoms are linked with depleted dopamine in the basal ganglia. As such, the first line of therapy in the management of PD is administration of L-dopa, which was first investigated in 1961 (1).

Use of L-dopa is long established, but a number of limitations persist, namely:

- Penetration of L-dopa into the brain is limited by the presence of L-dopa decarboxylase and monoamine oxidase within the capillary endothelial cells. Together these form an enzymatic blood-brain barrier that limits passage of L-dopa into the brain.
- Systemic L-dopa that does not pass the blood brain barrier causes side effects in the peripheral nervous system requiring co-administration of a L-amino acid decarboxylase inhibitor (DCI; typically, benserazide or carbidopa in combination with L-dopa).
- Lastly, a progressive decline in L-dopa responsiveness occurs that leads to switches between mobility and immobility (ON and OFF periods, respectively) in L-dopa-treated patients. These ON/OFF oscillations have

been reported in at least 50% of PD patients who have been receiving L-dopa for 5–10 years and constitute a major cause of disability in advanced PD.

Impel's INP103 drug-device combination product is designed to deliver drugs (in this case L-dopa with or without DCI) to the upper nasal cavity. This region of the nasal cavity has many advantages for drug delivery. Administering drugs to the upper nasal cavity may reduce the overall variability and improve bioavailability by minimizing the amount of drug that drips out of the nose or runs into the posterior pharynx after nasal administration. In addition, the upper nasal cavity is highly vascularized for rapid drug absorption into the plasma. The upper nasal cavity is the only region of the body that has direct connections to the central nervous system via the olfactory and trigeminal nerve routes (2). Therefore, administration of central nervous system drugs to this region of the nasal cavity may lead to direct uptake into the brain. All of these factors make the upper nasal cavity a desirable route of administration for central nervous system-targeted drugs.

Impel has been developing both an INP103 levodopa-only formulation that would need to be administered in the presence of an oral DCI, and a variation of the INP103 formulation containing carbidopa to obviate the need for an oral DCI to be administered 60 minutes before dosing. Both DCIs to be used in this study are approved for use in Australia.

INP103 is anticipated to rapidly deliver L-dopa, the dopamine precursor, to the brain via the vasculature and potentially the direct nose-to-brain pathway, thereby permitting rapid and efficient resolution of OFF periods in subjects in receipt of oral L-dopa. The present study is a proof of concept investigation of the INP103 drug-device combination product incorporating the nasal delivery of L-dopa (with or without carbidopa) by the I231 POD Device.

1.2. Summary of Non-Clinical and Clinical Studies

1.2.1. Non-Clinical Studies

Oral L-dopa has been extensively used in the treatment of PD and is supported by a literature evidence base. A review of literature is provided in the Investigator's Brochure. In addition, Impel NeuroPharma has performed the following studies:

- Six studies in the cynomolgus monkey examined the PK of powder L-dopa formulations, including two studies testing L-dopa formulations containing carbidopa, using a non-human primate version of the clinical POD Device (nhpPOD). The dose of L-dopa per nasal surface area varied from approximately 0.5 to 1.2 mg/cm^2, similar to the local nasal concentrations estimated to be achieved clinically (0.4375–0.875 mg/cm^2) following doses of 35–140 mg L-dopa to the nose. No clinical observations were noted.

- Study 1: Following intranasal administration of unmodified crystalline L-dopa (of particle size D_{50} = 50 μm) in the absence of benserazide, dose-dependent PK was shown (10-40 mg dose range). The C_{max} following 40 mg L-dopa administration was 150 ng/mL, and the T_{max} was delayed, showing an average of ≥75 minutes. A smaller particle size (20-40 μm) crystalline L-dopa material was also tested and indicated a higher exposure compared to an equivalent dose of an unmodified L-dopa formulation.
- Study 2: The PK of intranasal L-dopa in combination with oral benserazide was explored (4 x 5mg administered over 24hr predose), demonstrating similar PK across four L-dopa formulations containing crystalline particle size sifted L-dopa (20-40 μm), spray dried L-dopa only (particle size D_{50} 10-30 μm), spray dried L-dopa with sodium chloride (L-dopa:NaCl) and spray dried L-dopa with sodium chloride and HPMC (L-dopa:HPMC:NaCl). C_{max} concentrations of >900 ng/mL were achieved following a dose of 20 mg (10 mg/nostril) of each formulation, which is above the threshold necessary for efficacy of OFF episode treatment. C_{max} was approximately 10-fold higher in the presence of benserazide. Median T_{max} was 45 to 60 minutes, an improvement over the T_{max} observed in the absence of benserazide.
- Study 3: A third study in the monkey explored the PK of intranasal L-dopa in a further five spray dried formulations in combination with oral benserazide (see below). All formulations achieved similar or up to 1.7-fold greater total exposure (AUC) and up to 2.3-fold increased C_{max} compared to spray dried formulations tested in the second PK study. Median T_{max} (53–105 minutes) for Groups 1, 2, 3 and 5 was similar or greater than T_{max} in the second study. T_{max} for Group 4 was significantly faster (median 30 minutes, with all four monkeys achieving >400 ng/mL L-dopa within 7 minutes of dosing). Since the product is intended to achieve plasma concentrations of L-dopa (>400 ng/mL) sufficient to rapidly switch a patient from OFF to ON, the maltoside-containing formulation was selected for testing in the proposed clinical study.

  Group 1: L-dopa:NaCl:HPMC:DSPC (68:2:16:14)

  Group 2: L-dopa:NaCl:HPMC:DSPC (68:2:23:7)

  Group 3: L-dopa:NaCl:HPMC:DSPC (68:2:23:7, minor manufacturing change compared to Group 2)

  Group 4: L-dopa:NaCl:HPMC:Maltoside (68:2:23:7)

  Groups 1 to 4 received pre-treatment with benserazide at -24, -16, -8 hours and -45 minutes

Group 5: L-dopa:NaCl:benserazide:HPMC:DSPC (68:2:7:16:7), pre-treated with benserazide at -24, -16 and -8 hours

- Study 4: A fourth study determined PK of intranasal L-dopa in five spray dried formulations with a reduced concentration of maltoside (1% w/w) in combination with oral benserazide. All formulations contained 68% L-dopa and 2% NaCl; three formulations included 29% w/w HPMC and 1% w/w maltoside (prepared by small modifications of the spray drying process) and two formulations contained 29.9% w/w HPMC with 0.1% w/w maltoside or 29.5% HPMC with 0.5% w/w maltoside. Each group (N=4) received four oral 5 mg benserazide pre-treatments at -24, -16, -8 and -0.75 hours before L-dopa formulation delivery by the nhpPOD Device. All formulations tested achieved similar AUC and C_{max} levels compared to the third monkey PK study. Compared to the formulation in the third monkey PK study containing 7% maltoside, median T_{max} was slightly delayed (<2.3-fold, range 37.5-68 minutes across all groups compared to 30 minutes). However, while T_{max} was slightly delayed, individual plasma levels following the Group 3 formulation (29% HPMC with 1% maltoside) increased rapidly and more consistently to achieve levels >400 ng/mL L-dopa within 15 minutes. This formulation was selected for GMP manufacture and for inclusion in the proposed clinical study.
- Study 5: A PK and safety study of the nasal administration of L-dopa powder formulation containing carbidopa (Study 2037-017, N=20), in the absence of an orally administered DCI, demonstrated plasma exposures similar to the above referenced monkey PK studies (2037-003, 2037-004, 2037-006, 2037-007) where formulations of levodopa were nasally administered after administration of an oral DCI (benserazide). Maximum plasma concentration (C_{max}) of 560 ng/mL - 1,608 ng/ml were achieved following 20 mg L-dopa administration with median T_{max} between 38-68 minutes. The group receiving a formula the same as the formula to be used in Cohorts 4-5 (BG54-126; levodopa: carbidopa: HPMC: maltoside:NaCl (68: 6.8: 22.2: 1: 2) resulted in an AUC of 149,941 ± 22,112 ng*min/ml, a C_{max} of 1,608 ± 198 pg/ml, and a T_{max} of 53 minutes. These values are similar to the levodopa alone formulation administered in the above reference monkey study 2037-007 in which a formula representative of that being used in Cohorts 1-3 of the clinical study resulted in an AUC of 92,404 ± 18,094 ng*min/ml, a C_{max} of 1,310 ± 413 pg/ml, and a T_{max} of 53 minutes.
- Study 6: A PK and safety study in monkey (Study 2037-019, N=20) was conducted to explore the PK of nasal administration of L-dopa with the DCI carbidopa present in the formulation, in a ratio of either 1:4, 1:10, or 1:20. The goal of this study was to evaluate the potential effect on

safety and plasma exposure of different ratios of carbidopa in the formulation. This study resulted in similar plasma exposures to the previous study (2037-017) with C_{max} values between 899 – 1,167 ng*min/ml and T_{max} between 45 – 60 minutes. There were no clinical signs of intolerance or safety signals observed in the study.

In all six studies, detailed clinical observations of each animal were performed pretest and at various intervals post dosing ranging from 15 minutes up to 120 minutes after dosing. The clinical observations included, but were not limited to, evaluation of the nose, oral cavity, skin, fur, eyes, ears, thorax, abdomen, external genitalia, limbs and feet, respiratory and circulatory effects, autonomic effects such as salivation, and nervous system effects. No observations were made indicating an issue with tolerability or irritation from the intranasal formulation to be used in the clinical trial.

1.2.2. Clinical Studies

This is the first Impel sponsored clinical study using INP103.

1.3. Summary of Potential Risks and Benefits

The risk/benefit profile of L-dopa in combination with benserazide is well known and is described in the Madopar® prescribing information. Similarly, the risk/benefit profile of L-dopa plus carbidopa is well described in the Sinemet® prescribing information. Inhaled formulations of L-dopa have previously undergone clinical investigation and have shown benefit in reversing OFF episodes. However, this is the first investigation of L-dopa using Impel's proprietary POD Device technology, which is specifically designed to target delivery of a drug product to the upper nasal space. In addition, drug formulation and nonclinical work has shown beneficial PK effects of co-administration of carbidopa with levodopa when given by POD to primates, suggesting that PD patients may experience enhanced benefit by administering the L-dopa with carbidopa nasally compared to giving the DCI orally and L-dopa only by POD.

Oral formulations of L-dopa are combined with carbidopa or benserazide to prevent L-dopa from being rapidly destroyed by the ubiquitous epithelial decarboxylase. By changing the route of administration from oral to intranasal, the administration of INP103 is anticipated to improve the benefit: risk profile of L-dopa by increasing L-dopa penetration of the blood brain barrier and decreasing systemic L-dopa. Nonetheless, inhibition of the nasal epithelial decarboxylase in primates (oral benserazide) continues to lead to much higher levels of L-dopa after intranasal dosing compared to primates receiving the same dose of intranasal L-dopa without benserazide. While all subjects in the present study will be required to suspend use of their usual anti-PD medication on the morning of dosing for the purpose of

demonstrating proof of concept, subjects in Cohorts 1, 2 and 3 will still receive a single dose of oral benserazide 25 mg at 60 ± 5 minutes prior to dosing. Subjects in Cohort 4 receiving the combined L-dopa/carbidopa formulation will NOT receive oral benserazide, but will be dosed with INP103 containing carbidopa (or placebo) as soon as their OFF episode has been confirmed and all baseline assessments have been completed. All subjects will be permitted to resume use of their usual PD medication (usual morning dose as standard and rescue therapy if required) from 120 minutes post-dosing.

INP103 is designed to intranasally deliver a dry powder formulation of L-dopa with or without carbidopa.

To date, there are no known risks of using the I231 POD Device. Nasal inspection will be conducted throughout the present study.

INP103 is anticipated to have a favourable risk benefit ratio given the anticipated benefit of rapid delivery of L-dopa to and across the blood brain barrier for subjects experiencing an OFF episode, and the requirement of rapid resolution of OFF episodes in patients on steady L-dopa-containing medications who encounter regular OFF episodes. Given the anticipated favourable risk benefit ratio for INP103, and the ready availability of their usual oral L-dopa containing medication (120 minutes post-dosing) during the study for patients who do not respond to INP103, the study is considered to have a favourable risk benefit ratio.

1.4. Dosage and Treatment Periods

Dosage will be in five placebo-controlled cohorts:

Cohort	Treatment (Study Drug)
1	INP103 35 mg L-dopa (n=6); (1 POD actuation) or Placebo (n=2)
2	INP103 70 mg L-dopa (n=6); (2 POD actuations) or Placebo (n=2)
3	INP103 140 mg L-dopa (n=6); (4 POD actuations) or Placebo (n=2)
4	INP103 70 mg L-dopa/7.0 mg carbidopa (n=6, maximum 9) (2 POD actuations) or Placebo (n=2, maximum 3)

In the proposed clinical study, patients are to receive a single dose only, and thus any potential irritancy is expected to be minimal, transient and reversible.

1.5. Study Population

This study will be conducted in PD patients who are responsive to L-dopa and who meet all of the inclusion criteria and none of the exclusion criteria. Safety, tolerability, PK and PDyn parameters will be assessed.

1.6. Ethical Principles

This study will be conducted in accordance with the principles of the current Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects), and with the National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research (2007, incorporating all updates as at May 2015). The conduct of the study will be in accordance with the Notes for Guidance on Good Clinical Practice (GCP; CPMP/ICH/135/95) established from the International Conference on Harmonization guidelines and adopted by the Australian Therapeutic Goods Administration (2000).

This study will be conducted under a protocol reviewed and approved by an EC responsible for each site and investigations will be undertaken by scientifically and medically qualified persons; where the benefits of the study are in proportion to the risks. The study will be overseen by a Principal Investigator (PI) who, prior to study start, will have read and agreed understanding of the protocol requirements and will agree to conduct the study in accordance with the above.

2. OBJECTIVES

2.1. Primary Objectives

The primary objective of the study is:

- To compare the safety and tolerability of intranasal single doses of INP103 in the presence of a DCI with PD during an OFF episode

2.2. Secondary Objectives

The secondary objectives of the study are:

1. To characterize the PK of single doses of INP103
2. To explore the effect of single doses of INP103 versus placebo on motor function
3. To explore the PK/PDyn relationship of single doses of INP103 and motor function

3. STUDY DESIGN

This is a Phase IIa randomized, double-blind, placebo controlled study to compare the safety and PK/PDyn of L-dopa following administration of INP103 in the presence of a DCI to that of placebo to PD patients during an OFF episode. See Figure 1 for a study design flow chart.

Subjects will attend a Screening visit up to Day -21 (Visit 1). During the maximum 21-day window between Screening and study dosing (i.e. between Visit 1 and Visit 3), subjects deemed eligible from Visit 1 assessments will be invited to attend a second Screening visit (Visit 2) to the clinical unit to confirm dopaminergic responsiveness. For Visit 2, subjects will discontinue all PD medication from 22:00 the previous evening (i.e. Day -10 if attending Visit 2 on Day -9). At the discretion of sites, patients may be domiciled overnight for this visit. In addition, subjects will miss their usual morning) L-dopa dose (50–250 mg). Missed morning dose will include missed DCI if a DCI (such as benserazide if Madopar, or carbidopa if Sinemet) comprises the subject's usual PD medication. At the start of Visit 2, the subject will have their OFF state confirmed and characterised using the full Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) scale. The subject will then take their usual L-dopa containing medication (including DCI if part of the subject's usual PD medication) and repeat the MDS-UPDRS Part III test (motor examination) at 15, 30, 45, 60, 90 and 120 minutes thereafter for C1, C2, C3, and at 30, 60, 90 and 120 minutes for C4. Subjects showing at least a 30% improvement in MDS-UPDRS Part III score during this visit will be deemed to be dopamine responsive and will be eligible to be randomized and return for Visit 3 on Day 0.

If subjects usually obtain a satisfactory response to their OFF treatment (in their opinion), but fail to do so on Visit 2, the Investigator is allowed to repeat the Visit 2 response assessment within the screening period to determine if a more representative response (i.e. >30% improvement in MDS-UPDRS score) can be obtained.

Subjects may be domiciled at the clinic overnight to enable scheduled assessments on the morning of, and prior to, Visit 2 (standard medications) and Visit 3 (test article) dosing, or will have transport provided to ensure they arrive at the clinical research unit on the morning of Visit 2 and Visit 3. Regardless of time of arrival at the study site, all subjects will be required to suspend dosing of usual PD medication (e.g. regular Madopar® or Sinemet® doses, DAs and/or COMT inhibitors doses and any required anti-OFF medication [e.g. Madopar rapid]) from 22:00 pm on Day -1, the day prior to study dosing. Suspension of usual PD medication will include on the morning of Day 0.

On Day 0, upon arrival at the research site (or upon waking if the subject was domiciled overnight at the research unit), and at 60 ± 5 minutes before dosing with INP103 or placebo, all subjects in **Cohorts 1, 2, and 3** will take oral benserazide hydrochloride (benserazide) 25 mg (provided by the Sponsor). Subjects in **Cohort 4** will NOT receive oral benserazide. Subjects who arrive at the study site on Day 0 (or who were domiciled overnight) and are determined by the Investigator to be in an ON state up to the scheduled time of dosing will not be dosed and will be excluded from further study participation but may be replaced at Sponsor's discretion.

On their scheduled day of dosing (Day 0; or on arrival at the unit on Day -1), eight subjects in each of three dose cohorts (35, 70 or 140 mg of INP103 L-dopa) and at least eight (8) (maximum 12) subjects in Cohort 4 (70/7.0 mg of INP103 L-dopa:carbidopa) will be randomized in a 3:1 fashion to one of two treatment arms. All subjects in Cohorts 1, 2 and 3 will receive oral benserazide 25 mg 60 ± 5 minutes before dosing with the study drug. Subjects in Cohort 4 will not receive oral benserazide before dosing with the study drug:

- INP103 (n=6 or maximum 9 in Cohort 4)
- Placebo (n=2 or maximum 3 in Cohort 4)

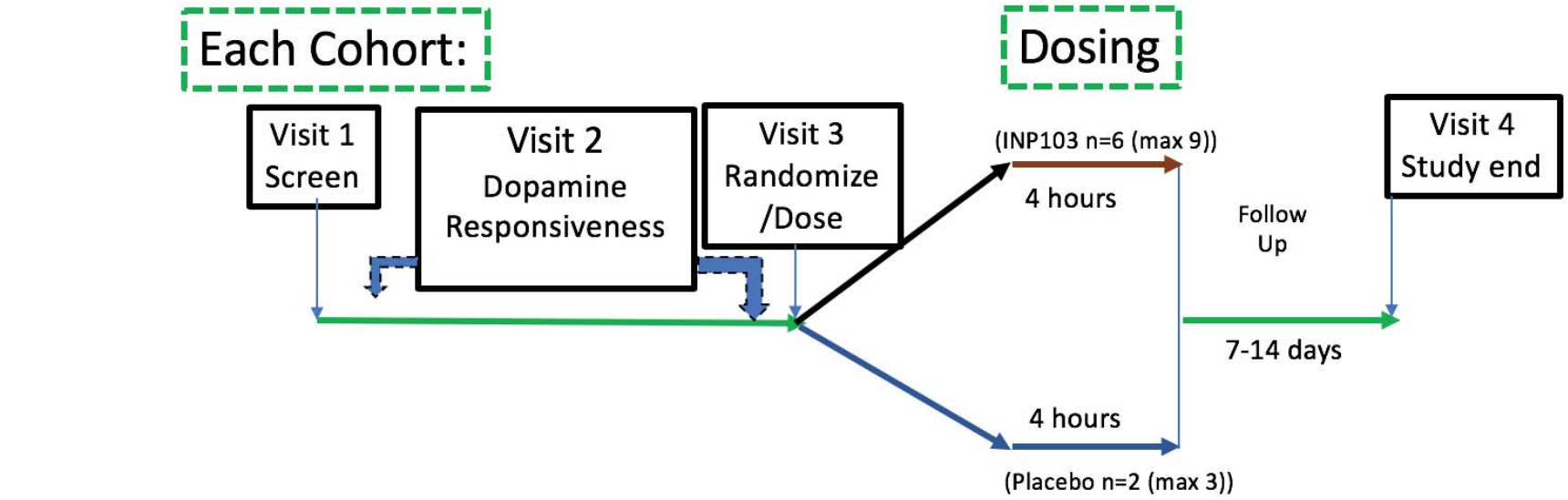
Use of usual anti-PD medication (usual regular dosing [e.g. regular Madopar or Sinemet] and use of anti-OFF treatment, if required) may resume at 120 minutes after use of INP103 or placebo.

Subjects will be monitored for 7 days after the final administration of INP103 or placebo. All subjects will be observed as in-patients for at least 240 minutes post-dosing at visit 3. Follow-up evaluations will occur 7 days after dosing.

Once dosing has been completed (for all subjects) in a cohort, data will be collected through to 7 days post dosing (Visit 4, follow-up). This data will then be reviewed by a Safety Monitoring Committee (SMC) for cohorts 1 and 2 only, and if no INP103 or placebo-related serious adverse events (SAEs) or severe AEs have been reported, dosing may commence in the next cohort. The SMC will have 7-14 days between dosing of cohorts to review safety and available PK data compiled by the site and the biostatistics analysis provider.

Interim analysis of data will be conducted upon completion of Cohort 1 and 2 study procedures, at the discretion of the Sponsor, depending on rate of recruitment. In this scenario, Cohort 1 and 2 data will be soft-locked, treatment assignment will be unblinded (limited to CNS staff; Impel staff will remain blinded) and tables, listings and figures of selected collected data will be produced. Unblinding of Cohort 1 and 2 data will not jeopardise blinding of any enrolled Cohort 3 (or subsequent Cohort) subjects at the time of the interim analysis.

Figure 1: Study Design



Cohort 1: INP103 35 mg (n=6); placebo (n=2)

Cohort 2: INP103 70 mg (n=6); placebo (n=2)

Cohort 3: INP103 140 mg (n=6); placebo (n=2)

Safety Monitoring Committee 1

Safety Monitoring Committee 2

Cohort 4: INP103 70/7.0mg (n=6, max 9); placebo (n=2, max 3)

3.1. Primary Endpoints

Safety and tolerability, including the assessment of physical examinations (including nasal inspection), electrocardiograms (ECGs), vital signs (including supine and standing blood pressure, all other vital signs supine only), clinical laboratory results, and AEs (specifically, levodopa induced dyskinesia assessment, see Section 6.4.2) over the immediate 240 minutes following dosing and over 7 days of follow-up.

3.2. Secondary Endpoints

1. PK profile of L-dopa (and carbidopa in Cohort 4) for 120 minutes following dosing ($AUC_{0\text{-}2h}$, C_{max} and T_{max})
2. Motor function, evaluated as:
    - Change from baseline to 30 minutes post-dose in MDS-UPDRS Part III score (primary motor function endpoint)
    - Change from baseline to 15, 45, 60, 90, and 120 minutes post-dose in MDS-UPDRS Part III score for cohorts 1, 2, and 3, and 60, 90, and 120 minutes in cohort 4.
    - Cumulative proportion of responders by post-dose time point (15, 30, 45, 60, 90 and 120 minutes for cohorts 1, 2, and 3, and 30, 60, 90, and 120 minutes in cohort 4), where response is defined as an improvement of 30% in MDS-UPDRS Part III score from baseline
    - Time to response, where response is defined as an improvement of 30% in MDS-UPDRS Part III score from baseline
    - Duration of response, where response is defined as an improvement of 30% in MDS-UPDRS Part III score from baseline
    - Area Under the Curve (AUC) of changes in MDS-UPDRS Part III scores from pre-dose at 15, 30, 45, 60, 90 and 120 minutes for cohorts 1, 2, and 3, and 30, 60, 90, and 120 minutes in cohort 4
    - Maximum response in MDS-UPDRS Part III scores from pre-dose to 15, 30, 45, 60, 90 and 120 minutes for cohorts 1, 2, and 3, and 30, 60, 90, and 120 minutes in cohort 4
    - Subjective time to ON, as evaluated by the Investigator and subject self-assessment
3. The PK/PDyn relationship of single doses of INP103 and motor function

4. STUDY POPULATION

4.1. Description of Numbers

At least thirty-two (32) (maximum 36) L-dopa-responsive PD patients will be randomized into the study.

4.2. Inclusion Criteria

Subjects who meet all of the following criteria will be considered for inclusion in the study:

1. Adult males and females, 40 to 80 years of age (inclusive) at the time of Screening (Visit 1)
2. Diagnosed with Idiopathic PD (per UK Brain Bank Criteria) with Modified Hoehn & Yahr (H&Y) Stage I-III during an ON period at Visit 1
3. Subjects who are prone to (and recognize) OFF episodes (when their usual PD medication has worn off)
4. Shown to be responsive to L-dopa medication (≥ 30% improvement in MDS-UPDRS Part III Motor Examination score) as assessed during Screening (Visit 2)
5. On a stable dose of L-dopa containing medication for at least 2 weeks prior to Visit 1 (up to 1200 mg/day) with no single dose exceeding 250 mg. All other anti-PD medication (e.g. dopamine agonists [DAs], monoamine oxidase-B inhibitor (MAOB-I) or catechol-O-methyl transferase (COMT) inhibitors ARE allowed if the subject has been on a stable dose for at least 30 days prior to Visit 1.
6. Willing to omit their (usual) PD drugs (e.g. usual regular anti-PD medication including any L-dopa containing medication, DAs and/or COMT inhibitors) and any required anti-OFF treatment) from 22:00 pm the evening prior to study dosing until 120 minutes post study treatment.

   Subjects in Cohorts 1, 2 and 3 ONLY will take oral benserazide 25 mg 60 ± 5 minutes before Visit 3 dosing with INP103 or placebo.

   Cohort 4 will OMIT oral benserazide and may dose subjects once OFF episode confirmed and all baseline assessments have been completed.
7. If female and of childbearing potential must agree to use adequate contraception (see Section 4.4) during the study
8. Able and willing to attend the necessary visits at the study centre
9. Willing to provide voluntary written informed consent signed prior to entry into the study

4.3. Exclusion Criteria

The presence of any of the following criteria will constitute cause for the exclusion of the subject:

1. Severe dyskinesia (defined as per MDS-UPDRS) during a 'normal day' that would significantly interfere with the subject's ability to perform study assessments
2. In receipt of L-dopa containing medication at > 1200 mg/day
3. History of significant psychotic episode(s) within the previous 12 months in the opinion of the Investigator, or currently receiving anti-psychotic medication at a moderate dose (quetiapine >50 mg/day, risperidone >1 mg/day or olanzapine >2.5 mg/day)
4. Mini Mental State Examination (MMSE) ≤ 25, as documented within the previous 36 months or assessed by Investigator during Screening
5. History of suicidal ideation or attempted suicide within previous 12 months
6. Narrow-angle glaucoma
7. Presence of skin lesions that, in the opinion of the Investigator, may be cancerous
8. Females who are pregnant, planning a pregnancy or lactating
9. Subjects with any underlying physical condition that, in the opinion of the Investigator, would make it unlikely that the subject will comply with or be able to complete the study requirements
10. Use of any medication likely to interact with benserazide, carbidopa or INP103 (see Appendix 5)
11. Laboratory test abnormalities at Screening (Visit 1) deemed clinically significant by the Investigator.
12. History or presence of alcoholism or drug abuse within the 2 years prior to the first INP103 or placebo administration
13. Administration of an investigational product in another trial within 30 days or 5 half-lives (whichever is longer) prior to the first INP103 or placebo administration
14. Significant nasal congestion, physical blockage in either nostril, or significantly deviated nasal septum as evaluated by the PI or other suitably trained healthcare professional.
15. Subjects who have previously shown hypersensitivity to L-dopa or benserazide (for Cohorts 1, 2 and 3), or L-dopa or carbidopa (for Cohort 4) or any of their excipients

4.4. Contraceptive Requirements

Female subjects of childbearing potential must not become pregnant and must use two methods of adequate contraceptive during the study. Adequate contraception is defined as complete abstinence or a condom AND one other form of the following:

- Birth control pills (The Pill)
- Depo Shot or injectable birth control (e.g. Implanon)
- IUD (Intrauterine Device)
- NuvaRing®
- Documented evidence of surgical sterilization at least 6 months prior to Screening Visit 1 (i.e., tubal ligation or hysterectomy).

4.5. Concomitant Medication

All medications including over-the-counter medications and herbal supplements will be recorded and reviewed by the Investigator. Prior and concomitant medications will be recorded by their generic name and will be coded using the most current World Health Organization (WHO) drug dictionary.

Treatment with another investigational product (drug or device), or approved medication for investigational use within 30 days or 5 half-lives (whichever is longer) before anticipated dosing is prohibited.

Anti-psychotic medication at a moderate dose (quetiapine >50 mg/day, risperidone >1 mg/day or olanzapine >2.5 mg/day) is prohibited.

Any medication likely to interact with INP103 is prohibited (see Appendix 5).

All subjects will be permitted to take their usual PD medications (e.g. regular Madopar® dosing) at all time points with the exception of:

- From 22:00 on the evening prior to Visit 2 (study site visit between Screening [Visit 1] until they are confirmed to be OFF at Visit 2, and
- From 22:00 on the evening prior to attending dosing on Day 0, Visit 3, until 120 minutes after administration of INP103 or placebo.

In addition to exclusion of usual morning dose of anti-PD medication (e.g. regular Madopar or Sinemet morning dose), all anti-OFF medication is prohibited from 22:00 on the evening prior to Day 0 until 120 minutes post-dose on Visit 3.

Other regular medication required (provided it has been prescribed at a stable dose for at least 30 days) may be continued throughout the trial.

4.6. Diet, Activity and Other Restrictions

Subjects will refrain from consumption of alcohol for 24 hours before INP103 or placebo dosing and for the duration of the study.

Subjects should not consume food or drink containing grapefruit juice within 14 days prior to initial dosing and during the entire study.

INP103 or placebo should be administered whilst in a seated position.

4.7. Meal Schedule

Subjects who arrive at the study site the evening prior to dosing will receive a standard meal and snacks. All subjects will be offered, and encouraged to consume, a light breakfast in the morning 30 minutes prior to dosing. This is 30 minutes prior to dosing with normal PD medications in Visit 2 and 15 minutes before pre-dose blood draw at Visit 3. Thereafter, subjects may be offered a standard meal and/or snacks (if they can consume it in an OFF period, or once that OFF period has resolved). Light breakfast is defined as: cereal with milk or milk substitute, toast with jam or butter, muffin and applesauce, plain/fruit yogurt or suitable alternative as advised by local dietician.

5. STUDY MEDICATION

5.1. Investigational Product Identification

INP103 is a drug-device combination product where the drug component is L-dopa and the device component is the I231 POD Device. The I231 POD Device is a handheld, manually actuated, dose administration device intended to deliver a powder drug formulation to the nasal cavity (i.e. L-dopa).

The INP103 product is designed to administer an intranasal dry powder formulation of L-dopa with a total target dose of 35 mg with each actuation. As such, Cohort 1 will receive a total target dose of 35 mg delivered nasally by one actuation to one nostril. Cohort 2 will receive a total target dose of 70 mg delivered nasally by two actuations, one to each nostril, and Cohort 3 will receive a total target dose of 140 mg delivered nasally by four actuations, two to each nostril.

Cohort 4 will receive INP103 containing a total target dose of 70 mg L-dopa plus 7.0 mg carbidopa delivered nasally by two actuations, one to each nostril.

Any technical issues occurring with the I231 POD Device should be reported to Impel as outlined in the Pharmacy Manual.

Oral benserazide hydrochloride (25 mg), provided as pure active pharmaceutical ingredient (API) in a single dose of 1 Vcaps Plus (HPMC) size 3 capsule, will be administered to all subjects in Cohorts 1, 2 and 3 only, on the morning of Visit 3 dosing upon waking at 60 ±5 minutes before dosing with L-dopa.

5.1.1. Placebo

Placebo will be microcrystalline cellulose. Microcrystalline cellulose is a fine white powder (similar to L-dopa with or without carbidopa) and will come packed and labelled as per identical capsules to those used for INP103 with or without carbidopa. Similar to INP103, placebo will be delivered using the I231 POD Device. The number of actuations will be matched between the placebo treatment and IP treatment.

5.2. Randomization

At least thirty-two (32), maximum 36, subjects will be randomized, and as this is a multi-centre study, centralized randomization will be performed. Treatment assignment will be randomised by blocks of 4 in sequential cohorts, with subjects assigned to either INP103 with or without carbidopa, or placebo delivered via the POD device with one, two, or four actuations, depending on cohort. Ratio of active to placebo assignment is 3:1. Randomization may occur on the day prior to (Day -1) or day of (Day 0) Visit 3 dosing. Subjects who are randomized but not dosed may be replaced at the Sponsor's discretion.

5.3. Blinding

This is a double-blind, randomized, placebo-controlled study. Doses of INP103 and placebo will be prepared by pharmacy personnel who will not be involved in the study assessments. Doses will be provided to blinded study personnel for administration.

5.4. Dosage and Treatment

5.4.1. Study Supplies

Impel NeuroPharma will supply all INP103, oral benserazide, and placebo product through a third-party vendor, PCI Pharma Services (formerly known as Pharmaceutical Packaging Professionals, or PPP), to the investigational sites. INP103 (with and without carbidopa), benserazide, and placebo supplies provided for this study will be manufactured under current good manufacturing practices (cGMP), subject to release, and suitable for human use.

PCI will be responsible for the packaging and labelling of the investigational drug, benserazide, placebo, and device. Impel NeuroPharma will be responsible for providing details of batch numbers, safety, and stability data.

PCI will label the products in accordance with local regulatory requirements and will ship INP103, benserazide, and placebo at a temperature below 25ºC in light-resistant containers (not refrigerated or frozen) to the clinical site.

5.4.2. Storage, Dispensing and Investigational Product Accountability

Upon receipt at the investigational site, INP103, benserazide and placebo must be stored at controlled room temperature in light-resistant containers (not refrigerated or frozen), as specified in the pharmacy manual. A record will be maintained by the investigational site, which will account for all dispensing and return of any used and unused INP103, benserazide, or placebo. At the end of the study, INP103, benserazide and placebo will be reconciled, and a copy of the record given to the study monitor.

Upon completion of the study, any surplus supplies will either be destroyed at the site in accordance with the site's standard operating procedures (SOPs) and upon receipt of written approval from the Sponsor with evidence of destruction supplied to the study monitor or will be returned to an appropriate storage facility as indicated by the Sponsor.

The Investigator will be fully responsible for the security, accessibility, and storage of all drug products whilst they are at the investigational site.

Following training on the use of INP103 and the placebo by an authorized Impel NeuroPharma trainer, the Investigator will then be responsible for the education of study staff in the correct administration of the products.

Further information about the storage, preparation and administration of drug products can be found in the Investigator's Brochure, Pharmacy Manual and Instructions for Use.

6. STUDY PROCEDURES

Study visits should be completed as indicated in the Study Schedule located in Table 1.

Blood samples for L-dopa PK should be collected at the time points and within the windows designated in Table 1

Sites should prioritise in the following order: PK blood draws; UPDRS/Dyskinesia assessments; other safety assessments. All procedures should be completed as close to the prescribed/scheduled times as possible and may be conducted in sequence by the sites according to their standard practice. Due to variability in assessment length, assessments collected out of window, with the exception of PK samples and UPDRS, will not be considered deviations. Any non-scheduled procedures required for urgent evaluation of safety concerns take precedence over all scheduled routine procedures.

6.1. Medical History

Medical history will be recorded at Screening (Visit 1).

6.2. Demographics

Date of birth, age (calculated), sex, ethnicity, and race will be recorded at Screening (Visit 1).

6.3. Body Weight and Height/ Body Mass Index

Body mass index (BMI) is calculated by dividing the subject's body weight in kilograms by the subject's height in meters squared (BMI = kg/m^2). Body height (centimetres) and body weight (kilograms) will be measured at Screening (Visit 1). Body weight and height will be obtained with the subject's shoes and jacket or coat removed.

6.4. Safety Assessments

This study primarily assesses the safety and tolerability of INP103. Safety will be determined by evaluating Physical Examination findings, ECGs, vital signs, clinical laboratory parameters, concomitant medication usage and AEs. If deemed necessary, additional safety measurements will be performed at the discretion of the PI and/or Sponsor's Medical Monitor.

6.4.1. Nasal Inspection

Nasal inspection will be performed before and after the single dose at times noted in Table 1 and on an ongoing basis throughout the study. Any signs of inflammation, ulceration, contact bleeding, oedema, or other abnormalities will be reported.

6.4.2. Overall Dyskinesia Assessment

Following dosing with INP103 or placebo, at each inquiry into AEs, or when conducting the MDS-UPDRS Part III assessment, the Investigator or suitably trained designee (who is familiar with rating dyskinesias), must assess the overall level of dyskinesia, based on the scale below. The most severe grade of dyskinesia observed at that time point, as determined by the same assessor (Investigator or suitable trained designate), and as per usual practice, will be recorded.

0 (Normal)	No dyskinesia.
1 (Slight)	Dyskinesias impact on a few activities.
2 (Mild)	Dyskinesias impact on many activities.
3 (Moderate)	Dyskinesias impact on activities to the point that the patient usually cannot perform some activities.
4 (Severe)	Dyskinesias impact on function to the point that the patient usually does not perform activities.

6.4.3. Physical Examination

Complete physical examinations will be performed by a licensed physician at the time-points specified in Table 1.

Complete physical examinations include: general appearance, head, ears, eyes, throat, dentition, thyroid, chest (heart, lungs), abdomen, skin, neurological, extremities, back, neck, musculoskeletal, and lymph nodes. A nasal inspection will also be completed (Section 6.4.1).

Directed physical examination (120 to 180 minutes post-dose only) includes: head, ears, eyes, throat, chest (heart, lungs), abdomen, skin, musculoskeletal, and lymph nodes and any pertinent system based on any prior findings.

Physical examinations may be performed at various unscheduled time-points if deemed necessary by the PI.

6.4.4. Mini Mental Status Examination (MMSE)

Subjects should have an MMSE score of >25 documented within the previous 36 months. If MMSE score is not available, the assessment should be conducted by the Investigator during Screening to confirm eligibility.

6.4.5. Vital Signs

Subjects should be resting in a supine position for at least 3 minutes prior to and during vital signs measurement obtained. Blood pressure, heart rate, respiration rate and temperature should be measured when the subject is supine. Immediately following supine vital signs assessments, blood pressure only will be measured again when standing. When the time of vital signs measurement coincides with a

blood draw, the vital signs will be taken after the scheduled blood draw, while ensuring the blood draw is within the window specified in the protocol. When vital signs and other safety assessments occur at the same timepoints, clinic staff may follow the sequence of their usual standard practice.

Additional vital signs may be performed at other times if deemed necessary.

6.4.6. Electrocardiogram Monitoring

A 12-lead ECG will be taken at the time-points delineated in Table 1.Table 1ECGs (heart rate, PR, RR, RS, QRS, QT and assessment of clinical significance of abnormalities) will be performed with subjects in a recumbent position. Subjects must be in this position for at least 3 minutes before the reading is taken.

All ECG tracings will be reviewed by the PI or his/her designate and classified as normal; abnormal, not clinically significant or abnormal and clinically significant. If possible, the ECG electrodes will remain in place until the last ECG in the domiciled period.

When the time of ECG monitoring coincides with a blood draw, the ECG will be taken after the scheduled blood draw while ensuring the blood draw is within the window specified in the protocol. When ECG monitoring coincides with other assessments, clinic staff may follow the sequence of their usual standard practice.

6.4.7. Laboratory Investigations

Safety laboratory tests (haematology, serum chemistry, and urinalysis [UA]) will be performed at the time-points specified in Table 1and analysed by an appropriately certified central laboratory.

Medically indicated laboratory tests (emergency or unscheduled tests) should be conducted at the local laboratory.

6.4.7.1. Haematology and Serum Chemistry

A blood sample will be taken from each subject for haematology and serum chemistry analysis at the time-points delineated inTable 1 (see Appendices 1 and 2 for parameters to be tested). Additional clinical laboratory tests may be performed at other times if deemed necessary.

6.4.7.2. Urinalysis

A urinalysis test (dipstick) will be performed for each subject by a central laboratory. Urine analysis will be performed at Screening (Visit 1), and when the subject is admitted to the institution on Day 0 and other times according to the Study Schedule (see Appendix 3 for parameters to be tested). Urine microscopy will be performed in the event of an abnormal dipstick.

A urine pregnancy test will be performed at Visit 2, 3 and 4 as specified in the Study Schedule.

6.4.8. MDS-UPDRS

A full MDS-UPDRS (Parts I-IV) will be assessed at Visit 1 (screening) and on arrival at clinic for dopaminergic responsiveness assessment (Visit 2). Subjects will omit their usual anti PD medication from 22:00 the previous evening and should arrive at the clinic for both Visits 2 and 3 in an OFF state. Once a full MDS-UPDRS assessment has been undertaken, at visit 2 they will take their usual regular PD medication as well as any additional rescue medication they would usually take for OFF episodes at home followed by MDS-UPDRS Part III (motor) assessment at +15, +30, +45, +60, +90 and +120 minutes post PD medication for Cohorts 1, 2 and 3, and +30, +60, +90, and +120 minutes for Cohort 4. Subjects demonstrating a 30% improvement in MDS-UPDRS Part III at visit 2 will be deemed dopamine responsive and will be eligible for randomization.

A full MDS-UPDRS (Parts I-IV) will also be assessed prior to dosing on Visit 3 and during follow-up (Visit 4).

Further (post-dose) MDS-UPDRS III assessments (motor scores) will occur at the time points delineated in the Study Schedule in Table 1.

MDS-UPDRS criteria and questions are provided in Appendix 4.

6.4.9. Subject Questionnaire

At 120 up to 180 minutes after dosing with INP103 or placebo, subjects will be asked the questions in the questionnaire provided in Appendix 6. This should follow all other assessments.

6.5. Pharmacokinetic Assessments

6.5.1. Sampling and Processing

An intravenous cannula will be inserted prior to all medication dosing at Visit 3 to enable baseline PK and subsequent blood draws to be performed.

Blood samples for PK analysis of L-dopa (and carbidopa in Cohort 4) will be obtained, according to the site's SOPs, within 15 minutes prior to INP103 or placebo dosing and at the time-points (related to INP103/placebo dosing), and within the windows, delineated in the Study Schedule in Table 1.

The actual collection time of each sample must be recorded in the source data documentation, on the collection tube and in the electronic case report form (eCRF). The allowed time deviation window for blood sample collection is + 1 minute for samples up to 30 minutes, and then ± 2 minutes for the 44, 59, 89 and 119 minutes sample time points (following INP103/placebo dosing) before a deviation is recorded. PK blood draws will precede UPDRS assessments. Due to variability in

assessment length, assessments collected out of window, with the exception of PK samples and UPDRS, will not be considered deviations

The Sponsor will supply complete written instructions for handling, processing, storage, and shipping of PK samples in the laboratory manual prior to study initiation.

6.5.2. Analytical Methods

Plasma PK sample analyses will be performed using validated procedures and methods at AIT Bioscience.

6.6. Pharmacodynamic Assessments

6.6.1. MDS-UPDRS

See Section 6.4.8.

6.6.2. Assessment of ON

Subjects will provide a self-assessment of their ON or OFF state, and Investigators will provide an assessment of the ON or OFF state of the subject, at the time points delineated in the Study Schedule in Table 1.

7. STUDY SCHEDULE

7.1. Screening (Up to 21 Days Prior to Visit 3 Dosing) (Visit 1)

(Refer also to study synopsis and Table 1)

Prior to enrolling in the study, and before performing any study-related procedures, potential subjects will attend the first of two Screening Visits, at which time they will be provided with full information concerning details of the study assessments and procedures. They will also be provided with the Subject Information Sheet and Informed Consent Form. Prior to being asked to sign the consent form, subjects will be given time to review study information and ask any questions.

After the consent form is signed, Screening assessments will be carried out as follows:

- Review of medications, medical history and inclusion/exclusion criteria.
- Administer MMSE (if required) to confirm eligibility
- Record of pre-treatment AEs.
- Measurement of height and weight.
- Recording demographic information.
- Complete physical examination (including nasal examination), including full MDS-UPDRS (see Appendix 4).
- 12-Lead ECG.
- Vital signs (blood pressure [supine and standing]; and heart rate, respiratory rate and oral temperature [supine only]).
- Clinical laboratory testing (non-fasting haematology, serum chemistry and urinalysis).
- Serum pregnancy test (WOCBP only).
- FSH (post-menopausal women only).

Due to variability in assessment length, assessments collected out of window, with the exception of PK samples and UPDRS, will not be considered deviations.

7.2. Admission to Clinic (Day prior to Visit 2 and Visit 3)

Depending on private arrangements, capability, and logistics, subjects may be domiciled in the study clinic from the evenings prior to Visit 2 and Visit 3. Subjects will receive a standard meal and snacks and be offered a light breakfast in the morning before dosing and thereafter may be offered a standard meal and/or snacks. Subjects will not complete any study procedures until the morning of both Visit 2 and Visit 3.

7.3. Evaluation of Dopamine Responsiveness (Screening [Visit 2])

Subjects considered eligible for study participation as per the outcome of Screening (Visit 1) are to return to the study clinic for Screening (Visit 2) on one day between Screening Visit 1 and Day 0 (Visit 3), i.e. within the maximum 21-day Screening window.

For this visit (Visit 2), the subject will suspend their usual anti PD medication from 22:00 pm the previous evening (including any DCIs). If not domiciled, they should arrive at the clinical research site in an OFF state, which will be confirmed and characterised by full MDS-UPDRS assessment. The subjects will then have a light breakfast 30 minutes before they take their usual L-dopa containing medication (including any rescue medication they would normally take for an OFF episode) and repeat the MDS-UPDRS Part III (motor examination) tests only at +15, +30, +45, +60, +90 and +120 minutes thereafter for Cohorts 1, 2 and 3, and +30, +60, +90 and +120 minutes for Cohort 4.

Subjects showing at least a 30% improvement in MDS-UPDRS Part III score during this visit will be deemed to be dopamine responsive, will be eligible to be randomized and will proceed to Visit 3/Day 0.

If the subject normally responds (subjective) to their dopaminergic medication but has an unexpectedly poor response (<30%) at Visit 2, which although unexpected could be explained (e.g. due to slow gastric emptying), then the dopamine responsiveness assessment may be repeated prior to Visit 3.

Data from screen failures at the Visit 2 (dopamine responsiveness visit) will be collected and reviewed but data from screen failures at Visit 1 will not be recorded in the eCRF. Reasons for screen failures will be collected in study Screening logs.

7.4. Dosing and Admission to Clinic (Day 0) (Visit 3)

7.4.1. Before Dosing

Subjects not domiciled in the study clinic on the evening of Day -1 will be transported to the study clinic as early as possible on the morning of Day 0.

All subjects, irrespective of date or time of arrival at the study clinic, will have their usual anti-PD medication (e.g. usual regular Madopar® dosing and any required anti-OFF treatment [e.g. Madopar rapid]) withheld from 22:00 on the evening before Day 0 until at least 120 minutes post-dosing with INP103 or placebo. Subjects determined as being in an ON state during the pre-dose assessments will not participate further in the study.

At visit 3, subjects will be offered, and encouraged to consume, a light breakfast, 30 minutes before dosing (and 15 minutes before pre-dose PK blood draw).

Pre-dose PK sample will be obtained once an IV cannula has been inserted, approximately 15 minutes prior to INP103 or placebo dosing. Prior to dosing, subjects will be sequentially assigned a randomization number. The subject identification number will remain the same throughout the study.

Subjects will be offered standard meal and/or snacks after dosing as appropriate.

All subjects in Cohorts 1, 2 and 3 will receive oral benserazide (25 mg) 60 ± 5 minutes before INP103 or placebo dosing.

Subjects in Cohort 4 will not receive oral benserazide but will be dosed with INP103 (with carbidopa) or placebo once OFF state confirmed and all other baseline assessments have been completed.

The following assessments will be carried out prior to dosing (in an order consistent with site's standard practice) on Day 0:

- Review to determine whether the subject continues to satisfy the study inclusion and exclusion criteria
- Vital signs (blood pressure [supine and standing]; and heart rate, respiratory rate and oral temperature [supine only])
- 12-Lead ECG
- Complete physical examination including nasal inspection
- Safety laboratory analysis sample collection (haematology, clinical chemistry and urinalysis)
- Urine pregnancy test (WOCBP only)
- Record of pre-treatment AEs (post randomization, pre-treatment emergent, including rating of dyskinesias)
- Review of the subject's concomitant medications, including non-prescription medications
- Investigator and subject self-evaluation of ON/OFF
- Full MDS-UPDRS assessment (I to IV)
- Administration of Benserazide **(60 ± 5 minutes before INP103 or placebo dosing – Cohorts 1, 2 and 3 only)**
- Blood sample collection for baseline PK readings **(within 15 minutes prior to dosing)** (see Table 1).

Due to variability in assessment length, assessments collected out of window, with the exception of PK samples and UPDRS, will not be considered deviations.

7.4.2. Dosing (Visit 3)

Subjects will be dosed by delegated clinic staff and according to the treatment arm to which they have been randomized. Additional details about the preparation and dosing of INP103 or placebo are provided in the Pharmacy Manual.

7.4.3. After Dosing

The subjects will remain in the study clinic post-dose through to the completion of all scheduled post-dose procedures 240 minutes after dosing.

The subject's usual rescue (anti-OFF [e.g. Madopar rapid]) medication will be permitted from 120 minutes post-dose (once all 120 minute assessments have been completed, but can precede ECG, physical examination and subject questionnaire) – if they are still OFF. In addition, subjects should take their regular anti PD medication (e.g. their regular morning Madopar dose) at 120 minutes post dosing whether or not they have returned to ON.

The following in-patient assessments will be performed after dosing:

1. Adverse Events (including overall dyskinesia rating) and concomitant medications will be continually monitored post-dose.
2. Vital signs will be measured at 30, 60 and 120 minutes post-dose. Blood pressure (supine and standing) and heart rate, respiratory rate and oral temperature (supine only) will be measured at all time points. Vital signs will be collected after MDS-UPDRS assessment (where both procedures are scheduled at the same time point) and will not be deemed protocol deviations if they occur outside the time window at each timepoint.
3. PK blood samples will be collected at 4, 9, 14, 29, (all + 1 minute) 44, 59, 89 and 119 (all ± 2 minutes at each timepoint) minutes post-dose and will precede UPDRS assessments.
4. MDS-UPDRS III only at 15, 30, 45, 60, 90 and 120 minutes post-dose for Cohorts 1, 2 and 3) and 30, 60, 90, 120 minutes for Cohort 4 (± 2 minutes at each timepoint)
5. Investigator and subject self-assessment of ON/OFF at 30, 45, 60, 90, 120 and 240 minutes post-dose (± 10 minutes at each timepoint)
6. At 120 minutes, the subject's usual morning dose of all Parkinson's medications should be given following completion of assessments 1-5, regardless of ON/OFF state. In addition, if subject is still OFF, their usual OFF medication may be given (prior to completing assessments 7, 8 and 9).
7. Directed physical examination (including nasal inspection) will be performed at 120-180 minutes post-dose

8. 12-Lead ECG will be performed at 120-180 minutes post dose. In cases where vital signs are scheduled at the same time point, ECG will be completed in sequence with vital signs per the usual practice of the study sites.
9. Subject questionnaire will be completed as the last assessment from 120-180 minutes post-dose

Due to variability in assessment length, assessments collected out of window, with the exception of PK samples and UPDRS, will not be considered deviations.

Subjects will be discharged from the study site following satisfactory completion of assessments.

7.5. Follow-Up/End of Study (Day 7 + 2 days)

The subjects will return to the institution on Day 7 (+2 days). In exceptional circumstances, if a subject is unable to attend the end of study visit on Day 7 (+ 2 days, as indicated), the Investigator (or qualified designee) should discuss appropriate re-scheduling to a maximum of +4 days with the Sponsor's Medical Monitor (or appropriate designee). The following assessments will again be carried out:

- Adverse Events (including overall dyskinesia rating) and concomitant medications
- 12-Lead ECG
- Vital signs (blood pressure [supine and standing]; and heart rate, respiratory rate and oral temperature [supine only])
- Complete physical examination
- Clinical laboratory testing (haematology, serum chemistry and urinalysis)
- Full MDS-UPDRS

Due to variability in assessment length, assessments collected out of window, with the exception of PK samples and UPDRS, will not be considered deviations

8. ADVERSE EVENTS

In this study, AEs will be reported for all subjects from signing of consent until the completion of the end of study Day 7 follow-up visit. SAEs will be reported in all subjects (enrolled and not enrolled) from the time of consent. Treatment-emergent AEs (TEAEs) will be reported from dosing on Day 0. Study procedure-related AEs will be evaluated specifically from the time of consent until INP103 or placebo administration. Treatment-emergent AEs will be evaluated from INP103 or placebo dosing until the end of study visit. AEs that are ongoing at the end of study visit will be marked as ongoing on the AE eCRF page.

All AEs resulting from spontaneous subject self-reporting, direct enquiry or observation by study staff, will be recorded in the subject's medical records and the eCRF.

8.1. Safety Monitoring Committee

Once dosing has been completed for all subjects in Cohort 1, a Safety Monitoring Committee (composed of the Principal Investigators, the contract research organization (CRO)'s Medical Monitor and the Sponsor's Medical Monitor) will review the AEs reported for the completed cohort. If they assess the benefit:risk ratio of the completed cohort acceptable, that decision will be documented, and the subsequent cohort given permission to proceed with dosing. This will be repeated for Cohort 2. No SMC meeting is planned following Cohort 3, unless safety concerns were raised during the SMC meetings occurring after Cohorts 1 and 2. The rationale for no SMC meeting prior to Cohort 4 is because the dose of L-dopa and DCI is less than for Cohort 3. However, all other usual safety monitoring will remain in place for the duration of the study.

8.2. Definition of an Adverse Event

An AE is any event, side-effect, or other untoward medical occurrence that occurs in conjunction with the use of a medicinal product in humans, whether or not considered to have a causal relationship to this treatment. An AE can, therefore, be any unfavourable and unintended sign (that could include a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition

- New conditions detected or diagnosed after INP103, or placebo administration that occur during the AE reporting periods, even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either INP103 or placebo or a concomitant medication (overdose per se will not be reported as an AE/SAE)

Events that do not meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure should be reported as an AE if it meets the criteria of an AE
- Situations where an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

If there is evidence of an AE through report or observation, the Investigator or designee will evaluate further and record the following information:

- Time of onset and resolution
- Severity
- Causality/relation to study treatment
- Action taken regarding INP103 or placebo
- Outcome

8.2.1. Severity of an Adverse Event

Severity of adverse events will be graded by the Investigator as one of:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention

8.2.2. Causal Relationship of an Adverse Event

The Investigator will assess the relationship between INP103 or placebo and the occurrence of each AE. The Investigator's assessment of the relationship of each AE to investigational product will be recorded in the source documents and the eCRF. Alternative causes, such as medical history, concomitant therapy, other risk factors, and the temporal relationship of the event to INP103, or placebo administration should be considered and investigated, if appropriate. The following definitions are general guidelines to help assign grade of attribution:

- Not related: The event is clearly related to other factors such as the subject's clinical state, therapeutic interventions or concomitant drugs administered to the subject. This is especially so when an event occurs prior to the commencement of treatment with INP103 or placebo.
- Unlikely: The event was most likely produced by other factors such as the subject's clinical state, therapeutic interventions, or a concomitant drug administered to the subject and does not follow a known response to INP103 or placebo.
- Possible: The event follows a reasonable temporal sequence from the time of INP103 or placebo administration or follows a known response to INP103 or placebo but could have been produced by other factors such as the subject's clinical state, other therapeutic interventions, or concomitant drugs administered to the subject.
- Probable: The event follows a reasonable temporal sequence from the time of INP103 or placebo administration and follows a known response to INP103 or placebo and cannot be reasonably explained by other factors such as the subject's clinical state, other therapeutic interventions, or concomitant drugs administered to the subject.

8.2.3. Action Taken with Study Medications

Action taken with study medications will be recorded on the AE eCRF page, as one of the following options:

- Dose Interrupted
- Dose Withdrawn
- Not Applicable
- Unknown

8.2.4. Outcome

Outcome of an AE will be recorded on the AE eCRF as follows:

- Recovered / Resolved

- Recovering / Resolving
- Recovered / Resolved with Sequelae
- Not Recovered / Not Resolving
- Fatal
- Unknown

8.3. Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

Important medical events that may not be one of the above may be considered an SAE by the Investigator when, based upon appropriate medical judgement, are considered clinically significant and may jeopardise the subject, or may require medical or surgical intervention to prevent one of the outcomes listed above.

An AE is considered life-threatening if, in the opinion of either the Investigator or the Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

8.3.1. Notification of a Serious Adverse Event

In order to meet the requirements for expedited reporting of SAEs meeting specific requirements to applicable regulatory authorities and institutional ECs, all SAEs, must be reported to CNS within 24 hours from the time the site investigational team first become aware of the event. This may be initially achieved by telephone, or by completing an SAE report form and e-mailing to CNS via the email address

Safety@clinical.net.au

Initial notification of an SAE by telephone must be confirmed in writing 24 hours from the time the site investigational team first become aware of the event using the SAE report form as described above.

As further information regarding the SAE becomes available, such follow-up information should be documented on a new SAE report form, marked as a follow-up report, scanned and e-mailed to the address at the bottom of the report form.

Withdrawal from the study in the event of a SAE and therapeutic measures taken shall be at the discretion of the Investigator. A full explanation for the discontinuation from the study should be made in the subject's medical records and in the eCRF.

8.4. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events and Serious Adverse Events

Abnormal laboratory findings (e.g., clinical chemistry, haematology, and urinalysis) or other abnormal assessments (e.g., ECG and vital signs) per se are not reported as AEs. However, those abnormal findings that are deemed **clinically significant** or are associated with signs and/or symptoms must be recorded as AEs if they meet the definition of an AE (and recorded as an SAE if they meet the criteria of being serious) as described previously. Clinically significant abnormal laboratory or other abnormal findings that are detected after consent or that are present at baseline and worsen after consent are included as AEs (and SAEs if serious).

The Investigator should exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Usually, the abnormality should be associated with a clinically evident sign or symptom, or be likely to result in an evident sign or symptom in the near term, to be considered clinically significant. A clinically significant laboratory abnormality in the absence of clinical symptoms may jeopardize the subject and may require intervention to prevent immediate consequences. For example, a markedly low serum glucose concentration may not be accompanied by coma or convulsions, yet be of a magnitude to require glucose administration to prevent such sequelae.

8.5. Documenting Adverse Events

Any AE occurrence during the study must be documented in the subject's medical records in accordance with the Investigator's normal clinical practice and on the AE page of the eCRF. SAEs that occur during the study must be documented in the subject's medical record, on the AE eCRF, and on the SAE form.

The Investigator should attempt to establish a diagnosis of the event based on the signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE (and SAE if serious) and not the individual signs/symptoms.

If a clinically significant abnormal laboratory finding or other abnormal assessment meets the definition of an AE, then the AE eCRF page must be completed as appropriate. In addition, if the abnormal assessment meets the criteria for being serious, the SAE form must also be completed. A diagnosis, if known, or clinical signs or symptoms if the diagnosis is unknown, rather than the clinically significant laboratory finding or abnormal assessment, should be used to complete the AE/SAE page. If no diagnosis is known and clinical signs or symptoms are not present, then

the abnormal finding should be recorded. If an SAE report is completed, pertinent laboratory data should be recorded on the SAE form, preferably with baseline values and copies of laboratory reports.

The SAE page should be completed as thoroughly as possible and signed by the Investigator before transmittal to the study Sponsor and CNS. It is very important that the Investigator provide an assessment of the causal relationship between the event and INP103 or placebo at the time of the initial report, as this will be useful for submissions to regulatory authorities.

8.6. Regulatory Authorities

The reporting of any SAEs to applicable regulatory authorities will be the responsibility of the Sponsor in compliance with applicable country regulations.

All SAEs must be reported to the HREC by the Investigator in accordance with their regulations.

8.7. Follow-Up of Adverse Events and Serious Adverse Events

All AEs and SAEs that are deemed related, possibly related or probably related to INP103 or placebo must be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject dies or is lost to follow-up. The Investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the AE/SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

The Sponsor may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations. If a subject dies during participation in the study or during a recognized follow-up period, the Sponsor should be provided with a copy of any post-mortem findings, including histopathology.

8.8. Pregnancy

Females who are pregnant, planning a pregnancy or lactating are to be excluded from the study. In the case of a pregnancy occurring during study participation or at any time during the 30 days following INP103 or placebo, it must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to CNS within 5 days of the PI learning of its occurrence. The pregnancy should be followed up to determine outcome (including premature termination) and status of mother and child. The subject will be requested to provide written informed consent to enable collection of information pertaining to the outcome of the pregnancy. Pregnancy complications and elective terminations for medical reasons

must be reported as an AE or SAE. Spontaneous abortions must be reported as an 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 INP103 or placebo, must be promptly reported to CNS.

In addition, the Investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to CNS as described above.

9. STUDY COMPLETION AND DISCONTINUATION

9.1. Subject Withdrawal

In accordance with applicable regulations, a subject has the right to withdraw from the study at any time and for any reason, without prejudice to his future medical care.

Subjects may be withdrawn from the study for any of the following reasons:

- Subject is unable or unwilling to continue participation in the study
- Adverse event (whether or not related to INP103 or placebo) that precludes further participation in the study in the judgment of the Investigator and/or Sponsor
- Protocol noncompliance
- Informed consent withdrawn
- The Investigator considers that it is in the subject's best interest for the subject not to continue participation in the study

If a subject is withdrawn because of an AE, the Investigator must arrange for the subject to have appropriate follow-up care until the AE is resolved or has stabilized. Unresolved AEs will be followed until the last scheduled follow-up visit or until the PI and Medical Monitor determine that further follow-up is no longer indicated. In addition to AEs, other reasons for removal of subjects from the study might include, but are not limited to, withdrawal of consent, administrative decision by the Investigator or the Sponsor, protocol deviation, or subject noncompliance.

If a subject asks or decides to withdraw from the study, all efforts will be made to complete and report the observations, especially the listed primary and secondary objectives, as thoroughly as possible up to the date of withdrawal. The primary reason for withdrawal will be identified and recorded on the appropriate eCRF, along with the date of withdrawal.

9.2. Subject Replacement

At least thirty-two subjects are planned for enrolment in the study. Subjects who consent but then do not receive INP103 or placebo for any reason may be replaced at the Sponsor's discretion. Subjects will not be replaced once dosed.

10. TERMINATION OR SUSPENSION OF THE STUDY

The Sponsor, Investigator, and the HREC reserve the right to terminate or suspend the study at any time; however, this should be discussed between the relevant parties beforehand and the reason for such decision recorded. Should this occur, all data available will also be recorded in the eCRFs. The Investigator should notify the relevant institutional HREC in writing of the study's completion or early discontinuation.

11. STUDY MONITORING AND DATA MANAGEMENT

11.1. Study Monitoring

The Sponsor has appointed Clinical Network Services (CNS) Pty Ltd to manage and monitor the study so as to assure them of the adequate conduct of the study and to act as the contact with the investigational site. A study monitor will be identified and will be responsible for liaison with, and support of, the investigational site.

The study monitor and regulatory authority inspectors are responsible for contacting and visiting the investigative site for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (e.g., eCRFs, essential documentation, and other pertinent data) provided that subject confidentiality is respected.

11.2. Access to the Study

The Sponsor, study monitor, HREC and applicable regulatory agencies may require access to all study documents held at the investigational site, as well as access to all members of the investigational site personnel. It is expected that such access would normally be arranged by agreement with the investigational site.

11.3. Source Document and Data Verification

The study monitor will visit the investigational site periodically where s/he shall:

- Meet with the Investigator and any other applicable site staff.
- Inspect the eCRFs throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRFs. The Investigator will cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved. The monitor will identify of any data to be recorded directly on the eCRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.
- Review the investigational site file and regulatory documentation.
- Collect copies of documents and completed eCRFs for use by the appointed data management group and retention by the Sponsor.
- Verify with reference to the INP103, benserazide, and placebo records, that drug products have been stored appropriately, and administered correctly, to eligible subjects.

All eCRFs should be maintained on the system with details of any changes logged accordingly.

11.4. Data Management

All data will be recorded in individual source documents. An eCRF will be created by the data management group for recording of the required data in the study database. All eCRF information is to be filled in by site staff. If an item is not available or is not applicable, this fact should be indicated. Blank spaces should not be present unless otherwise directed.

The study monitor will perform source data verification of data entered into the eCRF; when discrepancies are noted, the study monitor will raise queries for correction by the site. The data entered into the eCRF will be subject to data validation checks for consistency and completeness by the data management group. Data queries will then be generated and sent to the investigational site for response before the database is locked and released for statistical analysis.

12. STATISTICAL ANALYSES

This protocol section describes the statistical analyses as they are foreseen at the time of planning the study. A separate Statistical Analysis Plan (SAP) will be prepared prior to performing any unblinded analysis. The SAP will serve as a complement to the study protocol and supersedes it in case of differences.

12.1. Sample Size Calculation

Thirty-two (32) subjects (8 per dose group) are considered sufficient for assessment of safety and tolerability of SADs of INP103. However, we are proposing that Cohort 4 may enrol an additional 4 patients (for a maximum of 12) under the same randomization scheme (3:1). With at least eight subjects per group, the study has 80% power to detect an improvement of 13 points from baseline in MDS-UPDRS Part III scores within each dose level, assuming a standard deviation of 11 points, using a two-sided significance level of 0.05. This study is not powered for between-group comparisons of the pharmacodynamic endpoints.

12.2. Analysis Populations

Safety Population: All subjects who receive any amount of INP103 or placebo will be included in the Safety Population. A pooled placebo group (of subjects from each of the five cohorts) will be used for comparisons. The data will be analysed according to the treatment received.

Benserazide Safety Population: All subjects who receive any amount of benserazide in Cohorts 1, 2 and 3 (as provided by the Sponsor) will be included in the Benserazide Safety Population. This population will be used for the analysis of the safety data collected after receiving benserazide (as provided by the Sponsor) and before receiving INP103 or placebo. This population will not be applicable to Cohort 4.

PK Population: All subjects who receive any amount of INP103 or placebo and have sufficient samples collected for non-compartmental analysis will be included in the PK Population. The data will be analysed according to the treatment received.

Intention-to-Treat (ITT) Population: All randomized subjects who have baseline and at least one post-dose assessment of motor function will be included in the ITT Population. A pooled placebo group (of subjects from each of the five cohorts) will be used for comparisons. The data will be analysed according to the randomized treatment group.

12.3. Safety Analysis

Continuous safety data will be summarised with descriptive statistics (arithmetic mean, SD, median, minimum, and maximum) by treatment. Categorical safety data will be summarised with frequency counts and percentages by treatment.

AEs will be coded using the most current Medical Dictionary for Regulatory Activities (MedDRA®) available at CNS. A by-subject AE data listing, including verbatim term, preferred term, system organ class, treatment, severity, and relationship to INP103 or placebo, will be provided. A treatment emergent AE (TEAE) is defined as an AE with onset after the first dose of INP103 or placebo. The number of subjects experiencing TEAEs and number of individual TEAEs will be summarized by treatment, system organ class and preferred term. TEAEs will also be summarized by seriousness, severity, relationship to INP103 or placebo and the time of onset relative to dosing.

In addition to the TEAEs, the AEs with onset after the first dose of benserazide (as provided by the Sponsor) and before the first dose of INP103 or placebo will be summarized by system organ class and preferred term.

Dyskinesia assessment, nasal inspection, laboratory evaluations, vital signs assessments (including supine and standing blood pressure, all other vital signs supine only) and ECG parameters will be summarized by treatment and protocol specified collection time point. A summary of change-from-baseline at each protocol specified time-point by treatment will be presented.

In addition, the proportion of subjects experiencing orthostatic hypotension or abnormal ECGs will be summarized by treatment group. The orthostatic hypotension is defined as a reduction in systolic blood pressure of 20 mmHg or more, and/or a reduction in diastolic blood pressure of 10 mmHg or more, for the standing measurement compared to the supine measurement. For ECGs, in addition to the overall assessment done by the physician, the proportion of subjects meeting the following criteria based on QTc values (defined both using the correction by Bazett and by Fridericia) will be summarized: QTc value >500 msec, QTc value increasing >15% from baseline if baseline value is ≥440 msec, QTc value increasing >30% from baseline if baseline value is <440 msec, QTc value increasing >30% from baseline, QTc value increasing >60% from baseline.

Proportion of subjects with abnormal physical examination findings will be summarized by treatment group.

Prior and concomitant medications will be listed by subject and coded using the most current WHO drug dictionary and summarized by therapeutic class (Level 4 for anti-PD medications and Level 2 for other medications) and preferred name.

Medical history will be listed by subject.

12.4. Pharmacokinetic Analysis

The levodopa concentrations will be summarized with descriptive statistics (arithmetic and geometric mean, SD, median, minimum, and maximum) by treatment group and time point. In addition, the PK parameters ($AUC_{0\text{-}0.5h}$, $AUC_{0\text{-}1h}$, $AUC_{0\text{-}2h}$, C_{max}, T_{max}) will be summarized with descriptive statistics by treatment group. Carbidopa concentrations from Cohort 4 will also be analysed and summarized.

12.5. Pharmacodynamic Analysis

The changes from baseline in MDS-UPDRS Part III scores will be summarized by treatment groups and estimated using a Mixed Model for Repeated Measures (MMRM) with treatment group (INP103 35 mg, INP103 70 mg, INP103 140 mg, INP103 70mg with 7.0 mg carbidopa, or placebo), time point (15, 30, 45, 60, 90 or 120 minutes for INP103 and benserazide [C1, C2, C3] and 30, 60, 90, 120 minutes for INP103 and carbidopa [C4])) and the interaction between treatment group and time point as fixed factors. The baseline score will be included as a covariate. The focus will be on the estimation of changes within each treatment group. An unstructured covariance structure will be used for the MMRM. In case the model does not converge with the unstructured covariance structure, the heterogeneous compound symmetry (CSH) or heterogeneous Toeplitz structure (TOEPH) will be used instead. The denominator degrees of freedom will be computed using the Kenward-Roger method. The least square (LS) means, standard errors and two-sided 95% confidence intervals will be provided for changes within each treatment group. In addition, the differences between each treatment group and placebo will be estimated.

The cumulative proportion of responders will be summarized descriptively by treatment group and time point.

The endpoint related to time of response and time to ON will be evaluated with Kaplan-Meier methods. The figures of Kaplan-Meier estimate and summary statistics (25th percentile, median, and 75th percentile and their 95% confidence intervals) will be presented.

For subjects who received study drug administration and achieve response within 120 minutes post dosing, the duration of response will be summarized by treatment group. If the subject did not achieve response after 120 minutes post dosing, this subject will be regarded as censored and the duration of response will be treated as missing.

The AUC of MDS-UPDRS Part III scores from pre-dose to 15, 30, 45, 60, 90 and 120 minutes will be calculated as $AUC_{0\text{-}15}$, $AUC_{0\text{-}30}$, $AUC_{0\text{-}45}$, $AUC_{0\text{-}60}$, $AUC_{0\text{-}90}$ and $AUC_{0\text{-}120}$ (omitting $AUC_{0\text{-}15}$ and $AUC_{0\text{-}45}$ for Cohort 4). These AUC parameters will be summarized by treatment groups as well as analysed with an Analysis of Covariance (ANCOVA) model with treatment group as a fixed factor and baseline MDS-UPDRS Part III score as a covariate. The least square (LS) means, standard errors and two-

sided 95% confidence intervals will be provided for changes within each treatment group. In addition, the differences between each treatment group and placebo will be estimated.

The individual maximum response scores will be defined as the maximum MDS-UPDRS Part III score post dosing from the baseline across all time points post dose (from 15, 30, 45, 60, 90 and 120 minutes for C1, C2, and C3, and 30, 60, 90, 120 minutes for C4) of each subject and will be summarized by treatment groups as well as analysed with an Analysis of Covariance (ANCOVA) model with treatment group as a fixed factor and baseline MDS-UPDRS Part III score as a covariate. The least square (LS) means, standard errors and two-sided 95% confidence intervals will be provided for changes within each treatment group. In addition, the differences between each treatment group and placebo will be estimated.

12.6. Pharmacokinetic/Pharmacodynamic relationship

The analyses required to investigate the PK/PDyn relationship of INP103 will be defined in the SAP which will be completed before the database is locked.

13. REGULATORY REQUIREMENTS

13.1. Regulatory Approvals

CNS will act as the legal Australian Representative for Impel NeuroPharma, the Sponsor of the study, and will fulfil the obligations that this role entails. CNS shall, to the extent required by the applicable laws and regulations, interact with Australian Therapeutic Goods Administration (TGA) on behalf of the Sponsor in connection with this study. The planned regulatory pathway for this trial is through the Clinical Trial Notification (CTN) Scheme. Aside from approval by the EC and notification of the TGA no other regulatory approval will be required.

An L-dopa formulation, in the absence of a DCI, does not have marketing authorization in any ICH territory, although an inhaled form of L-dopa, CVT301, has now successfully completed clinical development. L-dopa in combination with DCI (benserazide or carbidopa) is approved in many regions/countries around the world, including in Australia (e.g. Madopar and Sinemet respectively). These products are administered orally. There are no globally approved L-dopa-containing or L-dopa/carbidopa containing products for nasal administration.

13.2. Human Research Ethics Committee (HREC) Approval

Prior to the commencement of the study, written approval will be required by the relevant institutional HREC responsible for the investigational site.

13.3. Subject Informed Consent

It is the Investigator's responsibility to ensure that each subject gives informed consent to participate in the study. The Investigator will explain the nature of the study, its purpose, procedures, expected duration, and the potential benefits, risks and inconveniences in participation. In addition, a subject information sheet/consent form containing relevant information will be prepared by Impel in conjunction with the investigational site and will be provided to all subjects.

The subjects will be informed of their rights to privacy but will be made aware that the study data will be submitted to the Sponsor and possibly to drug regulatory authorities for review and evaluation. They will be informed also that the study monitor may inspect their medical records to verify the accuracy and completeness of the study records and results.

The subjects will be informed of their right to withdraw from the study at any time without prejudice.

The subjects will be given an opportunity to ask questions and allowed sufficient time to decide whether they wish to participate. If the subject decides to participate in the study, they will voluntarily sign the written informed consent form.

The acquisition of informed consent should be documented in the subject's medical records, as required by Notes for Guidance on GCP (CPMP/ICH/135/95), as adopted by the Australian Therapeutic Goods Administration (2000), and the NHMRC National Statement on Ethical Conduct in Human Research (2007, incorporating all updates as at May 2015). The informed consent form will be signed and personally dated by the subject and by the person who conducted the informed consent discussion (not necessarily an investigator). The original signed informed consent form will be retained in accordance with institutional policy, and a copy of the signed consent form will be provided to the subject or legal representative. The date that informed consent was signed will be recorded on the eCRF.

13.4. Data Protection

Subjects will be informed that data will be held on file by Impel and that these data may be viewed by staff including the study monitor and by external auditors on behalf of Impel and appropriate regulatory authorities. Subjects will also be informed that a study report will be prepared and may be submitted to regulatory authorities and for publication. However, subjects will be identified in such reports only by study identification number, gender and age. All subject data will be held in strict confidence.

14. ADMINISTRATIVE PROCEDURES

14.1. Liability/Indemnity/Insurance

The study Sponsor will ensure sufficient insurance is available to enable it to indemnify and hold the Investigator(s) and relevant staff as well as any hospital, institution, EC or the like, harmless from any claims for damages for unexpected injuries, including death, that may be caused by INP103, benserazide or placebo but only to the extent that the claim is not caused by the fault or negligence of the subjects or Investigator(s).

14.2. Recording of Data and Retention of Records

All source data, clinical records and laboratory data relating to the study will be archived for 15 years after the completion of the study. All data will be available for retrospective review or audit.

Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include, but are not limited to: hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, angiograms, investigational product accountability logs, and correspondence. eCRF entries may be considered source data if the eCRF is the site of the original recording (i.e., there is no other written or electronic record of data). In this case, a note to the file should indicate which eCRFs are considered source documents.

The Investigator and study staff are responsible for maintaining a comprehensive filing system of all study-related (essential) documentation. These include, but are not limited to: EC correspondence, investigational product accountability logs, and curricula vitae of all personnel participating in the study. These files must be suitable for inspection at any time by the Sponsor, monitor, and/or applicable regulatory authorities. All essential documentation should be retained by the institution for 15 years (as required in Australia).

No study document should be destroyed without prior written agreement between the Sponsor and the Investigator. If the Investigator wishes to assign the study records to another party or move them to another location, he/she must notify the Sponsor in writing of the new responsible person and/or the new location.

14.3. Publication of Results

Publication and reporting of results and outcomes of this trial will be accurate and honest, undertaken with integrity and transparency and in accordance with Impel's Publication Policy.

Publication of results will be subjected to fair peer-review. Authorship will be discussed between researchers prior to study commencement (or as soon as possible thereafter) and reviewed whenever there are changes in participation.

All conflicts arising through disputes about authorship will be reviewed by Impel. Authorship should be consistent with the guidelines described in the Australian Code for Responsible Conduct of Research (section on Authorship).

Acknowledgment will be given to collaborating institutions and hospitals and other individuals and organisations providing finance or facilities. Subject confidentiality will be maintained by referring to individual subjects by their identifying code used in the trial. Data will not be released publicly until the manuscript is accepted for publication. In the case of no publication, information will only be released to the public and media in accordance with Impel's Policy.

The study protocol and subsequent results summary will be posted to a Clinical Trials Registry as required by legal agreement, local law or regulation.

14.4. Disclosure and Confidentiality

By signing this protocol, the Investigator agrees to keep all information provided by the Sponsor in strict confidence and to request similar confidentiality from his/her staff and the local EC. Study documents provided by the Sponsor (protocol, IB, eCRFs, etc.) will be stored appropriately to ensure their confidentiality. The information provided by the Sponsor to the Investigator may not be disclosed to others without direct written authorization from the Sponsor, except to the extent necessary to obtain informed consent from subjects who wish to participate in the study.

The Investigator must ensure that the subject's anonymity is also maintained. Subjects should only be identified by their initials and a subject study number on the eCRFs and other source documents. Other study-related documents (e.g., signed informed consent forms) should be kept in strict confidence by the Investigator.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1. Compliance with Good Clinical Practice

The study will be carried out in accordance with the current version of the Declaration of Helsinki, concerning medical research in humans (Ethical Principles for Medical Research Involving Human Subjects), ICH harmonised tripartite guideline for GCP (ICH GCP) 1996 adopted by TGA (2000), the national statement on ethical conduct in human research (NHMRC, 2007), and the applicable local regulations.

15.2. Archiving and Regulatory Inspection

All study-related documents and records are to be retained for a minimum of 15 years after trial completion. Written agreement from the Sponsor must precede destruction of the same.

In accordance with ICH GCP, this study may be selected for audit. Inspection of site facilities (e.g., pharmacy, medication storage areas, laboratories) and review of study-related records may occur by the Sponsor, Sponsor's representative or regulatory authority to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

16. CLINICAL STUDY REPORT

A clinical study report will be prepared with reference to ICH Guidance E3 to include:

- Details of where the study was carried out
- Dates of the start and completion of each period of the study
- Details of the investigational product and a statement of production will be provided by Impel
- A statement confirming that the applicable HREC gave written approval for the study in accordance with local regulations
- A demographic listing for all subjects
- A list of all adverse events according to INP103, benserazide, or placebo
- Details of any occurrences which may be of significance to the study outcome
- Details of all operations, calculations and transformations performed on the reported data
- The statistical analysis plan and report will be produced by Impel, or their agents, and will be incorporated into the final report.
- All data from any withdrawn subject not included in the statistical analysis not including screen failures
- A scientific interpretation of the results
- A description of the study methods used

Consideration will be given to any comments on a draft report. The report will incorporate the analytical and statistical results and methods produced by Impel or their agents. A final report will be prepared to contain all the sections in the draft report and responses to comments on the draft report. A statement of compliance covering all the areas of the study conducted according to GCP at the investigational site and the report, will be included. The report will be issued under the Sponsor's responsibility.

Where required by the applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The Investigator will be provided reasonable access to statistical tables, figures and relevant reports and will have the opportunity to review complete study results. Impel will also provide the Investigator with the full summary of study results.

17. SPONSOR AND INVESTIGATOR OBLIGATIONS

17.1. Protocol Amendments

Neither the Investigator nor the Sponsor will modify or alter this protocol without the agreement of the other. All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant institutional EC for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial subjects. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

17.2. Protocol Deviations

Should any significant protocol deviation occur, it must be reported to the study monitor as soon as is reasonably practical. The deviation and the reason for its occurrence must be documented, reported to the relevant HREC (if required) and included in the study report.

Protocol deviations are to be reported to the institutional EC as per each HRECs guidelines and captured in the eCRF with the following attributes:

- Date
- Protocol Deviation category
- In/Exclusion criteria not met
- INP103, benserazide or placebo not taken as per protocol
- Non-compliance with visit schedule
- Other
- Description of the deviation

A deviation will be categorized as major if it meets any one of the following criteria:

- Compromises the safety of the subject
- Creates a potentially unsafe condition for other subjects on the cohort or study
- Compromises the validity of results for a cohort or the study
- Impairs conduct of the study
- Violates regulatory constraints or guidance
- Prematurely unblinds a study subject

- Compromises the privacy of a subject

All major protocol deviations are also to be reported to the study monitor within 24 hours of awareness on a protocol deviation form.

18. REFERENCES

1. Tolosa E, Marti MJ, Valldeoriola F, Molinuevo JL. History of levodopa and dopamine agonists in Parkinson's disease treatment. Neurology. 1998 Jun;50(6 Suppl 6):S2-10; discussion S44-48.

2. Lochhead JJ, Thorne RG. Intranasal delivery of biologics to the central nervous system. Adv Drug Deliv Rev. 2012 May 15;64(7):614–28.

APPENDIX 1: BLOOD BIOCHEMISTRY PARAMETERS

The following parameters will be tested:

- Urea (UREA)
- Creatinine (CREAT)
- Total Bilirubin (BILI) and Direct Bilirubin (BILDIR)
- Albumin (ALB)
- Total Protein (PROT)
- Alkaline Phosphatase (ALP)
- Creatine Kinase (CK)
- Gamma-Glutamyl Transferase (GGT)
- Aspartate Amino Transferase (AST)
- Alanine Amino Transferase (ALT)
- Glucose (GLUC)
- Sodium (SODIUM)
- Potassium (K)
- Calcium (CA)
- Chloride (CL)
- Phosphate (PHOS)
- Bicarbonate (BICARB)

APPENDIX 2: HAEMATOLOGY PARAMETERS

The following parameters will be tested:

- Haemoglobin (HGB)
- Haematocrit (HCT)
- Erythrocytes (RBC)
- Platelets (PLAT)
- Leukocytes (WBC) with differential [(including Eosinophils (EOS), Neutrophils (NEUT), Basophils (BASO), Lymphocytes (LYM), Monocytes (MONO) and Reticulocytes (RETI)]

APPENDIX 3: URINARY ANALYSIS PARAMETERS

The following parameters will be tested:

Macroscopic:

- pH (PH)
- Specific Gravity (SPGRAV)
- Protein (PROT)
- Glucose (GLUC)
- Ketones (KETONES)
- Total Bilirubin (BILI)
- Occult Blood (OCCBLD)
- Nitrite (NITRITE)
- Urobilinogen (UROBIL)
- Leukocytes (WBC)

If abnormality is noted for protein, blood, nitrite or leukocyte esterase, at the discretion of the Investigator a microscopic examination of RBC, WBC, bacteria and casts will be performed.

APPENDIX 4: MDS-UPDRS

Provided as an external file.

APPENDIX 5: PROHIBITED CONCOMITANT MEDICATIONS

The following medications will be prohibited in the study:

- Atrosept
- Azuphen MB
- Balacet
- Benzoic acid
- Cystemms-V
- Methylene blue
- Darcalma
- Darpaz
- Darvocet A500/Darvocet N100/N50
- Darvon/-N
- Dolsed
- Furazolidone
- Hyolev MB
- Hyophen
- Hyoscyamine/methanamine/phenyl salicylate
- Indiomin MB
- Isocarboxazid
- Linezolid
- Olanzapine >2.5 mg/day
- Procarbazine
- Propoxyphene (e.g. with acetaminophen or aspirin and caffeine)
- Phenelzine
- Quetiapine >50 mg/day
- Risperidone >1 mg/day
- Sodium oxybate
- Tranylcypromine

APPENDIX 6: SUBJECT QUESTIONNAIRE

Site: _____
Randomisation number: _____

Instructions:

Please ask the patient the following questions during the assessment at 120 (up to 180) minutes post-dosing. Please record the patient's answers on this sheet and also transcribe into the eCRF:

1. How did it feel to use the POD device to deliver your dose of L-dopa via your nose? *Tick one response only*

a. ☐ Comfortable
b. ☐ Uncomfortable

2. How would you feel about using a POD device, and delivering your (OFF episode) rescue drug with it on a long-term basis? *Tick one response only*

a. ☐ Very happy
b. ☐ Acceptable
c. ☐ No opinion/it was just OK (why?)
d. ☐ Unacceptable (why?)
e. ☐ I really did not like it (why?)

If the subject answers c, d or e above, please record the reason given below:

_____

_____

3. What drug do you normally take when you have an "OFF" episode?

_____

(Please ensure this is also captured in the eCRF Concomitant medication page)

4) If the POD was available tomorrow, which would you prefer to use for "Off" episodes? *Please record reason below*

☐ "usual" treatment
☐ New POD

Why:

_____

_____

To be completed by the site staff conducting the interview and entering the responses on this sheet:

Name (printed) _____

Signed _____ Date _____

MDS-UPDRS Permissions

Permission is required to use the MDS-developed Rating Scales (with the exception of personal/individual use). Reproduction, translation, modification, sale, or distribution of any portion of the MDS Rating Scales is strictly prohibited. MDS Rating Scales may not be incorporated into clinical trials, training or certification programs or materials, software programs, or otherwise except through use of the Permissions Request Form and payment of applicable fees.

Continue to p. 2 to view the MDS-UPDRS

MDS-UPDRS

The *Movement* Disorder Society (MDS)-sponsored new version of the UPDRS is founded on the critique that was formulated by the Task Force for Rating Scales in Parkinson's disease (*Mov Disord* 2003;18:738-750). Thereafter, the MDS recruited a Chairperson to organize a program to provide the Movement Disorder community with a new version of the UPDRS that would maintain the overall format of the original UPDRS, but address issues identified in the critique as weaknesses and ambiguities. The Chairperson identified subcommittees with chairs and members. Each part was written by the appropriate subcommittee members and then reviewed and ratified by the entire group. These members are listed below.

The MDS-UPDRS has four parts: Part I (non-motor experiences of daily living), Part II (motor experiences of daily living, Part III (motor examination) and Part IV (motor complications). Part I has two components: IA concerns a number of behaviors that are assessed by the investigator with all pertinent information from patients and caregivers, and IB is completed by the patient with or without the aid of the caregiver, but independently of the investigator. These sections can, however, be reviewed by the rater to ensure that all questions are answered clearly and the rater can help explain any perceived ambiguities. Part II is designed to be a self-administered questionnaire like Part IB, but can be reviewed by the investigator to ensure completeness and clarity. Of note, the official versions of Part IA, Part IB and Part II of the MDS-UPDRS do not have separate on or off ratings. However, for individual programs or protocols the same questions can be used separately for on and off. Part III has instructions for the rater to give or demonstrate to the patient; it is completed by the rater. Part IV has instructions for the rater and also instructions to be read to the patient. This part integrates patient-derived information with the rater's clinical observations and judgments and is completed by the rater.

The authors of this new version are:

Chairperson: Christopher G. Goetz
Part I: Werner Poewe (chair), Bruno Dubois, Anette Schrag
Part II: Matthew B. Stern (chair), Anthony E. Lang, Peter A. LeWitt
Part III: Stanley Fahn (chair), Joseph Jankovic, C. Warren Olanow
Part IV: Pablo Martinez-Martin (chair), Andrew Lees, Olivier Rascol, Bob van Hilten
Development Standards: Glenn T. Stebbins (chair), Robert Holloway, David Nyenhuis
Appendices: Cristina Sampaio (chair), Richard Dodel, Jaime Kulisevsky
Statistical Testing: Barbara Tilley (chair), Sue Leurgans, Jean Teresi,
Consultant: Stephanie Shaftman, Nancy LaPelle

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July 1, 2008

Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)

Overview: This portion of the scale assesses the non-motor impact of Parkinson's disease (PD) on patients' experiences of daily living. There are 13 questions. Part 1A is administered by the rater (six questions) and focuses on complex behaviors. Part 1B is a component of the self-administered Patient Questionnaire that covers seven questions on non-motor experiences of daily living.

Part 1A:
In administering Part IA, the examiner should use the following guidelines:

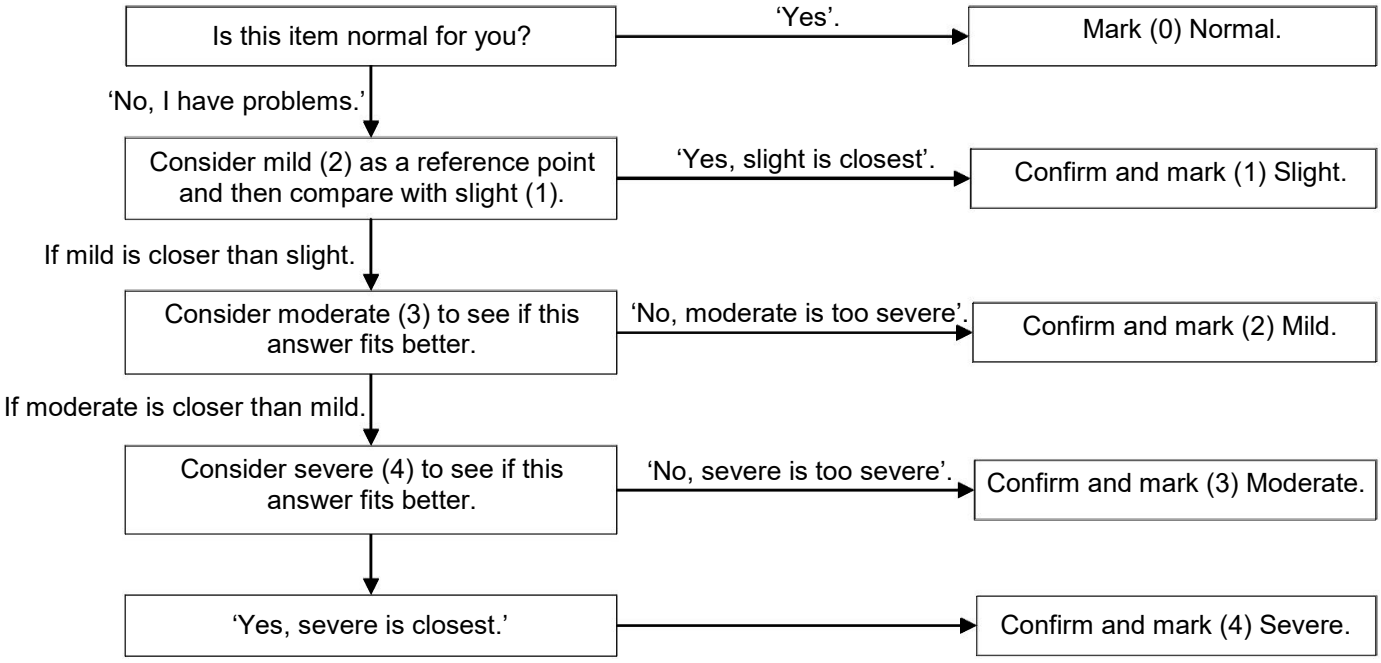
1. Mark at the top of the form the primary data source as patient, caregiver, or patient and caregiver in equal proportion.
2. The response to each item should refer to a period encompassing the prior week including the day on which the information is collected.
3. All items must have an integer rating (no half points, no missing scores). In the event that an item does not apply or cannot be rated (e.g., amputee who cannot walk), the item is marked UR for Unable to Rate.
4. The answers should reflect the usual level of function and words such as "usually", "generally", "most of the time" can be used with patients.
5. Each question has a text for you to read (Instructions to patients/caregiver). After that statement, you can elaborate and probe based on the target symptoms outlined in the Instructions to examiner. You should NOT READ the RATING OPTIONS to the patient/caregiver, because these are written in medical terminology. From the interview and probing, you will use your medical judgment to arrive at the best response.
6. Patients may have co-morbidities and other medical conditions that can affect their function. You and the patient must rate the problem as it exists and do not attempt to separate elements due to Parkinson's disease from other conditions.

EXAMPLE OF NAVIGATING THROUGH THE RESPONSE OPTIONS FOR PART 1A

Suggested strategies for obtaining the most accurate answer:
After reading the instructions to the patient, you will need to probe the entire domain under discussion to determine Normal vs. problematic: If your questions do not identify any problem in this domain, record 0 and move on to the next question.

If your questions identify a problem in this domain, you should work next with a reference anchor at the mid-range (option 2 or Mild) to find out if the patient functions at this level, better or worse. <u>You will not be reading the choices of responses to the patient as the responses use clinical terminology. You will be asking enough probing questions to determine the response that should be coded.</u>

Work up and down the options with the patient to identify the most accurate response, giving a final check by excluding the options above and below the selected response.



_____ Patient Name or Subject ID	_____ Site ID	_____ - _____ - _____ (mm-dd-yyyy) Assessment Date	_____ Investigator's Initials

MDS UPDRS
Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)

Part 1A: Complex behaviors: [completed by rater]

Primary source of information:

☐ Patient ☐ Caregiver ☐ Patient and Caregiver in Equal Proportion

To be read to the patient: I am going to ask you six questions about behaviors that you may or may not experience. Some questions concern common problems and some concern uncommon ones. If you have a problem in one of the areas, please choose the best response that describes how you have felt MOST OF THE TIME during the PAST WEEK. If you are not bothered by a problem, you can simply respond NO. I am trying to be thorough, so I may ask questions that have nothing to do with you.

SCORE

1.1 COGNITIVE IMPAIRMENT

Instructions to examiner: Consider all types of altered level of cognitive function including cognitive slowing, impaired reasoning, memory loss, deficits in attention and orientation. Rate their impact on activities of daily living as perceived by the patient and/or caregiver.

Instructions to patients [and caregiver]: Over the past week have you had problems remembering things, following conversations, paying attention, thinking clearly, or finding your way around the house or in town? [If yes, examiner asks patient or caregiver to elaborate and probes for information.]

0: Normal: No cognitive impairment.

1: Slight: Impairment appreciated by patient or caregiver with no concrete interference with the patient's ability to carry out normal activities and social interactions. ☐

2: Mild: Clinically evident cognitive dysfunction, but only minimal interference with the patient's ability to carry out normal activities and social interactions.

3: Moderate: Cognitive deficits interfere with but do not preclude the patient's ability to carry out normal activities and social interactions.

4: Severe: Cognitive dysfunction precludes the patient's ability to carry out normal activities and social interactions.

	SCORE
1.2 HALLUCINATIONS AND PSYCHOSIS Instructions to examiner: Consider both illusions (misinterpretations of real stimuli) and hallucinations (spontaneous false sensations). Consider all major sensory domains (visual, auditory, tactile, olfactory and gustatory). Determine presence of unformed (for example sense of presence or fleeting false impressions) as well as formed (fully developed and detailed) sensations. Rate the patient's insight into hallucinations and identify delusions and psychotic thinking. *Instructions to patients [and caregiver]: Over the past week have you seen, heard, smelled or felt things that were not really there?* [If yes, examiner asks patient or caregiver to elaborate and probes for information.] 0: Normal: No hallucinations or psychotic behavior. 1: Slight: Illusions or non-formed hallucinations, but patient recognizes them without loss of insight. 2: Mild: Formed hallucinations independent of environmental stimuli. No loss of insight. 3: Moderate: Formed hallucinations with loss of insight. 4: Severe: Patient has delusions or paranoia.	☐
1.3 DEPRESSED MOOD Instructions to examiner: Consider low mood, sadness, hopelessness, feelings of emptiness or loss of enjoyment. Determine their presence and duration over the past week and rate their interference with the patient's ability to carry out daily routines and engage in social interactions. *Instruction to the patient (and caregiver): Over the past week have you felt low, sad, hopeless or unable to enjoy things? If yes, was this feeling for longer than one day at a time? Did it make it difficult for you carry out your usual activities or to be with people?* [If yes, examiner asks patient or caregiver to elaborate and probes for information.] 0: Normal: No depressed mood. 1: Slight: Episodes of depressed mood that are not sustained for more than one day at a time. No interference with patient's ability to carry out normal activities and social interactions. 2: Mild: Depressed mood that is sustained over days, but without interference with normal activities and social interactions. 3: Moderate: Depressed mood that interferes with, but does not preclude, the patient's ability to carry out normal activities and social interactions. 4: Severe: Depressed mood precludes patient's ability to carry out normal activities and social interactions.	☐

	SCORE
1.4 ANXIOUS MOOD Instructions to examiner: Determine nervous, tense, worried or anxious feelings (including panic attacks) over the past week and rate their duration and interference with the patient's ability to carry out daily routines and engage in social interactions. *Instructions to patients [and caregiver]: Over the past week have you felt nervous, worried or tense? If yes, was this feeling for longer than one day at a time? Did it make it difficult for you to follow your usual activities or to be with other people*? [If yes, examiner asks patient or caregiver to elaborate and probes for information.] 0: Normal: No anxious feelings. 1: Slight: Anxious feelings present but not sustained for more than one day at a time. No interference with patient's ability to carry out normal activities and social interactions. 2: Mild: Anxious feelings are sustained over more than one day at a time, but without interference with patient's ability to carry out normal activities and social interactions. 3: Moderate: Anxious feelings interfere with, but do not preclude, the patient's ability to carry out normal activities and social interactions. 4: Severe: Anxious feelings preclude patient's ability to carry out normal activities and social interactions.	☐
1.5 APATHY Instructions to examiner: Consider level of spontaneous activity, assertiveness, motivation and initiative and rate the impact of reduced levels on performance of daily routines and social interactions. Here the examiner should attempt to distinguish between apathy and similar symptoms that are best explained by depression. *Instructions to patients (and caregiver): Over the past week, have you felt indifferent to doing activities or being with people?* [If yes, examiner asks patient or caregiver to elaborate and probes for information.] 0: Normal: No apathy. 1: Slight: Apathy appreciated by patient and/or caregiver, but no interference with daily activities and social interactions. 2: Mild: Apathy interferes with isolated activities and social interactions. 3: Moderate: Apathy interferes with most activities and social interactions. 4: Severe: Passive and withdrawn, complete loss of initiative.	☐

1.6 FEATURES OF DOPAMINE DYSREGULATION SYNDROME

SCORE

Instructions to examiner: Consider involvement in a variety of activities including atypical or excessive gambling (e.g. casinos or lottery tickets), atypical or excessive sexual drive or interests (e.g., unusual interest in pornography, masturbation, sexual demands on partner), other repetitive activities (e.g. hobbies, dismantling objects, sorting or organizing), or taking extra non-prescribed medication for non-physical reasons (i.e., addictive behavior). Rate the impact of such abnormal activities/behaviors on the patient's personal life and on his family and social relations (including need to borrow money or other financial difficulties like withdrawal of credit cards, major family conflicts, lost time from work, or missed meals or sleep because of the activity).

Instructions to patients [and caregiver]: Over the past week, have you had unusually strong urges that are hard to control? Do you feel driven to do or think about something and find it hard to stop? [Give patient examples such as gambling, cleaning, using the computer, taking extra medicine, obsessing about food or sex, all depending on the patients.]

0: Normal: No problems present.

1: Slight: Problems are present but usually do not cause any difficulties for the patient or family/caregiver.

2: Mild: Problems are present and usually cause a few difficulties in the patient's personal and family life.

3: Moderate: Problems are present and usually cause a lot of difficulties in the patient's personal and family life.

4: Severe: Problems are present and preclude the patient's ability to carry out normal activities or social interactions or to maintain previous standards in personal and family life.

The remaining questions in Part I (Non-motor Experiences of Daily Living) [Sleep, Daytime Sleepiness, Pain and Other Sensation, Urinary Problems, Constipation Problems, Lightheadedness on Standing, and Fatigue] are in the **Patient Questionnaire** along with all questions in Part II [Motor Experiences of Daily Living].

Patient Questionnaire:

Instructions:

This questionnaire will ask you about your experiences of daily living.

There are 20 questions. We are trying to be thorough, and some of these questions may therefore not apply to you now or ever. If you do not have the problem, simply mark 0 for NO.

Please read each one carefully and read all answers before selecting the one that best applies to you.

We are interested in your average or usual function over the past week including today. Some patients can do things better at one time of the day than at others. However, only one answer is allowed for each question, so please mark the answer that best describes what you can do most of the time.

You may have other medical conditions besides Parkinson's disease. Do not worry about separating Parkinson's disease from other conditions. Just answer the question with your best response.

Use only 0, 1, 2, 3, 4 for answers, nothing else. Do not leave any blanks.

Your doctor or nurse can review the questions with you, but this questionnaire is for patients to complete, either alone or with their caregivers.

Who is filling out this questionnaire (check the best answer):

☐ Patient ☐ Caregiver ☐ Patient and Caregiver in Equal Proportion

Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)

SCORE

1.7 SLEEP PROBLEMS

Over the past week, have you had trouble going to sleep at night or staying asleep through the night? Consider how rested you felt after waking up in the morning.

0: Normal: No problems.

1: Slight: Sleep problems are present but usually do not cause trouble getting a full night of sleep.

2: Mild: Sleep problems usually cause some difficulties getting a full night of sleep.

3: Moderate: Sleep problems cause a lot of difficulties getting a full night of sleep, but I still usually sleep for more than half the night.

4: Severe: I usually do not sleep for most of the night.

☐

1.8 DAYTIME SLEEPINESS

Over the past week, have you had trouble staying awake during the daytime?

0: Normal: No daytime sleepiness.

1: Slight: Daytime sleepiness occurs but I can resist and I stay awake.

2: Mild: Sometimes I fall asleep when alone and relaxing. For example, while reading or watching TV.

3: Moderate: I sometimes fall asleep when I should not. For example, while eating or talking with other people.

4: Severe: I often fall asleep when I should not. For example, while eating or talking with other people.

☐

	SCORE
1.9 PAIN AND OTHER SENSATIONS Over the past week, have you had uncomfortable feelings in your body like pain, aches tingling or cramps? 0: Normal: No uncomfortable feelings. 1: Slight: I have these feelings. However, I can do things and be with other people without difficulty. 2: Mild: These feelings cause some problems when I do things or am with other people. 3: Moderate: These feelings cause a lot of problems, but they do not stop me from doing things or being with other people. 4: Severe: These feelings stop me from doing things or being with other people.	☐
1.10 URINARY PROBLEMS Over the past week, have you had trouble with urine control? For example, an urgent need to urinate, a need to urinate too often, or urine accidents? 0: Normal: No urine control problems. 1: Slight: I need to urinate often or urgently. However, these problems do not cause difficulties with my daily activities. 2: Mild: Urine problems cause some difficulties with my daily activities. However, I do not have urine accidents. 3: Moderate: Urine problems cause a lot of difficulties with my daily activities, including urine accidents. 4: Severe: I cannot control my urine and use a protective garment or have a bladder tube.	☐

	SCORE
1.11 CONSTIPATION PROBLEMS Over the past week have you had constipation troubles that cause you difficulty moving your bowels? 0: Normal: No constipation. 1: Slight: I have been constipated. I use extra effort to move my bowels. However, this problem does not disturb my activities or my being comfortable. 2: Mild: Constipation causes me to have some troubles doing things or being comfortable. 3: Moderate: Constipation causes me to have a lot of trouble doing things or being comfortable. However, it does not stop me from doing anything. 4: Severe: I usually need physical help from someone else to empty my bowels.	☐
1.12 LIGHT HEADEDNESS ON STANDING Over the past week, have you felt faint, dizzy or foggy when you stand up after sitting or lying down? 0: Normal: No dizzy or foggy feelings. 1: Slight: Dizzy or foggy feelings occur. However, they do not cause me troubles doing things. 2: Mild: Dizzy or foggy feelings cause me to hold on to something, but I do not need to sit or lie back down. 3: Moderate: Dizzy or foggy feelings cause me to sit or lie down to avoid fainting or falling. 4: Severe: Dizzy or foggy feelings cause me to fall or faint.	☐

	SCORE
1.13 FATIGUE Over the past week, have you usually felt fatigued? This feeling is <u>not</u> part of being sleepy or sad. 0: Normal: No fatigue. 1: Slight: Fatigue occurs. However it does not cause me troubles doing things or being with people. 2: Mild: Fatigue causes me some troubles doing things or being with people. 3: Moderate: Fatigue causes me a lot of troubles doing things or being with people. However, it does not stop me from doing anything. 4: Severe: Fatigue stops me from doing things or being with people.	☐

Part II: Motor Aspects of Experiences of Daily Living (M-EDL)

	SCORE
2.1 SPEECH Over the past week, have you had problems with your speech? 0: Normal: Not at all (no problems). 1: Slight: My speech is soft, slurred or uneven, but it does not cause others to ask me to repeat myself. 2: Mild: My speech causes people to ask me to occasionally repeat myself, but not everyday. 3: Moderate: My speech is unclear enough that others ask me to repeat myself every day even though most of my speech is understood. 4: Severe: Most or all of my speech cannot be understood.	☐

	SCORE
2.2 SALIVA AND DROOLING Over the past week, have you usually had too much saliva during when you are awake or when you sleep? 0: Normal: Not at all (no problems). 1: Slight: I have too much saliva, but do not drool. 2: Mild: I have some drooling during sleep, but none when I am awake. 3: Moderate: I have some drooling when I am awake, but I usually do not need tissues or a handkerchief. 4: Severe: I have so much drooling that I regularly need to use tissues or a handkerchief to protect my clothes.	☐
2.3 CHEWING AND SWALLOWING Over the past week, have you usually had problems swallowing pills or eating meals? Do you need your pills cut or crushed or your meals to be made soft, chopped or blended to avoid choking? 0: Normal: No problems. 1: Slight: I am aware of slowness in my chewing or increased effort at swallowing, but I do not choke or need to have my food specially prepared. 2: Mild: I need to have my pills cut or my food specially prepared because of chewing or swallowing problems, but I have not choked over the past week. 3: Moderate. I choked at least once in the past week. 4: Severe: Because of chewing and swallowing problems, I need a feeding tube.	☐

	SCORE
2.4 EATING TASKS Over the past week, have you usually had troubles handling your food and using eating utensils? For example, do you have trouble handling finger foods or using forks, knives, spoons, chopsticks? 0: Normal: Not at all (no problems). 1: Slight: I am slow, but I do not need any help handling my food and have not had food spills while eating. 2: Mild: I am slow with my eating and have occasional food spills. I may need help with a few tasks such as cutting meat. 3: Moderate: I need help with many eating tasks but can manage some alone. 4: Severe: I need help for most or all eating tasks.	☐
2.5 DRESSING Over the past week, have you usually had problems dressing? For example, are you slow or do you need help with buttoning, using zippers, putting on or taking off your clothes or jewelry? 0: Normal: Not at all (no problems). 1: Slight: I am slow but I do not need help. 2: Mild: I am slow and need help for a few dressing tasks (buttons, bracelets). 3: Moderate: I need help for many dressing tasks. 4: Severe: I need help for most or all dressing tasks.	☐

	SCORE
2.6 HYGIENE Over the past week, have you usually been slow or do you need help with washing, bathing, shaving, brushing teeth, combing your hair or with other personal hygiene? 0: Normal: Not at all (no problems). 1: Slight: I am slow but I do not need any help. 2: Mild: I need someone else to help me with some hygiene tasks. 3: Moderate: I need help for many hygiene tasks. 4: Severe: I need help for most or all of my hygiene tasks.	☐
2.7 HANDWRITING Over the past week, have people usually had trouble reading your handwriting? 0: Normal: Not at all (no problems). 1: Slight: My writing is slow, clumsy or uneven, but all words are clear. 2: Mild: Some words are unclear and difficult to read. 3: Moderate: Many words are unclear and difficult to read. 4: Severe: Most or all words cannot be read.	☐
2.8 DOING HOBBIES AND OTHER ACTIVITIES Over the past week, have you usually had trouble doing your hobbies or other things that you like to do? 0: Normal: Not at all (no problems). 1: Slight: I am a bit slow but do these activities easily. 2: Mild: I have some difficulty doing these activities. 3: Moderate: I have major problems doing these activities, but still do most. 4: Severe: I am unable to do most or all of these activities.	☐

	SCORE
2.9 TURNING IN BED Over the past week, do you usually have trouble turning over in bed? 0: Normal: Not at all (no problems). 1: Slight: I have a bit of trouble turning, but I do not need any help. 2: Mild I have a lot of trouble turning and need occasional help from someone else. 3: Moderate: To turn over I often need help from someone else. 4: Severe: I am unable to turn over without help from someone else.	☐
2.10 TREMOR Over the past week, have you usually had shaking or tremor? 0: Normal: Not at all. I have no shaking or tremor. 1: Slight: Shaking or tremor occurs but does not cause problems with any activities. 2: Mild: Shaking or tremor causes problems with only a few activities. 3: Moderate: Shaking or tremor causes problems with many of my daily activities. 4: Severe: Shaking or tremor causes problems with most or all activities.	☐
2.11 GETTING OUT OF BED, A CAR, OR A DEEP CHAIR Over the past week, have you usually had trouble getting out of bed, a car seat, or a deep chair? 0: Normal: Not at all (no problems). 1: Slight: I am slow or awkward, but I usually can do it on my first try. 2: Mild: I need more than one try to get up or need occasional help. 3: Moderate: I sometimes need help to get up, but most times I can still do it on my own. 4: Severe: I need help most or all of the time.	☐

	SCORE
2.12 WALKING AND BALANCE Over the past week, have you usually had problems with balance and walking? 0: Normal: Not at all (no problems). 1: Slight: I am slightly slow or may drag a leg. I never use a walking aid. 2: Mild: I occasionally use a walking aid, but I do not need any help from another person. 3: Moderate: I usually use a walking aid (cane, walker) to walk safely without falling. However, I do not usually need the support of another person. 4: Severe: I usually use the support of another person to walk safely without falling.	☐
2.13 FREEZING Over the past week, on your usual day when walking, do you suddenly stop or freeze as if your feet are stuck to the floor. 0: Normal: Not at all (no problems). 1: Slight: I briefly freeze but I can easily start walking again. I do not need help from someone else or a walking aid (cane or walker) because of freezing. 2: Mild: I freeze and have trouble starting to walk again, but I do not need someone's help or a walking aid (cane or walker) because of freezing. 3: Moderate: When I freeze I have a lot of trouble starting to walk again and, because of freezing, I sometimes need to use a walking aid or need someone else's help. 4: Severe: Because of freezing, most or all of the time, I need to use a walking aid or someone's help.	☐

This completes the questionnaire. We may have asked about problems you do not even have, and may have mentioned problems that you may never develop at all. Not all patients develop all these problems, but because they can occur, it is important to ask all the questions to every patient. Thank you for your time and attention in completing this questionnaire.

Part III: Motor Examination

Overview: This portion of the scale assesses the motor signs of PD. In administering Part III of the MDS-UPDRS the examiner should comply with the following guidelines:

At the top of the form, mark whether the patient is on medication for treating the symptoms of Parkinson's disease and, if on levodopa, the time since the last dose.

Also, if the patient is receiving medication for treating the symptoms of Parkinson's Disease, mark the patient's clinical state using the following definitions:

ON is the typical functional state when patients are receiving medication and have a good response.
OFF is the typical functional state when patients have a poor response in spite of taking medications.

The investigator should "rate what you see". Admittedly, concurrent medical problems such as stroke, paralysis, arthritis, contracture, and orthopedic problems such as hip or knee replacement and scoliosis may interfere with individual items in the motor examination. In situations where it is absolutely impossible to test (e.g., amputations, plegia, limb in a cast), use the notation "**UR**" for Unable to Rate. Otherwise, rate the performance of each task as the patient performs in the context of co-morbidities.

All items must have an integer rating (no half points, no missing ratings).

Specific instructions are provided for the testing of each item. These should be followed in all instances. The investigator demonstrates while describing tasks the patient is to perform and rates function immediately thereafter. For Global Spontaneous Movement and Rest Tremor items (3.14 and 3.17), these items have been placed purposefully at the end of the scale because clinical information pertinent to the score will be obtained throughout the entire examination.

At the end of the rating, indicate if dyskinesia (chorea or dystonia) was present at the time of the examination, and if so, whether these movements interfered with the motor examination.

3a Is the patient on medication for treating the symptoms of Parkinson's Disease? ☐ No ☐ Yes

3b If the patient is receiving medication for treating the symptoms of Parkinson's Disease, mark the patient's clinical state using the following definitions:

☐ ON: On is the typical functional state when patients are receiving medication and have a good response.

☐ OFF: Off is the typical functional state when patients have a poor response in spite of taking medications.

3c Is the patient on Levodopa ? ☐ No ☐ Yes

3.C1 If yes, minutes since last levodopa dose: _____

	SCORE
3.1 SPEECH Instructions to examiner: Listen to the patient's free-flowing speech and engage in conversation if necessary. Suggested topics: ask about the patient's work, hobbies, exercise, or how he got to the doctor's office. Evaluate volume, modulation (prosody) and clarity, including slurring, palilalia (repetition of syllables) and tachyphemia (rapid speech, running syllables together). 0: Normal: No speech problems. 1: Slight: Loss of modulation, diction or volume, but still all words easy to understand. 2: Mild: Loss of modulation, diction, or volume, with a few words unclear, but the overall sentences easy to follow. 3: Moderate: Speech is difficult to understand to the point that some, but not most, sentences are poorly understood. 4: Severe: Most speech is difficult to understand or unintelligible.	☐
3.2 FACIAL EXPRESSION Instructions to examiner: Observe the patient sitting at rest for 10 seconds, without talking and also while talking. Observe eye-blink frequency, masked facies or loss of facial expression, spontaneous smiling and parting of lips. 0: Normal: Normal facial expression. 1: Slight: Minimal masked facies manifested only by decreased frequency of blinking. 2: Mild: In addition to decreased eye-blink frequency, Masked facies present in the lower face as well, namely fewer movements around the mouth, such as less spontaneous smiling, but lips not parted. 3: Moderate: Masked facies with lips parted some of the time when the mouth is at rest. 4: Severe: Masked facies with lips parted most of the time when the mouth is at rest.	☐

SCORE

3.3 RIGIDITY

Instructions to examiner: Rigidity is judged on slow passive movement of major joints with the patient in a relaxed position and the examiner manipulating the limbs and neck. First, test without an activation maneuver. Test and rate neck and each limb separately. For arms, test the wrist and elbow joints simultaneously. For legs, test the hip and knee joints simultaneously. If no rigidity is detected, use an activation maneuver such as tapping fingers, fist opening/closing, or heel tapping in a limb not being tested. Explain to the patient to go as limp as possible as you test for rigidity.

0: Normal: No rigidity.

1: Slight: Rigidity only detected with activation maneuver.

2: Mild: Rigidity detected without the activation maneuver, but full range of motion is easily achieved.

3: Moderate: Rigidity detected without the activation maneuver; full range of motion is achieved with effort.

4: Severe: Rigidity detected without the activation maneuver and full range of motion not achieved.

☐ Neck

☐ RUE

☐ LUE

☐ RLE

☐ LLE

3.4 FINGER TAPPING

Instructions to examiner: Each hand is tested separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to tap the index finger on the thumb 10 times as quickly AND as big as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

0: Normal: No problems.

1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) the amplitude decrements near the end of the 10 taps.

2: Mild: Any of the following: a) 3 to 5 interruptions during tapping; b) mild slowing; c) the amplitude decrements midway in the 10-tap sequence.

3: Moderate: Any of the following: a) more than 5 interruptions during tapping or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st tap.

4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.

☐ R

☐ L

SCORE

3.5 HAND MOVEMENTS

Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to make a tight fist with the arm bent at the elbow so that the palm faces the examiner. Have the patient open the hand 10 times as fully AND as quickly as possible. If the patient fails to make a tight fist or to open the hand fully, remind him/her to do so. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

0: Normal: No problem.

1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the task.

☐ R

2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the task.

3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st open-and-close sequence.

☐ L

4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.

3.6 PRONATION-SUPINATION MOVEMENTS OF HANDS

Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to extend the arm out in front of his/her body with the palms down; then to turn the palm up and down alternately 10 times as fast and as fully as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

0: Normal: No problems.

1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the sequence.

☐ R

2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the sequence.

3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing c) the amplitude decrements starting after the 1st supination-pronation sequence.

☐ L

4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.

SCORE

3.7 TOE TAPPING

Instructions to examiner: Have the patient sit in a straight-backed chair with arms, both feet on the floor. Test each foot separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the heel on the ground in a comfortable position and then tap the toes 10 times as big and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

0: Normal:	No problem.
1: Slight:	Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) amplitude decrements near the end of the ten taps.
2: Mild:	Any of the following: a) 3 to 5 interruptions during the tapping movements; b) mild slowing; c) amplitude decrements midway in the task.
3: Moderate:	Any of the following: a) more than 5 interruptions during the tapping movements or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) amplitude decrements after the first tap.
4: Severe:	Cannot or can only barely perform the task because of slowing, interruptions or decrements.

☐ R

☐ L

3.8 LEG AGILITY

Instructions to examiner: Have the patient sit in a straight-backed chair with arms. The patient should have both feet comfortably on the floor. Test each leg separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the foot on the ground in a comfortable position and then raise and stomp the foot on the ground 10 times as high and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

0: Normal:	No problems.
1: Slight:	Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) amplitude decrements near the end of the task.
2: Mild:	Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowness; c) amplitude decrements midway in the task.
3: Moderate:	Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing in speed; c) amplitude decrements after the first tap.
4: Severe:	Cannot or can only barely perform the task because of slowing, interruptions or decrements.

☐ R

☐ L

SCORE

3.9 ARISING FROM CHAIR

Instructions to examiner: Have the patient sit in a straight-backed chair with arms, with both feet on the floor and sitting back in the chair (if the patient is not too short). Ask the patient to cross his/her arms across the chest and then to stand up. If the patient is not successful, repeat this attempt a maximum up to two more times. If still unsuccessful, allow the patient to move forward in the chair to arise with arms folded across the chest. Allow only one attempt in this situation. If unsuccessful, allow the patient to push off using his/her hands on the arms of the chair. Allow a maximum of three trials of pushing off. If still not successful, assist the patient to arise. After the patient stands up, observe the posture for item 3.13.

0: Normal:	No problems. Able to arise quickly without hesitation.
1: Slight:	Arising is slower than normal; or may need more than one attempt; or may need to move forward in the chair to arise. No need to use the arms of the chair.
2: Mild:	Pushes self up from arms of chair without difficulty.
3: Moderate:	Needs to push off, but tends to fall back; or may have to try more than one time using arms of chair, but can get up without help.
4: Severe:	Unable to arise without help.

☐

3.10 GAIT

Instructions to examiner: Testing gait is best performed by having the patient walking away from and towards the examiner so that both right and left sides of the body can be easily observed simultaneously. The patient should walk at least 10 meters (30 feet), then turn around and return to the examiner. This item measures multiple behaviors: stride amplitude, stride speed, height of foot lift, heel strike during walking, turning, and arm swing, but not freezing. Assess also for “freezing of gait” (next item 3.11) while patient is walking. Observe posture for item 3.13.

0: Normal:	No problems.
1: Slight:	Independent walking with minor gait impairment.
2: Mild:	Independent walking but with substantial gait impairment.
3: Moderate:	Requires an assistance device for safe walking (walking stick, walker) but not a person.
4: Severe:	Cannot walk at all or only with another person’s assistance.

☐

SCORE

3.11 FREEZING OF GAIT

Instructions to examiner: While assessing gait, also assess for the presence of any gait freezing episodes. Observe for start hesitation and stuttering movements especially when turning and reaching the end of the task. To the extent that safety permits, patients may NOT use sensory tricks during the assessment.

0: Normal: No freezing.

1: Slight: Freezes on starting, turning or walking through doorway with a single halt during any of these events, but then continues smoothly without freezing during straight walking.

2: Mild: Freezes on starting, turning or walking through doorway with more than one halt during any of these activities, but continues smoothly without freezing during straight walking.

3: Moderate: Freezes once during straight walking.

4: Severe: Freezes multiple times during straight walking.

☐

3.12 POSTURAL STABILITY

Instructions to examiner: The test examines the response to sudden body displacement produced by a quick, forceful pull on the shoulders while the patient is standing erect with eyes open and feet comfortably apart and parallel to each other. Test retropulsion. Stand behind the patient and instruct the patient on what is about to happen. Explain that s/he is allowed to take a step backwards to avoid falling. There should be a solid wall behind the examiner, at least 1-2 meters away to allow for the observation of the number of retropulsive steps. The first pull is an instructional demonstration and is purposely milder and not rated. The second time the shoulders are pulled briskly and forcefully towards the examiner with enough force to displace the center of gravity so that patient MUST take a step backwards. The examiner needs to be ready to catch the patient, but must stand sufficiently back so as to allow enough room for the patient to take several steps to recover independently. Do not allow the patient to flex the body abnormally forward in anticipation of the pull. Observe for the number of steps backwards or falling. Up to and including two steps for recovery is considered normal, so abnormal ratings begin with three steps. If the patient fails to understand the test, the examiner can repeat the test so that the rating is based on an assessment that the examiner feels reflects the patient's limitations rather than misunderstanding or lack of preparedness. Observe standing posture for item 3.13

0: Normal: No problems: Recovers with one or two steps.

1: Slight: 3-5 steps, but subject recovers unaided.

2: Mild: More than 5 steps, but subject recovers unaided.

3: Moderate: Stands safely, but with absence of postural response; falls if not caught by examiner.

4: Severe: Very unstable, tends to lose balance spontaneously or with just a gentle pull on the shoulders.

☐

	SCORE
3.13 POSTURE Instructions to examiner: Posture is assessed with the patient standing erect after arising from a chair, during walking, and while being tested for postural reflexes. If you notice poor posture, tell the patient to stand up straight and see if the posture improves (see option 2 below). Rate the worst posture seen in these three observation points. Observe for flexion and side-to-side leaning. 0: Normal: No problems. 1: Slight: Not quite erect, but posture could be normal for older person. 2: Mild: Definite flexion, scoliosis or leaning to one side, but patient can correct posture to normal posture when asked to do so. 3: Moderate: Stooped posture, scoliosis or leaning to one side that cannot be corrected volitionally to a normal posture by the patient. 4: Severe: Flexion, scoliosis or leaning with extreme abnormality of posture.	☐
3.14 GLOBAL SPONTANEITY OF MOVEMENT (BODY BRADYKINESIA) Instructions to examiner: This global rating combines all observations on slowness, hesitancy, and small amplitude and poverty of movement in general, including a reduction of gesturing and of crossing the legs. This assessment is based on the examiner's global impression after observing for spontaneous gestures while sitting, and the nature of arising and walking. 0: Normal: No problems. 1: Slight: Slight global slowness and poverty of spontaneous movements. 2: Mild: Mild global slowness and poverty of spontaneous movements. 3: Moderate: Moderate global slowness and poverty of spontaneous movements. 4: Severe: Severe global slowness and poverty of spontaneous movements.	☐
3.15 POSTURAL TREMOR OF THE HANDS Instructions to examiner: All tremor, including re-emergent rest tremor, that is present in this posture is to be included in this rating. Rate each hand separately. Rate the highest amplitude seen. Instruct the patient to stretch the arms out in front of the body with palms down. The wrist should be straight and the fingers comfortably separated so that they do not touch each other. Observe this posture for 10 seconds. 0: Normal: No tremor. 1: Slight: Tremor is present but less than 1 cm in amplitude. 2: Mild: Tremor is at least 1 but less than 3 cm in amplitude. 3: Moderate: Tremor is at least 3 but less than 10 cm in amplitude. 4: Severe: Tremor is at least 10 cm in amplitude.	☐ R ☐ L

SCORE

3.16 KINETIC TREMOR OF THE HANDS

Instructions to examiner: This is tested by the finger-to-nose maneuver. With the arm starting from the outstretched position, have the patient perform at least three finger-to-nose maneuvers with each hand reaching as far as possible to touch the examiner's finger. The finger-to-nose maneuver should be performed slowly enough not to hide any tremor that could occur with very fast arm movements. Repeat with the other hand, rating each hand separately. The tremor can be present throughout the movement or as the tremor reaches either target (nose or finger). Rate the highest amplitude seen.

0: Normal:	No tremor.
1: Slight:	Tremor is present but less than 1 cm in amplitude.
2: Mild:	Tremor is at least 1 but less than 3 cm in amplitude.
3: Moderate:	Tremor is at least 3 but less than 10 cm in amplitude.
4: Severe:	Tremor is at least 10 cm in amplitude.

☐ R

☐ L

3.17 REST TREMOR AMPLITUDE

Instructions to examiner: This and the next item have been placed purposefully at the end of the examination to allow the rater to gather observations on rest tremor that may appear at any time during the exam, including when quietly sitting, during walking and during activities when some body parts are moving but others are at rest. Score the maximum amplitude that is seen at any time as the final score. Rate only the amplitude and not the persistence or the intermittency of the tremor.
As part of this rating, the patient should sit quietly in a chair with the hands placed on the arms of the chair (not in the lap) and the feet comfortably supported on the floor for 10 seconds with no other directives. Rest tremor is assessed separately for all four limbs and also for the lip/jaw. Rate only the maximum amplitude that is seen at any time as the final rating.

Extremity ratings

0: Normal:	No tremor.
1: Slight:	≤ 1 cm in maximal amplitude.
2: Mild:	> 1 cm but < 3 cm in maximal amplitude.
3: Moderate:	3 - 10 cm in maximal amplitude.
4: Severe:	> 10 cm in maximal amplitude.

☐ RUE

☐ LUE

☐ RLE

☐ LLE

Lip/Jaw ratings

0: Normal:	No tremor.
1: Slight:	≤ 1 cm in maximal amplitude.
2: Mild:	> 1 cm but ≤ 2 cm in maximal amplitude.
3: Moderate:	> 2 cm but ≤ 3 cm in maximal amplitude.
4: Severe:	> 3 cm in maximal amplitude.

☐ Lip/Jaw

3.18 CONSTANCY OF REST TREMOR

SCORE

Instructions to examiner: This item receives one rating for all rest tremor and focuses on the constancy of rest tremor during the examination period when different body parts are variously at rest. It is rated purposefully at the end of the examination so that several minutes of information can be coalesced into the rating.

0: Normal: No tremor.

1: Slight: Tremor at rest is present ≤ 25% of the entire examination period.

2: Mild: Tremor at rest is present 26-50% of the entire examination period.

3: Moderate: Tremor at rest is present 51-75% of the entire examination period.

4: Severe: Tremor at rest is present > 75% of the entire examination period.

☐

DYSKINESIA IMPACT ON PART III RATINGS

A. Were dyskinesias (chorea or dystonia) present during examination? ☐ No ☐ Yes

B. If yes, did these movements interfere with your ratings? ☐ No ☐ Yes

HOEHN AND YAHR STAGE

0: Asymptomatic.

1: Unilateral involvement only.

2: Bilateral involvement without impairment of balance.

3: Mild to moderate involvement; some postural instability but physically independent; needs assistance to recover from pull test.

4: Severe disability; still able to walk or stand unassisted.

5: Wheelchair bound or bedridden unless aided.

☐

Part IV: Motor Complications

Overview and Instructions: In this section, the rater uses historical and objective information to assess two motor complications, dyskinesias and motor fluctuations that include OFF-state dystonia. Use all information from patient, caregiver, and the examination to answer the six questions that summarize function over the past week including today. As in the other sections, rate using only integers (no half points allowed) and leave no missing ratings. If the item cannot be rated, place UR for Unable to Rate. You will need to choose some answers based on percentages, and therefore you will need to establish how many hours generally are awake hours and use this figure as the denominator for "OFF" time and dyskinesias. For "OFF dystonia", the total "Off" time will be the denominator. Operational definitions for examiner's use.

Dyskinesias: Involuntary random movements
Words that patients often recognize for dyskinesias include "irregular jerking", "wiggling", "twitching". It is essential to stress to the patient the difference between dyskinesias and tremor, a common error when patients are assessing dyskinesias.

Dystonia: contorted posture, often with a twisting component:
Words that patients often recognize for dystonia include "spasms", "cramps", "posture".

Motor fluctuation: Variable response to medication:
Words that patients often recognize for motor fluctuation include "wearing out", "wearing off", "roller-coaster effect", "on-off", "uneven medication effects".

OFF: Typical functional state when patients have a poor response in spite of taking mediation or the typical functional response when patients are on NO treatment for parkinsonism. Words that patients often recognize include "low time", "bad time", "shaking time", "slow time", "time when my medications don't work."

ON: Typical functional state when patients are receiving medication and have a good response:
Words that patients often recognize include "good time", "walking time", "time when my medications work."

A. DYSKINESIAS [exclusive of OFF-state dystonia]

SCORE

4.1 TIME SPENT WITH DYSKINESIAS

Instructions to examiner: Determine the hours in the usual waking day and then the hours of dyskinesias. Calculate the percentage. If the patient has dyskinesias in the office, you can point them out as a reference to ensure that patients and caregivers understand what they are rating. You may also use your own acting skills to enact the dyskinetic movements you have seen in the patient before or show them dyskinetic movements typical of other patients. Exclude from this question early morning and nighttime painful dystonia.

Instructions to patient [and caregiver]: Over the past week, how many hours do you usually sleep on a daily basis, including nighttime sleep and daytime napping? Alright, if you sleep ___ hrs, you are awake ____ hrs. Out of those awake hours, how many hours in total do you have wiggling, twitching or jerking movements? Do not count the times when you have tremor, which is a regular back and forth shaking or times when you have painful foot cramps or spasms in the early morning or at nighttime. I will ask about those later. Concentrate only on these types of wiggling, jerking and irregular movements. Add up all the time during the waking day when these usually occur. How many hours ____ (use this number for your calculations).

0: Normal:	No dyskinesias.
1: Slight:	≤ 25% of waking day.
2: Mild:	26 - 50% of waking day.
3: Moderate:	51 - 75% of waking day.
4: Severe:	> 75% of waking day.

1. Total Hours Awake: _____
2. Total Hours with Dyskinesia: _____
3. % Dyskinesia = ((2/1)*100): _____

SCORE

4.2 FUNCTIONAL IMPACT OF DYSKINESIAS

Instructions to examiner: Determine the degree to which dyskinesias impact on the patient's daily function in terms of activities and social interactions. Use the patient's and caregiver's response to your question and your own observations during the office visit to arrive at the best answer.

Instructions to patient [and caregiver]: Over the past week, did you usually have trouble doing things or being with people when these jerking movements occurred? Did they stop you from doing things or from being with people?

0: Normal:	No dyskinesias or no impact by dyskinesias on activities or social interactions.
1: Slight:	Dyskinesias impact on a few activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods.
2: Mild:	Dyskinesias impact on many activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods.
3: Moderate:	Dyskinesias impact on activities to the point that the patient usually does not perform some activities or does not usually participate in some social activities during dyskinetic episodes.
4: Severe:	Dyskinesias impact on function to the point that the patient usually does not perform most activities or participate in most social interactions during dyskinetic episodes.

B. MOTOR FLUCTUATIONS

4.3 TIME SPENT IN THE OFF STATE

Instructions to examiner: Use the number of waking hours derived from 4.1 and determine the hours spent in the "OFF" state. Calculate the percentage. If the patient has an OFF period in the office, you can point to this state as a reference. You may also use your knowledge of the patient to describe a typical OFF period. Additionally you may use your own acting skills to enact an OFF period you have seen in the patient before or show them OFF function typical of other patients. Mark down the typical number of OFF hours, because you will need this number for completing 4.6.

Instructions to patient [and caregiver]: Some patients with Parkinson's disease have a good effect from their medications throughout their awake hours and we call that "ON" time. Other patients take their medications but still have some hours of low time, bad time, slow time or shaking time. Doctors call these low periods "OFF" time. Over the past week, you told me before that you are general awake ____ hrs each day. Out of these awake hours, how many hours in total do you usually have this type of low level or OFF function ____ (use this number for your calculations).

0: Normal:	No OFF time.
1: Slight:	≤ 25% of waking day.
2: Mild:	26 - 50% of waking day.
3: Moderate:	51 - 75% of waking day.
4: Severe:	> 75% of waking day.

1. Total Hours Awake: _____
2. Total Hours OFF: _____
3. % OFF = ((2/1)*100): _____

SCORE

4.4 FUNCTIONAL IMPACT OF FLUCTUATIONS

Instructions to examiner: Determine the degree to which motor fluctuations impact on the patient's daily function in terms of activities and social interactions. This question concentrates on the difference between the ON state and the OFF state. If the patient has no OFF time, the rating must be 0, but if patients have very mild fluctuations, it is still possible to be rated 0 on this item if no impact on activities occurs. Use the patient's and caregiver's response to your question and your own observations during the office visit to arrive at the best answer.

Instructions to patient [and caregiver]: Think about when those low or "OFF" periods have occurred over the past week. Do you usually have more problems doing things or being with people than compared to the rest of the day when you feel your medications working? Are there some things you usually do during a good period that you have trouble with or stop doing during a low period?

0: Normal: No fluctuations or No impact by fluctuations on performance of activities or social interactions.

1: Slight: Fluctuations impact on a few activities, but during OFF, the patient usually performs all activities and participates in all social interactions that typically occur during the ON state.

2: Mild: Fluctuations impact many activities, but during OFF, the patient still usually performs all activities and participates in all social interactions that typically occur during the ON state.

3: Moderate: Fluctuations impact on the performance of activities during OFF to the point that the patient usually does not perform some activities or participate in some social interactions that are performed during ON periods.

4: Severe: Fluctuations impact on function to the point that, during OFF, the patient usually does not perform most activities or participate in most social interactions that are performed during ON periods.

4.5 COMPLEXITY OF MOTOR FLUCTUATIONS

Instructions to examiner: Determine the usual predictability of OFF function whether due to dose, time of day, food intake or other factors. Use the information provided by the patients and caregiver and supplement with your own observations. You will ask if the patient can count on them always coming at a special time, mostly coming at a special time (in which case you will probe further to separate slight from mild), only sometimes coming at a special time or are they totally unpredictable? Narrowing down the percentage will allow you to find the correct answer.

Instructions to patient [and caregiver]: For some patients, the low or "OFF" periods happen at certain times during day or when they do activities like eating or exercising. Over the past week, do you usually know when your low periods will occur? In other words, do your low periods always come at a certain time? Do they mostly come at a certain time? Do they only sometimes come at a certain time? Are your low periods totally unpredictable?"

0: Normal: No motor fluctuations.

1: Slight: OFF times are predictable all or almost all of the time (> 75%).

2: Mild: OFF times are predictable most of the time (51-75%).

3: Moderate: OFF times are predictable some of the time (26-50%).

4: Severe: OFF episodes are rarely predictable (≤ 25%).

C. "OFF" DYSTONIA

4.6 PAINFUL OFF-STATE DYSTONIA

Instructions to examiner: For patients who have motor fluctuations, determine what proportion of the OFF episodes usually includes painful dystonia? You have already determined the number of hours of "OFF" time (4.3). Of these hours, determine how many are associated with dystonia and calculate the percentage. If there is no OFF time, mark 0.

Instructions to patient [and caregiver]: In one of the questions I asked earlier, you said you generally have ____ hours of low or "OFF" time when your Parkinson's disease is under poor control. During these low or "OFF" periods, do you usually have painful cramps or spasms? Out of the total ____ hrs of this low time, if you add up all the time in a day when these painful cramps come, how many hours would this make?

0: Normal: No dystonia OR NO OFF TIME.

1: Slight: ≤ 25% of time in OFF state.

2: Mild: 26-50% of time in OFF state.

3: Moderate: 51-75% of time in OFF state.

4: Severe: > 75% of time in OFF state.

1. Total Hours Off: _____
2. Total Off Hours w/Dystonia: _____
3. % Off Dystonia = ((2/1)*100): _____

Summary statement to patient: READ TO PATIENT

This completes my rating of your Parkinson's disease. I know the questions and tasks have taken several minutes, but I wanted to be complete and cover all possibilities. In doing so, I may have asked about problems you do not even have, and I may have mentioned problems that you may never develop at all. Not all patients develop all these problems, but because they can occur, it is important to ask all the questions to every patient. Thank you for your time and attention in completing this scale with me.

Patient Name or Subject ID	Site ID	Assessment Date (mm-dd-yyyy)	Investigator's Initials
_____	___ ___ ___	____ - ____ - ____	___ ___ ___

MDS UPDRS Score Sheet

1.A	Source of information	☐ Patient ☐ Caregiver ☐ Patient + Caregiver	3.3b	Rigidity– RUE	
			3.3c	Rigidity– LUE	
Part I			3.3d	Rigidity– RLE	
1.1	Cognitive impairment		3.3e	Rigidity– LLE	
1.2	Hallucinations and psychosis		3.4a	Finger tapping– Right hand	
1.3	Depressed mood		3.4b	Finger tapping– Left hand	
1.4	Anxious mood		3.5a	Hand movements– Right hand	
1.5	Apathy		3.5b	Hand movements– Left hand	
1.6	Features of DDS		3.6a	Pronation- supination movements– Right hand	
1.6a	Who is filling out questionnaire	☐ Patient ☐ Caregiver ☐ Patient + Caregiver	3.6b	Pronation- supination movements– Left hand	
			3.7a	Toe tapping– Right foot	
1.7	Sleep problems		3.7b	Toe tapping– Left foot	
1.8	Daytime sleepiness		3.8a	Leg agility– Right leg	
1.9	Pain and other sensations		3.8b	Leg agility– Left leg	
1.10	Urinary problems		3.9	Arising from chair	
1.11	Constipation problems		3.10	Gait	
1.12	Light headedness on standing		3.11	Freezing of gait	
1.13	Fatigue		3.12	Postural stability	
Part II			3.13	Posture	
2.1	Speech		3.14	Global spontaneity of movement	
2.2	Saliva and drooling		3.15a	Postural tremor– Right hand	
2.3	Chewing and swallowing		3.15b	Postural tremor– Left hand	
2.4	Eating tasks		3.16a	Kinetic tremor– Right hand	
2.5	Dressing		3.16b	Kinetic tremor– Left hand	
2.6	Hygiene		3.17a	Rest tremor amplitude– RUE	
2.7	Handwriting		3.17b	Rest tremor amplitude– LUE	
2.8	Doing hobbies and other activities		3.17c	Rest tremor amplitude– RLE	
2.9	Turning in bed		3.17d	Rest tremor amplitude– LLE	
2.10	Tremor		3.17e	Rest tremor amplitude– Lip/jaw	
2.11	Getting out of bed		3.18	Constancy of rest	
2.12	Walking and balance			Were dyskinesias present?	☐ No ☐ Yes
2.13	Freezing			Did these movements interfere with ratings?	☐ No ☐ Yes
3a	Is the patient on medication?	☐ No ☐ Yes		Hoehn and Yahr Stage	
3b	Patient's clinical state	☐ Off ☐ On	**Part IV**		
3c	Is the patient on Levodopa?	☐ No ☐ Yes	4.1	Time spent with dyskinesias	
3.C1	If yes, minutes since last dose:		4.2	Functional impact of dyskinesias	
Part III			4.3	Time spent in the OFF state	
3.1	Speech		4.4	Functional impact of fluctuations	
3.2	Facial expression		4.5	Complexity of motor fluctuations	
3.3a	Rigidity– Neck		4.6	Painful OFF-state dystonia	