STATISTICAL ANALYSIS PLAN
PHASE IIA

DATE OF PLAN:

Version 2.0, 10-June-2019

BASED ON:

Protocol Amendment 04, dated 01 February 2019

Electronic Case Report Form, dated 20 March 2019

STUDY DRUG:

INP103

PROTOCOL NUMBER:

INP103-201

STUDY 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)

SPONSOR:

Impel NeuroPharma

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United States

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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TECHNICAL SUMMARY REPORT (TSR)

Name of Sponsor/Company: Impel NeuroPharma, Inc.	**Individual Study Table Referring to Part of the Dossier:** N/A **Volume:** N/A	***(For National Authority Use Only)*:**
Name of Finished Product: INP103	**Page:** N/A	
Name of Active Ingredient: L-dopa		

Title of Study:

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)

Investigators/Study Centers: See Appendix

Studied period (years): Up to 30 days per subject from Screening (Visit 1) to follow-up (Visit 4)	**Phase of development:** Phase IIa

Primary Objective:

To compare the safety and tolerability of nasal 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/pharmacodynamic (PDyn) relationship of single doses of INP103 and motor function

Exploratory Objective:

To evaluate the plasma concentration-time profiles of carbidopa following single doses of INP103 in Cohort 4 and to determine PK parameters.

Study Design:

This is a Phase IIa randomized, double-blind, placebo controlled, single dose study to compare the safety, tolerability and PK/PDyn of nasal L-dopa in the presence of decarboxylase inhibitor (DCI) during an OFF episode.

Screening Assessment

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 with sponsor approval, 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, 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 jeopardize blinding of any enrolled Cohort 3 or 4 subjects at the time of the interim analysis.

Interim Analysis

An interim analysis (IA) will be completed after Cohorts 1 and 2. Cohorts 1 and 2 data will be soft-locked and a subset of tables and listing will be provided. Subject level treatment allocations will not be provided to the sponsor. The aim of this analysis is to generate preliminary safety, efficacy and PK information from Cohorts 1 and 2 only.

To maintain the overall blinding of this study in the first instance, the IA tables and listings will be provided in the following way:

- For the specified demographic/baseline, adverse event and other safety listings, treatment will not be included/printed in the presentation. Data for the specified demographics/baseline and adverse events will be summarized by Cohort only, with data from active subjects and placebo subjects pooled for each cohort.
- For the specified efficacy listings, treatment will not be included/printed in the individual

subject listing presentations. Data for the specified efficacy measures will be analyzed by an unblinded statistician and will be summarized by treatment for summary tables. Only summary statistics that do not allow the identification of individual patient level data will be presented (e.g. mean, SD). The summary statistics acceptable for presentation will be determined by the unblinded statistician based on comparison of the summary result values with individual subject data.

- For the specified PK data, only summary tables and figures will be produced. Data will be analyzed by an unblinded pharmacokineticist and will be summarized by treatment. No individual subject level data will be presented.

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.

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.

These primary endpoints, specific to the full study analysis, will also be considered the primary endpoints for the interim analysis (reviewed in a blinded manner). The data for the primary endpoints will also be reviewed at each safety monitoring committee meeting in a blinded manner.

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 Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III score (primary motor function endpoint).
    - Change from baseline to 15, 30, 45, 60, 90 and 120 minutes post-dose for Cohort 1 (C1), Cohort 2 (C2), Cohort 3 (C3) and change from baseline to 30, 60, 90, 120 minutes for Cohort 4 (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 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 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
- 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

Exploratory:

PK profile of carbidopa (Cohort 4 only) for 120 minutes following dosing with INP103 and where possible, determine $AUC_{0\text{-}2h}$, C_{max} and T_{max}.

Number of Participants (planned and analyzed):

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.

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 during the study
8. Able and willing to attend the necessary visits at the study center
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 or INP103
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

Investigational product, dosage and mode of 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 pre-dosing with oral benserazide.

Duration of treatment:

This is a single dose study. The total duration per subject from Screening (Visit 1) to follow-up (Visit 4) is up to 30 days.

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

Placebo is an inert, visually similar product without L-dopa or carbidopa (microcrystalline cellulose).

Criteria for evaluation:

Once dosing has been completed (for all 8 subjects) in a cohort (Cohorts 1, and 2), data will be collected through to 7 (± 2) days post dosing (Visit 4, follow-up). This data will then be reviewed by a Safety Monitoring Committee (SMC) 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 data compiled by the site and the biostatistics analysis provider.

Statistical methods:

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.

Analysis Populations:

If there is no difference between 2 (or more) populations, the analyses will not be repeated but will be assigned to the following populations – which are listed here in order:

Intention-to-Treat (ITT) Population: All subjects who randomized into this study, regardless of receiving the study drug (INP103 or placebo) or not, will be included in this population. In general, all data listings and subject disposition, will be generated on this population except PK and PDyn results. Summaries of demographics, prior and concomitant medications will be produced using this population.

Benserazide Safety Population: All subjects who receive any amount of benserazide (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.

Safety Population: All subjects who receive any amount of INP103 or placebo will be included in the Safety Population. The data will be analyzed according to the treatment received. All safety results will be generated on Safety Population.

PK Population (PKP): All subjects who receive placebo or the full planned dose of INP103 or active treatment subjects who receive partial dose (as reported by clinical observation of the number of puffs delivered) with exposure reasonably consistent with subjects who received the same actual dose amount (to be determined by clinical observation and review of data by pharmacokineticist) and have sufficient samples collected for calculation of at least one PK parameter through non-compartmental analysis will be included in the PK Parameter Population (PKP). The PK parameter data will be analyzed according to the treatment received. PK parameter results will be produced using this population. Placebo subjects included in the PKP will only have PK parameters derived from uncorrected L-dopa concentrations.

Safety and Tolerability:

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

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) version 21.0. 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 World Health Organization (WHO) drug dictionary, Version MAR-2018 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:

Reported (i.e. uncorrected) and baseline corrected L-dopa concentrations will be summarized with descriptive statistics (arithmetic and geometric mean, SD, CV% 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}) derived from both reported and baseline corrected L-dopa concentration data will be summarized with descriptive statistics by treatment group.

Exploratory Analysis

- PK profile of carbidopa (Cohort 4 only) for the first 120 minutes following dosing with INP103 will be summarized with the PK parameters of AUC0-2h, Cmax and Tmax.

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, INP103 70 mg, INP103 140 mg INP103 70 mg/7.0 mg L-dopa: carbidopa, or placebo), time point (15, 30, 45, 60, 90 or 120 minutes) 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, duration of response or 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 analyzed 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:

Change from baseline in MDS-UPDRS Part III score versus uncorrected plasma L-Dopa concentrations will be graphed. Relationships between PK Parameters (such as C_{max}, AUC parameters) and motor function will be assessed as data allows."

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ATC	Anatomical Therapeutic Chemical
AUC	Area under the plasma concentration-time curve
AUC_{0-2h}	Area under the plasma concentration-time curve from time zero to 2 hours
BLQ	Below the limit of quantitation
BMI	Body mass index
C1, C2, C3, C4	Cohort 1, Cohort 2, Cohort 3, Cohort 4
C_{max}	Maximum observed plasma concentration
CNS	Clinical Network Services
COMT	catechol-O-methyl transferase
CRF	Case Report Form
CS	Clinically significant
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DA	Dopamine Agonists
DBL	Database Lock
DBP	Diastolic blood pressure
DCI	Decarboxylase inhibitor
ECG	Electrocardiogram
FSH	Follicle Stimulating Hormone
H&Y	Hoehn & Yahr
HBsAg	Hepatitis B surface antigen
HCV-ab	Hepatitis C Virus Antibody
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
ITT	Intension-to-Treat
L-dopa	Levodopa
LOCF	Last Observation Carried Forward

ABBREVIATION	DEFINITION
LOQ	Limit of quantitation
MAOB-I	monoamine oxidase-B inhibitor
MDS-UPDRS	Movement Disorder Society Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities Terminology
MMRM	Mixed Model for Repeated Measures
N	Sample Size
NCA	Non-compartmental analysis
NCS	Not clinically significant
OC	Observed Cases
PD	Parkinson's Disease
PDyn	Pharmacodynamic
PK	Pharmacokinetic
POD	Precision Olfactory Delivery
PT	Preferred Term
QD	Administered once per day
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SBP	Systolic blood pressure
SD	Standard Deviation
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOP	Standard Operating Procedures
T_{max}	Time of observed maximum plasma concentration
$t_{½}$	Elimination half-life
TEAE	Treatment Emergent Adverse Event
ULN	Upper limit of normal
WHODD	World Health Organization Drug Dictionary

2. INTRODUCTION

This statistical analysis plan (SAP) for study (protocol: INP103-201) is developed based on Amendment 4 of the final protocol dated 01 February 2019 and CRF PDF Casebook generated on 20 March 2019. The purpose of this SAP is to ensure that all statistical results including the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are comprehensive and appropriate for the analysis of the study objectives specified in the protocol. Any amendments to the SAP will be made prior to final database lock and any additional analyses not described in the final SAP or deviation from the final SAP will be documented in the clinical study report (CSR).

This is a Phase IIa randomized, double-blind, placebo-controlled study, to compare the safety, tolerability 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.

3. STUDY OBJECTIVE(S) AND ENDPOINT(S)

3.1. Study Objective(s)

3.1.1. Primary Objectives

The primary objective of the study is:

- To compare the safety and tolerability of nasal 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.

3.1.2. Secondary Objectives

The secondary objectives of the study are:

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/pharmacodynamic (PDyn) relationship of single doses of INP103 and motor function

3.1.3. Exploratory Objectives

The exploratory objective of the study is:

- To evaluate the plasma concentration-time profiles of carbidopa following single doses of INP103 in Cohort 4 and to determine PK parameters.

3.2. Study Endpoints

3.2.1. 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 adverse events (AEs; specifically, overall dyskinesia assessments) over the immediate 240 minutes following dosing and over 7 days of follow-up.

These primary endpoints, specific to the full study analysis, will also be considered the primary endpoints for the interim analysis (reviewed in a blinded manner). The data for the primary endpoints will also be reviewed at each safety monitoring committee meeting in a blinded manner.

3.2.2. Secondary Endpoints

1. PK profile of L-dopa for 120 minutes following dosing with INP103 (AUC0-2h, Cmax and Tmax).
2. Motor function, evaluated as:
    - Change from baseline to 30 minutes post-dose in Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III score (primary motor function endpoint).

- Change from baseline to 15, 30, 45, 60, 90 and 120 minutes post-dose for Cohort 1 (C1), Cohort 2 (C2), Cohort 3 (C3) and change from baseline to 30, 60, 90, 120 minutes for Cohort 4 (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 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 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
- 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

3.2.3. Exploratory Endpoints

PK profile of carbidopa (Cohort 4 only) for 120 minutes following dosing with INP103 and where possible, determine $AUC_{0\text{-}2h}$, C_{max} and T_{max}.

3.3. Statistical Hypotheses

There are no formal statistical hypotheses defined for this Phase IIa study. All data will be compared descriptively.

3.4. Pharmacokinetic and Pharmacodynamic Hypotheses

There are no formal statistical hypotheses for PK and PDyn for this Phase IIa study.

4. STUDY DESIGN

This is a Phase IIa randomized, double-blind, placebo controlled, single dose study to compare the safety, tolerability and PK/PDyn of nasal L-dopa in the presence of decarboxylase inhibitor (DCI) during an OFF episode.

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 dopamine 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 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, with sponsor approval, 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, patients may be unblinded and tables, listings, and figures of collected data will be produced. Unblinding of Cohort 1 and 2 data will not jeopardize blinding of any enrolled Cohort 3 or 4 subjects at the time of the interim analysis.

4.1. Sample Size Considerations

4.1.1. Sample Size Justifications

Thirty-two (32) subjects (8 per dose group) are considered sufficient for assessment of safety and tolerability of SADs of INP103. Cohort 4 may enroll 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 compared to placebo 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 PDyn endpoints.

4.1.2. Sample Size Re-estimation

Not applicable for this study.

4.2. Randomization

At least thirty-two (32), maximum 36, subjects will be randomized, and as this is a multi-center study, centralized randomization will be performed. Treatment assignment will be randomized 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.

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)

For more detail, please refer to final Randomization Plan and Specification (version 3.0, dated: 22 FEB 2019).

4.3. Clinical Assessments

All clinical assessments are detailed in protocol amendment v4.0 (dated: 01 February 2019) Section 7. Study Schedule.

5. PLANNED ANALYSES

5.1. Interim Analyses

An interim analysis (IA) will be completed after Cohorts 1 and 2. Cohorts 1 and 2 data will be soft-locked and a subset of tables and listing will be provided. Subject level treatment allocations will not be provided to the sponsor. The aim of this analysis is to generate preliminary safety, efficacy and PK information from Cohorts 1 and 2 only.

To maintain the overall blinding of this study in the first instance, the IA tables and listings will be provided in the following way:

- For the specified demographic/baseline, adverse event and other safety listings, treatment will not be included/printed in the presentation. Data for the specified demographics/baseline and adverse events will be summarized by Cohort only, with data from active subjects and placebo subjects pooled for each cohort.
- For the specified efficacy listings, treatment will not be included/printed in the individual subject listing presentations. Data for the specified efficacy measures will be analyzed by an unblinded statistician and will be summarized by treatment for summary tables. Only summary statistics that do not allow the identification of individual patient level data will be presented (e.g. mean, SD). The summary statistics acceptable for presentation will be determined by the unblinded statistician based on comparison of the summary result values with individual subject data.
- For the specified PK data, only summary tables and figures will be produced. Data will be analyzed by an unblinded pharmacokineticist and will be summarized by treatment. No individual subject level data will be presented.

After review of the blinded IA results, it may be determined by the sponsor that the information provided is insufficient for the purposes of assessing safety, updating the study design for future cohorts, planning of future studies and/or reporting to various regulatory authorities and stakeholders. In this instance, and as described in protocol v3.0 (date: 26Jul2018), the sponsor is able to request the interim results be unblinded.

Unblinding of Cohort 1 and 2 will not bias the Cohort 3 dose escalation process or data collection. The soft-locked data for Cohorts 1 and 2 will not be modified based on the results observed from any unblinded IA data presentations. Any enrolled Cohort 3 subjects at the time of the IA will remain blinded at IA. The IA is for information only, and no formal trial stopping rule is set up at the IA.

All tables, listings and figures which will be presented in the IA are detailed in Section 17.2 *Table of Contents for Data Display* Specifications

5.2. Final Analysis

The final analysis will be conducted once all subjects have completed the study and the clinical database has been locked. Any changes made to Cohort 1 and/or 2 data after the IA may be listed if results at the final analysis lead to a different conclusion from the IA.

6. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

6.1. General Summary Table and Individual Subject Data Listing Considerations

Summary tables and listings will be prepared according to ICH Guideline E3.

Row entries in tables are made only if data exists for at least one subject (e.g., a row with all zeros will not appear). The only exception to this rule will apply to tables that summarize the study termination status of subjects (e.g., reasons for not completing the study). In this case, zeros will appear for study termination reasons that no subject satisfied. The summary tables will clearly indicate the number of subjects to which the data apply and unknown or not performed are distinguished from missing data.

Listings will be sorted by cohort, randomized treatment group, subject number, assessment visit and date/time.

In general, missing data will not be imputed unless otherwise specified. Any imputed or derived data will be flagged in the individual subject data listings. Imputed data will not be incorporated into any raw or primary datasets. These data will be retained in derived analysis datasets.

6.2. General Post Text Summary Table and Individual Subject Data Listing Format Considerations

The tables, figures and listings will be numbered using a decimal system to reflect main levels of unique tables and listings and sub-levels of replicate tables and listings with two digits per level (e.g., Table XX.YY.ZZ. …).

1. The first level number will be consistent with the corresponding Clinical Study Report (CSR) appendix in which the tables or listings will appear. For example, the post text tables will appear in Appendix 14 (and will be numbered 14.XX.YY) and the individual subject data listings will appear in Appendix 16 (and will be numbered 16.XX.YY). The subject disposition table will be first in the first section of the report and will be numbered Table 14.1. The supportive subject data listing will be Listing 16.1. Any subset table will have the number Table 14.1.1, Table 14.1.2, etc.
2. Table numbering will follow ICH E3 for Phase I CSRs. Subject disposition, baseline and demography and prior and concomitant medications tables should appear as the second level number (Table 14.1 series). Similar conventions will be applied to the subject data listings.
3. Each table and listing title will be complete, accurate and concise. The last line of the title will provide the analysis group being summarized (e.g., Safety Population).
4. If possible, variables being summarized, and statistics reported, will appear in the left most column of a table. The next columns for treatment formulations should report the data from left to right for the treatment formulations (i.e. Placebo, Dose Cohort 1, Dose Cohort 2, Dose Cohort 3, Dose Cohort 4 and Overall), respectively.

6.3. Data Management

All data will be recorded by the site in individual source documents. An electronic Case Report Form (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 and 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.

Data storage, data transfer and data cleaning will be conducted according to the relevant CNS Standard Operating Procedures (SOPs).

Derived datasets are created using SAS® software. Data analyses and summary tables will be generated using the currently supported version at the time of data analysis.

6.4. Data Presentation Conventions

Continuous safety variables (e.g., clinical laboratory values, vital signs and ECGs) will be reported to the same precision as the source data. Derived variables will be reported using the same precision as the value(s) from which they were derived. For the reporting of descriptive statistics, the mean and median will be reported to 1 decimal place more than the source data; the minimum and the maximum values will be presented to the same precision as the source data and standard deviations (SD) will be reported to 2 decimal places more than the source data. The coefficient of variation (CV%), as a percentage (i.e., x100%), will always be reported to 1 decimal place.

Pharmacokinetic concentration data that are presented by the lab in significant digits will be reported as received from the bioanalytical lab in by subject listings.

For categorical/discrete variables, the frequency count and the percentage (of available data) for each class of the variable will be presented and will be displayed in the form XX (XX.X%) where the percentage is in the parentheses.

Date variables will be formatted as ddMMMyyyy for presentation (where day and year are numeric and the first three letters of month in letters). Time will be formatted in 24-hour time as HH:MM for presentation.

Extra measurements (such as unscheduled or repeat assessments) will not generally be included in summary tables but will be included in subject listings. They may be used if a scheduled measurement is missing and the timing of the extra measurement is deemed suitable. They will be used in summary tables which are not ‘time specific’, for example, summaries of maximum post dose values. In the data listings and summary tables presented as part of the CSR, scheduled assessments will be identified by the protocol specified nominal visit day and scheduled time point.

Wherever possible, data will be decimal aligned.

The tables, figures and listings shells and table of contents as part of this Statistical Analysis Plan (SAP) provide the expected layout and titles of the tables, figures and listings. Any changes to format, layout, titles, numbering, or any other minor deviation will not necessitate a revision to the SAP, nor will it be considered a deviation from planned analyses. Only true differences in the analysis methods or data

handling will necessitate such documentation. The appropriate listings supporting the tables will be included and are not specified in the individual sections throughout the document.

Minor modifications may be necessary to the planned design of tables, listings and figures to accommodate data collected during the actual study conduct. Any major deviations from the final approved SAP (e.g., change in the population used, change from statistical method/assumption listed, transformation of data type [e.g., continuous data transformed to categorical], exclusion of planned analysis, etc.) or additional unplanned analyses will be documented (with justification) in the CSR.

6.5. Analysis Populations

Subject inclusion into each population will be determined before database lock for the final analysis except for pharmacokinetic population which will be decided by a pharmacokinetic scientist after database lock.

6.5.1. Screen Failures

Data from screen failures will not be recorded in the eCRF. Reasons for screen failures will be collected in study screening logs.

6.5.2. Intention-to-Treat (ITT) Population

All subjects who randomized into this study, regardless of receiving the study drug (INP103 or placebo) or not, will be included in this population. In general, all data listings and subject disposition, will be generated on this population except PK and PDyn results. Summaries of demographics, prior and concomitant medications will be produced using this population.

This definition of the ITT population differs from the definition provided in the protocol and will supersede the protocol definition.

6.5.3. Benserazide Safety Population

All subjects who receive any amount of benserazide (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.

6.5.4. Safety Population

All subjects who receive any amount of INP103 or placebo will be included in the Safety Population. The data will be analyzed according to the treatment received. All safety results will be generated on Safety Population.

6.5.5. PK Population (PKP)

All subjects who receive placebo or the full planned dose of INP103 or active treatment subjects who receive partial dose (as reported by clinical observation of the number of puffs delivered) with exposure reasonably consistent with subjects who received the same actual dose amount (to be determined by clinical observation and review of data by pharmacokineticist) and have sufficient samples collected for calculation of at least one PK parameter through non-compartmental analysis will be included in the PK Parameter Population (PKP). The PK parameter data will be analyzed according to the treatment received. PK

parameter results will be produced using this population. Placebo subjects included in the PKP will only have PK parameters derived from uncorrected L-dopa concentrations.

6.6. Baseline Definition

For all safety assessments, the baseline will be defined as the last available, non-missing observation prior to first study drug (benserazide, INP103 or placebo) administration, unless specifically mentioned otherwise.

For PDyn assessment, the baseline will be defined as the last available, non-missing observation prior to first study drug (INP103 or placebo) administration, unless specifically mentioned otherwise.

In general, Unknown, Not Done, Not Applicable and other classifications of missing data will not be considered when calculating baseline observations. However, valid categorical observations will be considered for baseline calculations.

6.7. Derived and Transformed Data

6.7.1. Age

Age, in completed years, at screening will be defined as:

Age (years) = integer value ([Date Signed Informed Consent – Date of Birth + 1] / 365.25)

6.7.2. Study Day

Study day will be calculated using the first investigational study drug (INP103 or placebo) administration date as the reference date. If the date of interest occurs on or after the first study drug administration date, then study day will be calculated as (date of interest – date of first study drug administration+1). If the date of interest occurs prior to the first study drug administration date, then study day will be calculated as (date of interest – date of first study drug administration).

Data listings will present study days in addition to assessment dates. The first day of dosing will be identified as Study "**Day 1**" per SDTM convention. There is no Study Day 0.

6.7.3. Change from Baseline

Change from baseline will be calculated as (post-baseline result – baseline result).

6.7.4. Observed Cases (OC) and Last Observation Carried Forward (LOCF), Missing Data and Outliers

Not applicable for this study.

6.7.5. Completers

Not applicable for this study.

6.7.6. Other Derivations

Body Mass Index (kg/m^2, to one decimal place) = Body Weight (kg) / ($Height^2$ (m)).

For any observed original results above the upper limit or below the lower limit in laboratory assessment, the original results will be presented in data listing and the upper limit value or the lower limit value will be used for summary table. For example, *0.1* will be used if the original result is "*<0.1*", while *1000* will be used if the original result is *">=1000*".

Treatment emergent adverse events will be defined as AEs which commence on or after the time of start of first study drug administration. AEs without an onset date or time will be defined as treatment emergent except if an incomplete date (e.g., month and year) clearly indicates that the event started prior to start of first study drug administration or if the AE stop date indicates that the event started and/or stopped prior to start of first study drug administration.

Adverse event time since study drug administration (in minutes) = (Onset Date + Onset Time) – (Study Drug Administration Date + Study Drug Administration Time).

Duration of AE (in minutes) = (Resolution Date + Resolution Time) - (Onset Date + Onset Time).

The response is defined as an improvement of ≥ 30% in MDS-UPDRS Part III score from baseline to post INP103/Placebo dosing time point for each patient.

Time to response = (Time at FIRST response [as defined above] post study drug administration [INP103/Placebo] – Time at the first study drug administration [INP103/Placebo] [Unit = minutes]).

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.

All AUC values will be calculated by using the trapezoidal rule.

7. TREATMENT COMPARISONS

7.1. Data Display Treatment and Other Sub-Group Descriptors

- All Placebo
- INP103 35 mg
- INP103 70 mg
- INP103 140 mg
- INP103 70 mg /7.0 mg carbidopa
- Overall

Note: All subjects randomized to placebo, from all cohorts, will be combined into a single placebo group (i.e. All Placebo Subjects).

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

The listings, figures and summary tables for the disposition, safety, PK, and PDyn data will be the responsibility of the study Biostatistician at CNS.

The currently supported version of SAS software will be used to perform all data analyses, excluding the estimation of PK parameters, which will be undertaken with WinNonlin. The actual SAS and WinNonlin versions used will be presented in the Clinical Study Report (CSR).

All data in the database will be presented in the data listings. Unless otherwise stated, all listings will be sorted by cohort, randomized treatment group, subject number and assessment date/time.

Unless otherwise stated, continuous variables will be summarized using descriptive statistics including number of non-missing observations, mean, standard deviation (SD), median, minimum and maximum values.

Categorical variables will be summarized with frequency counts and percentages. The population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Percentages will be rounded to one decimal place, with the denominator being the number of subjects in the relevant population, unless otherwise stated.

Only data from nominal protocol scheduled visits will be included in the summary tables. Data from unscheduled visits will not be included in the summary tables but will be included in the figures and listings.

8.1. Multicenter Studies

Subjects will be screened and enrolled across five study sites for this study. Due to limited data from each site, no adjustment or stratification for site will be performed.

8.2. Other Strata and Covariates

In ANCOVA model, baseline MDS-UPDRS Part III total score will be set as covariates.

8.3. Examination of Subgroups

No subgroup analyses are planned for this study.

8.4. Multiple Comparisons and Multiplicity

Not applicable for this study.

8.5. Data handling conventions

8.5.1. Premature Withdrawal and Missing Data

For subjects who are withdrawn from the study prior to study completion, all data compiled up to the point of discontinuation will be used for analysis. All withdrawals will be included in all analyses up to the time of withdrawal.

There will be no imputation for missing data, unless otherwise stated.

8.5.2. Handling of Dropouts

No imputation of missing data will be performed for early termination subjects. All data collected prior to drop out will be listed and included in data summaries.

8.5.3. Additional/Unscheduled Assessments and Missing Data

Generally, missing dates/times will not be imputed. Adverse events with missing or partial dates will be handled such that in the absence of contradictory information an AE is treatment emergent. For a missing start date (where the stop date is after the date of first study drug administration) the start date will be imputed as the first study drug administration date. Similarly, for a missing stop date, the stop date will be imputed as the date of last visit. If a partial date is recorded, the following convention will be used to assign the AE:

- If a start date is missing the day information and the month/year is the same as the first study drug administration date, then use the first study drug administration date, else '01' will be used for the day. If a start date is missing the month and the year is the same as the first study drug administration date, then use the first study drug administration date, else 'January' will be used for the start month.
- If a stop date is missing the day information and month/year is the same as the last study date, then use the last study date, else the last day of the given month will be used for the stop day. If a stop date is missing the month and the year is the same as the last study date, then use the last study date, else 'December' will be used for the stop month.

Extra measurements (such as unscheduled or repeat assessments) will not generally be included in summary tables but will be included in subject listings. They may be used if a scheduled measurement is missing and the timing of the extra measurement is deemed suitable. They will be used in summary tables which are not 'time specific'; for example, summaries of maximum post dose values.

The original data will always be presented in the listings.

8.5.4. Assessment Windows

No visit windows will be applied to assessments. All assessments will be included in the listings.

8.6. Derived and Transformed Data

The required endpoints and variables will be derived by the Statistical Programmers at CNS using the derivations specified in Section 6.7 of this SAP.

8.7. Values of Clinical Concern

Not applicable for this study.

9. STUDY POPULATION

Subject disposition, demographics, baseline characteristics, prior and concomitant medication analyses will be conducted on the ITT Population. These results will be summarized by cohort and treatment group.

9.1. Disposition of Subjects

A disposition listing will present date of informed consent, date of randomization, study completion or withdrawal, the reason for withdrawal, if applicable and whether included in each analysis population, for each subject.

A listing of whether or not all inclusion and exclusion criteria were met and if not, which criteria were not met, by subject, will also be presented.

The following will be summarized, by cohort and randomized treatment group and for all subjects:

- The number of subjects randomized
- The number of subjects treated
- Number of subjects who completed the study
- Number of subjects withdrawn and reason for withdrawal
- Number of subjects in each analysis population

9.2. Protocol Deviations

Subject data will be examined for evidence of protocol deviations in order to assess how well the protocol was followed. These will be assessed for the final analysis.

All protocol deviations will be detailed in listings.

9.3. Demographic and Baseline Characteristics

Subject demographic and baseline variables (age, sex, childbearing potential, ethnicity, race, height, body weight and BMI at screening) will be summarized and listed, by cohort and treatment group.

The following baseline characteristics will be listed only:

- Medical history
- Smoking history
- Parkinson’s Disease History
- Pregnancy test (Urine, Serum and FSH)

9.4. Treatment Compliance

The following drug administration data will be listed:

- Drug Administration: Benserazide
- Drug Administration: INP103/Placebo
- Administration of 'ON' Medication

9.4.1. Compliance to Study Drug

Not applicable for this study.

9.4.2. Measurement of Treatment Compliance

Not applicable for this study.

9.5. Prior and Concomitant Medications

The start dates of non-investigational medications will be used to assign medications into different categories.

- Prior medication: Any medication which started before the date of first study drug (benserazide, INP103 or placebo) administration. If the start date of the medication is not complete or missing, it will be treated as prior medication.
- Concomitant medication: Any medication which started on or after the date of first study drug (benserazide, INP103 or placebo) administration up to the final visit or premature study withdrawal, whichever is earliest.
- Prior and concomitant medication: Any medication which started before the date of first study drug (benserazide, INP103 or placebo) administration but continued after the date of first study drug administration.

Medications will be classified as a prior medication and/or a concomitant medication. If a medication has a missing or partial missing start/end date or time and it cannot be determined whether it was taken before the date of first study drug administration or concomitantly, it will be considered as both prior and concomitant.

Medications with a start date prior to the first administration of study drug and a treatment end data after the first administration of study drug will be assigned to both prior medication and concomitant medication categories.

Prior and concomitant medications will be coded by WHO-DDE Version MAR-2018. Concomitant medication data will be summarized by Anatomical Therapeutic Chemical (ATC) system (Level 4 for anti-PD medications and Level 2 for other medications) and drug preferred name. The summary table will show the number and percentage of subjects taking each medication by ATC Level and preferred name.

For the summaries of concomitant medications, subjects who take the same medication (in terms of the ATC Level and preferred name) more than once will only be counted once for that medication.

Prior medication and concomitant medications will be listed and concomitant medications will be summarized, separately, by cohort and treatment group and summary results will be presented in alphabetical order.

The following medications will be listed:

- Rescue OFF Tx Allowed
- Usual Morning anti-PD Medication
- Levodopa containing Medication

In addition, Rescue OFF Tx Allowed and Usual Morning anti-PD Medication will be summarized using frequency tabulations (Yes/No).

10. EFFICACY ANALYSES

The analyses of PDyn results will be treated as the exploratory analysis of preliminary efficacy in this study and all efficacy analyses will be conducted on the ITT population.

10.1. Change from baseline to 30 minutes post-dose in MDS-UPDRS Part III Score at Visit 3

For each subject, the individual scale from question 3.1 to 3.18 of MDS-UPDRS Part III questionnaire will be added as total score and it will be applied for following analysis of MDS-UPDRS Part III score.

The changes from baseline to 30 minutes post-dose in MDS-UPDRS Part III total score at Visit 3 will be summarized by treatment groups (INP103 35 mg, INP103 70 mg, INP103 140 mg, INP103 70 mg with 7.0 mg carbidopa, or placebo).

10.2. Change from baseline to post-dose timepoints in MDS-UPDRS Part III score

The changes from baseline in MDS-UPDRS Part III score will be summarized by time point (15, 30, 45, 60, 90 or 120 minutes for C1, C2 and C3; 30, 60, 90 or 120 minutes for C4) and treatment groups (INP103 35 mg, INP103 70 mg, INP103 140 mg, INP103 70mg with 7.0 mg carbidopa or placebo). In addition, the changes from baseline in MDS-UPDRS Part III score will be estimated using a Mixed Model for Repeated Measures (MMRM) with treatment group, time, and the interaction between treatment group and time point as fixed factors, and the baseline total 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 approximated using the Kenward-Roger method. The least squares (LS) means, standard errors and two-sided 95% confidence intervals will be provided for changes across time points within each treatment group.

In addition, the differences between each treatment group and placebo will be estimated across time points based on the same MMRM model, and LS mean, standard errors and 95% CI of differences will be presented.

Change from baseline in MDS-UPDRS III score will be plotted by each treatment group for each subject (y axis) against time from dosing (x-axis).

10.3. Cumulative proportion of responders by post-dose time point

The cumulative proportion of responders will be summarized by post-dose time point (15, 30, 45, 60, 90 or 120 minutes for C1, C2 and C3; 30, 60, 90 or 120 minutes for C4) and treatment groups (INP103 35 mg, INP103 70 mg, INP103 140 mg, INP103 70 mg with 7.0 mg carbidopa, or placebo) using frequency tabulations. Subjects that achieve response will count as a responder for all subsequent time points regardless of a return to "<30% improvement" post achievement of response.

10.4. Time to response

The time to response is defined as time from first dosing to the FIRST response of a 30% or greater improvement in MDS-UPDRS Part III total score post INP103/Placebo dosing of each patient. Subjects without response identified will be censored at the last assessment time. Survival analysis will be used to analyze the time to response. The analysis of time to response is based on the survivor function, which is the probability to survive or, more generally, to stay event-free beyond a certain point in time. The survival function will be estimated by the Kaplan-Meier method. The survival function will be summarized for 25th percentile, median, and 75th percentile and their 95% confidence intervals. The plot of Kaplan-Meier estimates for the treatment groups will be presented. The y-axis of Kaplan-Meier estimates will be plotted as cumulative event (response) rate (i.e. one minus survival rate).

10.5. Duration of response

Duration of response = *sum of **all** time intervals which observed a response*.

The duration of response will be calculated for each subject and summarized by treatment groups (INP103 35 mg, INP103 70 mg, INP103 140 mg, INP103 70 mg with 7.0 mg carbidopa, or placebo).

For example, if the subject achieves a response at 15, 45 and 90 and 120 minutes (data shown in table below), the duration of response will be calculated as the sum of the duration (95 minutes = 15 minutes + 0 minutes + 0 minutes + 15 minutes + 31 minutes + 34 minutes).

Schedule Timepoint	Actual Time	Response*	Derivation for Duration of Response*	Duration of Response*
Pre-dose	10:00	NA	NA	
15 mins post dose	10:15	Yes	Actual time at “15 mins post-dose” minus the Actual time at “Pre-dose”	15
30 mins post dose	10:30	No	NA	0
45 mins post dose	10:45	Yes	Actual time at “45 mins post-dose” minus the Actual time at “30 mins post-dose”	15
60 mins post dose	11:00	No	NA	0
90 mins post dose	11:31	Yes	Actual time at “60 mins post-dose” minus the Actual time at “90 mins post-dose”	31
120 mins post dose	12:05	Yes	Actual time at “90 mins post-dose” minus the Actual time at “120 mins post-dose”	34

* Response is defined as an improvement of at least 30% in MDS-UPDRS Part III score from baseline

10.6. Area Under the Curve (AUC) of changes in MDS-UPDRS Part III scores from pre-dose to post-dose timepoints

AUC of changes in MDS-UPDRS Part III total scores from pre-dose to post-dose will be calculated by trapezoid formula by the following formula:

Area under Curve of (*post-dose total score* minus *pre-dose total score* in MDS-UPDRS Part III score)

For each subject, AUC of changes in MDS-UPDRS Part III total scores from pre-dose to 15, 30, 45, 60, 90 and 120 minutes for C1, C2 and C3; 30, 60, 90 or 120 minutes for C4 will be calculated as: $AUC_{0\text{-}15mins}$, $AUC_{0\text{-}30\ mins}$, $AUC_{0\text{-}45\ mins}$, $AUC_{0\text{-}60\ mins}$, $AUC_{0\text{-}90\ mins}$ and $AUC_{0\text{-}120\ mins}$. (omitting $AUC_{0\text{-}15\ mins}$ and $AUC_{0\text{-}45\ mins}$ for Cohort 4).

These AUC parameters will be summarized by each treatment groups (INP103 35 mg, INP103 70 mg, INP103 140 mg, INP103 70 mg with 7.0 mg carbidopa, or placebo).

Each AUC parameter ($AUC_{0\text{-}15\ mins}$, $AUC_{0\text{-}30\ mins}$, $AUC_{0\text{-}45\ mins}$, $AUC_{0\text{-}60\ mins}$, $AUC_{0\text{-}90\ mins}$ and $AUC_{0\text{-}120\ mins}$) will be analyzed 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 squares (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.

10.7. Individual Maximum response in MDS-UPDRS Part III scores from pre-dose to 15, 30, 45, 60, 90 and 120 minutes post-dose.

The individual maximum response scores will be defined as the maximum MDS-UPDRS Part III score post INP103/Placebo dosing from the baseline across all time points post dose (from 15, 30, 45, 60, 90 and 120 minute for C1, C2, C3 and 30, 45, 60, 90, and 120 minutes for C4) for each subject.

The individual maximum response scores will be summarized by each treatment groups INP103 35 mg, INP103 70 mg, INP103 140 mg, INP103 70 mg with 7.0 mg carbidopa, or placebo).

The individual maximum response scores will be analyzed with an ANCOVA model with treatment group as a fixed factor and baseline MDS-UPDRS Part III score as a covariate. The least squares (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 active treatment group and placebo and their 95% CIs will be estimated.

10.8. Subjective time to ON

The time to ON is defined as time from first dosing to the first onset of ON status. Subjects without onset of ON status will be censored at the last assessment time. The analysis method for time to ON endpoint will be the same as that for time to response endpoint. Survival analysis will be used to analyze the time to ON. The analysis of time to ON is based on the survivor function, which is the probability to survive or, more generally, to stay event-free beyond a certain point in time. The survival function will be estimated by the Kaplan-Meier method. The survival function will be summarized for 25^{th} percentile, median, and 75^{th} percentile and their 95% confidence intervals. The plot of Kaplan-Meier estimates for the treatment groups will be presented. The y-axis of Kaplan-Meier estimates will be plotted as cumulative event (response) rate (i.e. one minus survival rate).

11. SAFETY ANALYSES

All safety analyses will be conducted on the Safety population.

Overall, data for adverse events, clinical laboratory assessment, vital signs, ECG and other safety measurements (orthostatic hypotension, dyskinesia assessment, nasal inspection, , physical examination, subject questionnaire, domiciled status) will be presented by subject in listings (including assessments of abnormality and clinical significance, where applicable). Summaries will be prepared for key variables (detailed below) by cohort and treatment group and protocol specified time-point (where applicable) for the Safety population.

No inferential statistical testing will be performed for any safety variable.

11.1. Adverse Events

Adverse events will be coded using MedDRA® Version 21.0. Adverse events will be grouped by system organ class (SOC) and preferred term (PT) and summarized, by actual treatment at time of onset of the AE. The summary tables will present the frequency and percentage of total subjects and number of events, by SOC and by PT.

For the summaries of AEs, subjects who experience the same AE (in terms of the MedDRA preferred term) more than once will only be counted once for that event in the number of subjects but all occurrences of the same event will be counted in the number of events.

AE summaries will include Treatment Emergent Adverse Events (TEAEs) and AE onset within benserazide period.

- TEAE is defined as AEs which commence on or after the time of first study drug administration (INP103 or placebo) through to the end of the study. AEs without an onset date or time will be defined as treatment emergent except if an incomplete date (e.g., month and year) clearly indicates that the event started prior to start of first study drug administration or if the AE stop date indicates that the event started and/or stopped prior to start of first study drug administration.
- AE onset within benserazide period: AE onset within the benserazide period is defined as the AE onset after the dose of benserazide and before the dose of INP103/ Placebo. AEs without an onset date or time will be defined into this category except if an incomplete date (e.g., month and year) clearly indicates that the event started prior to start of benserazide administration or if the AE stop date indicates that the event started and/or stopped prior to start of benserazide administration.

Incidence of adverse events as well as the duration, severity, relationship to treatment, outcome and actions taken will be listed for each subject. In addition, listings of AEs leading to discontinuation of the study, SAEs and deaths, will be provided if applicable.

'Treatment Related' TEAE is defined as any TEAE that is reported as having a *Definite, Probable* or *Possible* relationship to the study drug.

The following AE summaries will be provided:

- Overall summary of TEAEs, including below information
  - Any TEAE
  - AEs onset within Benserazide Period

  - Any severe TEAE
  - Any Treatment-related TEAE
  - Any serious TEAE
  - Any TEAE leading to study drug interruption
  - Any TEAE leading to study drug withdrawn
  - Any TEAE leading to discontinuation from study
  - Any Life threatening TEAE
  - Any TEAE leading to death
- Adverse Events onset within Benserazide Period by SOC and PT
- TEAEs overall and by SOC and PT
- TEAEs by severity, overall and by SOC and PT
- Treatment-related TEAEs overall and by SOC and PT
- Serious TEAEs overall and by SOC and PT

In the summary tables, AEs will be presented by decreasing frequency of total events overall within each SOC and then similarly by decreasing frequency of total events overall within each PT. SOCs or PTs with equal frequencies will be sorted alphabetically.

11.2. Serious Adverse Events

Incidence of SAEs as well as the duration, severity, relationship to treatment, outcome and actions taken will be listed for each subject.

11.3. Adverse Events Leading to Dose Interruption, Discontinuation of Investigational Product and/or Withdrawal from the Study and Other Significant Adverse Events

Incidence of AE's leading to study dose interruption, withdrawal or discontinuation from study, as well as the duration, severity, relationship to treatment, outcome and actions taken will be listed for each subject.

11.4. Clinical Laboratory Evaluations

All individual clinical laboratory results (hematology, biochemistry and urinalysis) will be presented in data listings. Values outside the laboratory reference range will be flagged (low-L, high-H).

When applicable, observed and change from baseline (prior to the first study drug administration [benserazide or INP103/placebo]) clinical laboratory data (hematology and biochemistry) will be summarized by cohort and treatment group and protocol specified collection time point. Urinalysis results will be summarized using frequency tabulation. Frequency tabulations of the number of normal and abnormal (low and high) records, as well as the number of clinically significant (CS) and not clinically significant (NCS) for clinical laboratory results (hematology, biochemistry and urinalysis) will also be summarized by cohort, treatment group and protocol specified collection time point.

Any available microscopic urinalysis will be listed only.

11.5. Vital Signs Evaluations

All individual vital signs results (supine and standing systolic blood pressure [mmHg], supine and standing diastolic blood pressure [mmHg], heart rate [beats per minute (bpm)], respiratory rate [breaths per minute] and oral temperature [°C]) will be presented in data listings. Observed vital signs parameter values and changes from baseline (prior to the first study drug administration [benserazide or INP103/placebo]) will be summarized by treatment and protocol specified collection time point.

11.6. ECG Evaluations

All individual ECG parameter values (Heart Rate [bpm], QT interval [msecs], PR interval [msecs], QRS interval [msec], RR interval [msecs], QTcF [msecs], and QTcB [msecs]) and overall ECG clinical interpretation will be presented in data listing. Observed ECG parameter values and changes from baseline (prior to the first study drug administration [benserazide or INP103/placebo]) will be summarized by treatment and protocol specified collection time point.

In addition, clinical assessment of the ECG (Normal, Abnormal NCS, and Abnormal CS) will be summarized by cohort and treatment group and protocol specified collection time point, using frequency tabulations.

Furthermore, 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 by treatment group, using frequency tabulations:

- 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

11.7. Other Safety Measures

11.7.1. Dyskinesia Examination

The result of dyskinesia examination will be presented in data listing. The Dyskinesia Grade (Grade 0 to 4) will be summarized by cohort and treatment group and protocol specified collection time point, using frequency tabulations.

11.7.2. Nasal Examination

The result of nasal examination will be presented in data listing. All nasal examination categories (Inflammation, Ulceration, Contact bleeding, Oedema, and Other) will be summarized by cohort and treatment group and protocol specified collection time point, using frequency tabulations.

11.7.3. Orthostatic hypotension

The proportion of subjects experiencing orthostatic hypotension will be summarized by cohort and treatment group and protocol specified collection time point, using frequency tabulations, if applicable.

11.7.4. Physical examination

Physical examination data will be presented in data listing. In addition, proportion of subjects with at least one new abnormal physical examination findings will be summarized by cohort and treatment group and protocol specified collection time point, using frequency tabulations.

11.7.5. Others

The following other safety measures will be listed only:

- Subject Questionnaire
- Domiciled Status
- General Comment

12. HEALTH OUTCOMES ANALYSES

Not applicable for this study.

13. CLINICAL PHARMACOLOGY DATA ANALYSES

13.1. Pharmacokinetic Analyses

As L-dopa is produced endogenously, pre-dose plasma concentrations, as well as post-dose concentrations for placebo subjects, may be observed. To account for circulating endogenous L-dopa, PK parameters will be estimated from both actual measured (i.e. uncorrected) concentration data and individual baseline (pre-dose) corrected data. For placebo subjects with measurable L-dopa concentrations, PK parameters will only be estimated using uncorrected concentration data.

Carbidopa plasma concentration-time profiles (Cohort 4 only) will be evaluated to address the exploratory objective of this study where data permit. PK parameters will be determined for carbidopa using non-compartment analysis (NCA) techniques, at the discretion of the PK scientist.

Baseline corrected concentrations will be calculated by subtracting the pre-dose concentration value from the measured value for each post-dose sample. Pre-dose concentrations reported as "BLQ" will be set to a value of zero for adjustment of post-dose concentrations (i.e. post-dose concentrations will not change if pre-dose concentration is "BLQ"). Post-dose concentrations reported as "BLQ" will remain as "BLQ" (i.e. no correction applied). Post-dose concentrations that are negative after correction will be set to the value "BLQ". Concentrations that are lower than the assay lower limit of quantification after correction (but positive in value) will be retained and the corrected value will be used in the PK parameter estimation (i.e. maximize the data that is available for PK parameter estimation).

13.1.1. Concentration-Time Data

Individual uncorrected and baseline corrected plasma L-dopa concentration-time data will be listed for each subject with actual sampling time (for placebo subjects only uncorrected concentrations will be listed). Plasma uncorrected and baseline corrected concentration-time data will be summarized by treatment and nominal sampling time point with descriptive statistics (number of non-missing observations, arithmetic mean, SD, median, minimum, maximum, geometric mean and coefficient of variation [CV%]). The number of values below limit of quantification (BLQ) will also be presented.

Concentrations that are BLQ will be treated as zero for the computation of descriptive statistics, except geometric mean. For the calculation of the geometric mean, concentrations that are BLQ will be treated as equal to the limit of quantification (LOQ). Missing values will be omitted from the calculation of descriptive statistics.

Individual and mean uncorrected and baseline corrected L-dopa concentration-time profiles for each dose regimen will be presented graphically on both linear and logarithmic concentration scales. Actual sampling times will be used for the graphical presentation of individual concentration-time data, and nominal sampling times will be used for mean concentration-time plots. For plots with a linear concentration scale, BLQ concentrations will be plotted as zero values. For plots with a logarithmic concentration scale, BLQ and zero mean values will not be plotted.

13.1.2. Plasma Pharmacokinetic Parameters

Pharmacokinetic parameters will be computed from the individual uncorrected and baseline corrected plasma L-dopa concentrations using NCA. For the interim analysis, PK parameters will only be estimated from uncorrected concentration data. For the end of study unblinded analysis, the actual PK sampling times

(presented as actual time from dose, with pre-dose time set to zero) will be used for the PK parameter calculations. For the interim analysis, nominal sampling times will be used. Phoenix WinNonlin v8.1 will be used.

For the estimation of PK parameters, reported concentrations for analysis of uncorrected data, and corrected concentrations for analysis of baseline corrected data that have a value of BLQ prior to the first quantifiable value will be set to 0. Concentrations that have a value of BLQ at the end of the sampling period after C_{max} (i.e., no further quantifiable concentrations) will be set to missing and will not be used for the estimation of PK parameter values. If a BLQ value falls between two quantifiable concentrations, the value will be set equal to the LOQ, unless its exclusion can be justified (e.g., implausibility given the profile observed and known PK properties) at the discretion and justification provided by the PK scientist.

The parameters that will be determined and their definitions are provided in the table below.

Table 1: Plasma Pharmacokinetic Parameters

Abbreviation	Parameter Definition
C_{max}	Maximum observed drug concentration.
T_{max}	Time to maximum observed drug concentration. If the maximum value occurs at more than one time-point, T_{max} is defined as the first time point with this value.
$AUC_{0\text{-}0.5h}$	Area under the drug concentration-time curve, calculated using linear-up log-down trapezoidal summation from time zero to 0.5 hours post INP103 administration.
$AUC_{0\text{-}1h}$	Area under the drug concentration-time curve, calculated using linear-up log-down trapezoidal summation from time zero to 1 hour post INP103 administration.
$AUC_{0\text{-}2h}$	Area under the drug concentration-time curve, calculated using linear-up log-down trapezoidal summation from time zero to 2 hours post INP103 administration.

$AUC_{0\text{-}2h}$, C_{max} and T_{max} parameters will also be determined for carbidopa (Cohort 4 only), where sufficient plasma concentration data is available.

In addition to non-compartmental pharmacokinetic analysis, exploratory population pharmacokinetic modelling may be undertaken if deemed appropriate. Analysis methods for this will be detailed in a separate population PK modelling analysis plan.

13.1.3. Statistical Methods for Pharmacokinetic Parameters

PK parameters will be summarized by INP103 dose group using descriptive statistics (number of non-missing observations, arithmetic mean, SD, median, minimum, maximum, geometric mean, coefficient of variation as a percent (CV%) and geometric CV%).

Additional analyses will be performed as deemed necessary upon review of the data.

13.1.4. Dose Proportionality

Dose proportionality will be evaluated for baseline corrected C_{max} and $AUC_{0\text{-}2h}$. Dose proportionality will be assessed using the power model with log-transformed PK parameter values and log-transformed dose. The power model will be used to estimate the slope parameter and the 90% confidence intervals for the slope.

The general form of the power model is described as:

$$\ln(\text{PK Parameter}) = \beta_0 + \beta_1 \ln(\text{Dose}) + \varepsilon$$

This approach is usually referred to as a power model because after exponentiation:

$$\text{PK Parameter} = \alpha \, \text{Dose}^{\beta_1}$$

where α only depends on β_0 and ε.

In exploratory studies which are not formally powered, dose proportionality is generally concluded if 90% confidence intervals (CI) around the slope (i.e., β_1) includes the value of 1.0.

In addition, graphs of baseline corrected C_{max} versus Dose and $AUC_{0\text{-}2h}$ versus Dose will be generated. The graphs will display the individual points and include the mean value as a distinct highlighted point.

13.2. Pharmacodynamic Analyses

Refer to section 10. Efficacy Analyses.

13.3. Pharmacokinetic/Pharmacodynamic relationship

Exploratory graphical analysis of the time-matched change from baseline in MDS-UPDRS Part III score versus uncorrected plasma L-Dopa concentrations

14. PHARMACOGENETIC DATA ANALYSES

Not applicable for this study.

15. VIRAL GENOTYPING/PHENOTYPING

Not applicable for this study.

16. REFERENCES

1. Study Protocol, amendment 4.0, dated: 01 February 2019.

2. Randomization Plan and specifications document, version 3.0, dated: 22 February 2019.

17. ATTACHMENTS

17.1. Information of Investigators/Study Centers

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17.2. Table of Contents for Data Display Specifications

17.2.1. Planned Data Listings

The following listings are planned to be generated for the INP103-201 study (Note: Numbering is indicative only and may be updated based on CSR requirements):

Header	Listing Number	Listing Title	Analysis Population	Interim Analysis	Priority
16.2		Subject Data Listings			
16.2.1		Subject Disposition			
	16.2.1.1	Study Enrolment and Completion/Discontinuation	ITT	N	1
	16.2.1.2	Visit Dates and Study Days	ITT	N	2
16.2.2		Protocol Deviations			
	16.2.2.1	Protocol Deviations	ITT	N	1
16.2.3		Subjects Excluded from Analyses			
	16.2.3.1	Population Assignment and Reason for Exclusion	ITT	N	1
16.2.4		Demographic and Other Baseline Data			
	16.2.4.1	Demographics	ITT	N	2
	16.2.4.2	Inclusion/Exclusion Criteria	ITT	N	2
	16.2.4.3	Medical History	ITT	N	2
	16.2.4.4	Smoking History	ITT	N	2
	16.2.4.5	Parkinson’s Disease History	ITT	N	2
	16.2.4.6	Pregnancy Test	ITT	N	2
	16.2.4.7.1	Prior Medications	ITT	Y	2

Header	Listing Number	Listing Title	Analysis Population	Interim Analysis	Priority
	16.2.4.7.2	Concomitant Medications	ITT	Y	2
	16.2.4.7.3	Rescue OFF Tx Allowed	ITT	Y	2
	16.2.4.7.4	Usual Morning anti-PD Medication	ITT	Y	1
	16.2.4.7.5	Levodopa Medication	ITT	Y	1
16.2.5		Compliance and/or drug concentration data			
	16.2.5.1	Subject Randomization	ITT	N	1
	16.2.5.2	Drug Administration: Benserazide	ITT	N	2
	16.2.5.3	Drug Administration: INP103/Placebo	ITT	N	2
	16.2.5.4	Drug Administration: ON medication	ITT	N	2
16.2.6		Pharmacokinetic and Efficacy Data Listing			
	16.2.6.1	Pharmacokinetic:			
	16.2.6.1.1.1	Plasma Pharmacokinetic Sample Collection Time and Levodopa Concentrations	ITT	N	1
	16.2.6.1.1.2	Plasma Pharmacokinetic Sample Collection Time Carbidopa Concentrations	ITT	N	2
Figure	16.2.6.1.2.1	Individual Uncorrected Plasma Levodopa Concentrations Over Time, by Treatment Group (Linear)	ITT	N	2
Figure	16.2.6.1.2.2	Individual Baseline-Corrected Plasma Levodopa Concentrations Over Time, by Treatment Group (Linear)	ITT	N	2
Figure	16.2.6.1.2.3	Individual Plasma Carbidopa Concentrations Over Time, by Treatment Group (Linear)	ITT	N	2
Figure	16.2.6.1.3.1	Individual Uncorrected Plasma Levodopa Concentrations Over Time, by Treatment Group (Semi-Log)	ITT	N	2

Header	Listing Number	Listing Title	Analysis Population	Interim Analysis	Priority
Figure	16.2.6.1.3.2	Individual Baseline-Corrected Plasma Levodopa Concentrations Over Time, by Treatment Group (Semi-Log)	ITT	N	2
Figure	16.2.6.1.3.3	Individual Plasma Carbidopa Concentrations Over Time, by Treatment Group (Semi-Log)	ITT	N	2
	16.2.6.1.4.1	Plasma Pharmacokinetic Parameter of Uncorrected Levodopa	PKP	N	1
	16.2.6.1.4.2	Plasma Pharmacokinetic Parameter of Baseline-Corrected Levodopa	PKP	N	2
	16.2.6.1.4.3	Plasma Pharmacokinetic Parameter of Carbidopa	PKP	N	2
	16.2.6.2	Efficacy data listing			
	16.2.6.2.1	Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Full Score	ITT	N	2
	16.2.6.2.2	Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III Motor Score	ITT	Y	1
	16.2.6.2.3	Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III Total Motor Score	ITT	Y	1
	16.2.6.2.4	Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III Total Motor Score - Response	ITT	Y	2
	16.2.6.2.5	Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III Total Motor Score - Area Under Curve	ITT	Y	2
	16.2.6.2.6	Evaluation of ON/OFF status	ITT	Y	2
	16.2.6.2.7	Time to ON/OFF status	ITT	Y	2
16.2.7		Adverse Event Listings			
	16.2.7.1	Adverse Events	ITT	Y	1

Header	Listing Number	Listing Title	Analysis Population	Interim Analysis	Priority
	16.2.7.2	Serious Adverse Events	ITT	Y	1
	16.2.7.3	Adverse Events leading to Study Discontinuation or Study Drug Withdrawal	ITT	Y	1
	16.2.7.4	Adverse Events Leading to Death	ITT	Y	1
16.2.8		Clinical Laboratory Data			
	16.2.8.1	Individual Hematology Results	ITT	Y	2
	16.2.8.2	Individual Biochemistry Results	ITT	Y	2
	16.2.8.3	Individual Urinalysis Results	ITT	Y	2
	16.2.8.4	Individual Microscopy Results	ITT	Y	2
16.4		Other Safety Data			
	16.4.1.1	Vital Signs	ITT	Y	2
	16.4.1.2	Detection of Orthostatic Hypotension	ITT	Y	2
	16.4.2	ECG Findings and Changes from Baseline	ITT	Y	2
	16.4.3	Dyskinesia Examination	ITT	Y	2
	16.4.4	Nasal Examination	ITT	Y	1
	16.4.5	Physical Examination	ITT	Y	2
	16.4.6	Subject Questionnaire	ITT	N	2
	16.4.7	Domiciled Status	ITT	N	2
	16.4.8	General Comments	ITT	N	2

17.2.2. Planned Summary Tables

The following tables are planned to be generated for the INP103-201 study (Note: Numbering is indicative only and may be updated based on CSR requirements):

Header	Table Number	Table Title	Analysis Population	Interim Analysis	Priority
14		Tables and Figures			
14.1		Demographic Data Summary and Tables			
	14.1.1	Subject Disposition			
	14.1.1.1	Study Participation and Disposition	ITT	N	1
	14.1.2	Demographics			
	14.1.2.1	Demographics	ITT	N	2
	14.1.3	Medications			
	14.1.3.1	Concomitant Medications	ITT	Y	2
	14.1.3.2	Rescue OFF Tx Allowed and Usual Morning anti-PD Medication	ITT	Y	2
14.2		Pharmacokinetic and Efficacy Summary Table			
	14.2.1	Pharmacokinetic – Levodopa			
	14.2.1.1.1	Uncorrected Plasma Levodopa Concentrations	ITT	Y	1
	14.2.1.1.2	Baseline-Corrected Plasma Levodopa Concentrations	ITT	N	2
	14.2.1.1.3	Plasma Carbidopa Concentrations	ITT	N	2
Figure	14.2.1.2.1	Mean Uncorrected Plasma Levodopa Concentrations (Linear)	ITT	Y	2
Figure	14.2.1.2.2	Mean Baseline-Corrected Plasma Levodopa Concentrations (Linear)	ITT	N	2
Figure	14.2.1.2.3	Mean Plasma Carbidopa Concentrations (Linear)	ITT	N	2

Header	Table Number	Table Title	Analysis Population	Interim Analysis	Priority
Figure	14.2.1.3.1	Mean Uncorrected Plasma Levodopa Concentrations (Semi-Log)	ITT	Y	2
Figure	14.2.1.3.2	Mean Baseline-Corrected Plasma Levodopa Concentrations (Semi-Log)	ITT	N	2
Figure	14.2.1.3.3	Mean Plasma Carbidopa Concentrations (Semi-Log)	ITT	N	2
	14.2.1.4.1	Plasma Pharmacokinetic Parameter of Uncorrected Levodopa	PKP	Y	2
	14.2.1.4.2	Plasma Pharmacokinetic Parameter of Baseline-Corrected Levodopa	PKP	N	2
	14.2.1.4.3	Plasma Pharmacokinetic Parameter of Carbidopa	PKP	N	2
	14.2.1.5	Dose Proportionality of Baseline-Corrected Levodopa	PKP	N	2
Figure	14.2.1.6	Relationship of Baseline-Corrected Levodopa Pharmacokinetic Parameters with Dose	PKP	N	2
	14.2.2	Efficacy summary table			
	14.2.2.1	Summary of Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III Score	ITT	Y	1
	14.2.2.2	MMRM of Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III Score	ITT	N	2
Figure	14.2.2.3	Individual Change from Baseline in Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III Score	ITT	N	2
	14.2.2.4	Summary of Cumulative Response	ITT	Y	2
	14.2.2.5	Summary of Time-to-Response	ITT	Y	2
	14.2.2.6	Duration of Response	ITT	N	2
Figure	14.2.2.7	Kaplan-Meier Plot for Time-to-Response	ITT	N	2
	14.2.2.8	Summary of AUC of change in Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III Score	ITT	N	2

Header	Table Number	Table Title	Analysis Population	Interim Analysis	Priority
	14.2.2.9	ANCOVA of AUC of change in Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III Score	ITT	N	2
	14.2.2.10	Summary of the Maximum Response	ITT	Y	2
	14.2.2.11	ANCOVA of The Maximum Response	ITT	N	2
	14.2.2.12	Summary of Time-to-ON	ITT	Y	2
Figure	14.2.2.13	Kaplan-Meier estimator for Time-to-ON status	ITT	N	2
	14.2.3	Pharmacokinetic versus Pharmacodynamic Relationship			
Figure	14.2.3.1	Time-matched Change from baseline in MDS-UPDRS Part III score versus uncorrected plasma L-Dopa concentrations	ITT	N	2
14.3		Safety Data Summary Tables			
	14.3.1	Adverse Events			
	14.3.1.1	Overall Summary of Treatment Emergent Adverse Events	Safety	Y	1
	14.3.1.2	Adverse Events onset within Benserazide Period	Benserazide Safety	N	2
	14.3.1.3	Treatment Emergent Adverse Events	Safety	Y	1
	14.3.1.4	Treatment Emergent Adverse Events by Severity	Safety	N	2
	14.3.1.5	Treatment-Related Treatment Emergent Adverse Events	Safety	N	2
	14.3.1.6	Serious Treatment Emergent Adverse Events	Safety	N	1
	14.3.2	Listings of Deaths, Other Serious and Significant Adverse Events	Not Applicable		

Header	Table Number	Table Title	Analysis Population	Interim Analysis	Priority
	14.3.3	Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events	Not Applicable		
	14.3.4	Clinical Laboratory Data			
	14.3.4.1	Hematology Results and Change from Baseline	Safety	N	2
	14.3.4.2	Biochemistry Results and Change from Baseline	Safety	N	2
	14.3.4.3	Urinalysis Results	Safety	N	2
	14.3.5	Vital Signs			
	14.3.5.1	Vital Signs Values and Change from Baseline	Safety	N	2
	14.3.5.2	Detection of Orthostatic hypotension	Safety	N	2
	14.3.6	ECG Findings			
	14.3.6.1	ECG Values and Change from Baseline	Safety	N	2
	14.3.6.2	ECG Clinical Assessment Results	Safety	N	2
	14.3.6.3	ECG Clinical Assessment Results: Criteria of QTc value	Safety	N	2
	14.3.7	Other Safety Result			
	14.3.7.1	Summary of Dyskinesia Examination	Safety	N	2
	14.3.7.2	Summary of Nasal Examination	Safety	N	2
	14.3.7.3	Summary of Abnormal Physical Examination	Safety	N	2