CLINICAL TRIAL CONSULTANTS AB

CONFIDENTIAL

Statistical analysis plan (SAP)

Sponsor:	*Sahlgrenska Academy,* *Gothenburg University*
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CTC project no:	*CTC project number*
Study title:	*Levodopa pharmacokinetics in patients with Parkinson's disease and symptom fluctuation: A phase I, open-label, randomized, multicentre, crossover study comparing intravenous and subcutaneous Infudopa with intestinal Duodopa*
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2 VERSION HISTORY

This statistical analysis plan (SAP) for study IPO-001 is based on the protocol dated 26 March 2019.

Table 1 SAP version history summary

SAP version	Approval date	Changes	Rationale
0.1	24JUN2020	-	Version ready for internal review
0.2	26JUN2020		Version ready for Sponsor review
1	11AUG2020	NA	Original version

3 INTRODUCTION

This SAP gives details regarding the statistical analyses and data presentation outlined in the final clinical study protocol (CSP) for the study *IPO-001*. Any changes from the final CSP are given in Section 9.

4 CLINICAL STUDY DETAILS

4.1 Clinical study objectives and endpoints

Table 2 Clinical study objective and endpoints

Objects	Estimations/Endpoints
Primary	
1. To demonstrate that Infudopa i.v. and s.c. yield steady state plasma concentrations of levodopa that are equivalent with those of Duodopa, and that the variability in plasma concentrations during the dosage interval is non-inferior to that obtained with Duodopa and to establish the absolute bioavailability of levodopa when given as Infudopa s.c. or Duodopa as compared to Infudopa i.v.	During the dosage interval in the subjects: 1.1 The steady-state plasma concentration of levodopa 1.2 The area under plasma concentration versus time curve (AUC) using log-linear trapezoidal rule - AUC calculated from time 0 to 16 hours (AUC_{0-16}) - AUC from 2 to 16 hours (AUC_{2-16}) - AUC from 8 to 16 hours (AUC_{8-16}) - AUC from time 0 to the last quantifiable plasma concentration (AUC_{0-last}) - AUC from time 0 to infinity (AUC_{0-inf}) 1.3 The coefficient of variation (CV) for plasma concentrations
Secondary	
2.1 To evaluate the safety of the products with special focus on the local tolerability at the injection sites of i.v. and s.c. administration.	2.1 Safety endpoints - Local tolerability scores at the injection site including pain, tenderness and itching rated by the subject using a horizontal 10-cm visual analogue scale (VAS) - Adverse events - Vital signs - Laboratory assessments - Draize scores
2.2 To establish the bioavailability of levodopa and carbidopa given s.c. and as Duodopa compared to the i.v. administration.	2.2 Bioavailability based on the AUC of levodopa and carbidopa given s.c. and as Duodopa compared to the i.v. administration
2.3 Compare other pharmacokinetic variables as well as motor function during treatment with s.c. and i.v. Infudopa versus Duodopa.	2.3.1 Video recordings endpoints - Percentage of ratings within the interval -1 to +1 on the treatment response scale (TRS) - Percentage of ratings within the interval -3 to -2 on the TRS - Percentage of ratings within the interval +2 to +3 on the TRS

	- Percentage of ratings within the interval -1 to +2 on the TRS 2.3.2 Parkinsons KinetiGraph (PKG) endpoints - Median bradykinesia score (BK) during normal active daytime (9–18) and for the full treatment time except the first hour - Median dyskinesia score (DK) during normal active daytime (9–18) and for the full treatment time except the first hour - Fluctuation score (FDS) during normal active daytime (9–18) and for the full treatment time except the first hour - FDS during normal active daytime (9–18) and for the full treatment time except the first hour - Percent time with tremor (PTT) during normal active daytime (9–18) and for the full treatment time except the first hour 2.3.3 Pharmacokinetic (PK) endpoints - Maximum observed concentration (C_{max}) - Time of the maximum observed plasma concentration (t_{max}) - The minimum plasma concentration during the 2-16 h dosing interval without interpolation (C_{min}) - Pre-administration observed plasma concentration (C_0). - Last determinable plasma concentration (C_{last}) - Elimination half-life determined from the terminal slope of the log-linear curve ($t_{1/2}$) - Average plasma concentration at the steady-state - Peak-trough fluctuation (PTF)
Tertiary/exploratory	
NA	NA

4.2 Clinical study design

This is a prospective, randomised, 3-period cross-over, open-label multicentre trial. Patients fulfilling all the inclusion and none of the exclusion criteria will be randomised to one of the three treatment arms. The trial includes patients with Parkinson's disease who are on Duodopa treatment because of severe on-off manifestation when on oral levodopa.

4.3 Statistical hypotheses

There will be no statistical hypothesis testing, besides the equivalence test.

4.4 Number of subjects

In the Pilot Study 5 subjects were included, receiving all treatments. In the Main Study, 20 subjects were included, of which 2 received only one treatment, giving 18 subjects with all treatments.

4.5 Randomisation

At randomisation, all eligible subjects were given a randomisation number that assigns them to one of the treatment groups. The randomisation numbers were sequentially allocated to the subjects in the order of randomisation. Each subject received the treatment regimen which is labelled with the randomisation number allocated to the patient.

Randomisation was performed by randomly assigning each research subject to one of the treatment groups in the specified ratio of 1:1:1.

Table 3. Randomisation table

	Dose group 1	**Dose group 2**	**Dose group 3**
Visit 2	Infudopa i.v.	Infudopa s.c.	LCIG
Visit 3	LCIG	Infudopa i.v.	Infudopa s.c.
Visit 4	Infudopa s.c.	LCIG	Infudopa i.v.

Subjects discontinuing treatment prematurely were replaced.

4.6 Blinding

This was an open-label study and no blinding was necessary. However, Draize scores and Video recordings (cf. Table 2) were blinded for the assessors.

5 STATISTICAL AND ANALYTICAL PLANS

5.1 Sample size determination

Sample size determinations are based on the primary pharmacokinetic variable from a similar study (Nyholm et al, 2013) regarding 16-hour intestinal infusion of Dudopa in advanced Parkinson's disease patients. Data from the five interim analysis patients (Pilot Study) are also used. A standard t-test model with continuity correction has been used (Microsoft Excel program, Pharm Assist Sweden AB). The Z-alpha level was 1.96 and Z-beta level was 0.84 for equivalence testing of 90% CI with the interval 0.80 to 1.25. The Z-alpha level was 1.65 and Z-beta level was 0.84 for non-inferiority testing of 90% CI with the interval 0.80 to 1.25.

The test suggests that 14 subjects are appropriate for the test of dose-normalized AUC_{0-inf} of levodopa. This number of subjects is valid both based on the Nyholm et al. 2013 data for levodopa-carbidopa intestinal gel (LCIG) (CV 24.5%), and the data in the interim study (CV 17.0% allowing as a safety margin for a 40% higher CV, 23.8%, giving n=14).

For the non-inferiority test of inter-subject CV, the sample size estimation suggests 18 subjects to be included.

Based both on the levodopa dose-adjusted AUC 0 to infinity and the inter-subject CV it is planned that 22 subjects will be recruited to the Main Study, also allowing for four dropouts.

5.2 Definition of analysis sets

5.2.1 Pilot Study (PS) analysis set

The Pilot Study analysis set (PSAS) consist of 5 subjects receiving all treatments and that were included in a first interim analysis of the study.

5.2.1.1 Pilot Study full analysis set (PS-FAS)

The FAS will consist of all subjects who have been randomised and received one dose of investigational medicinal product (IMP). This population will be used as the safety analysis set.

5.2.2 Main Study (MS) analysis set

The Main Study analysis set (MSAS) consist of 18 subjects receiving all treatments and 2 subjects receiving only one IMP, in total 20 subjects.

5.2.2.1 Main Study full analysis set (MS-FAS)

The MS-FAS will consist of all subjects who have been randomised and received one dose of investigational medicinal product (IMP). This population will be used as the safety analysis set.

5.2.2.2 Main Study pharmacokinetic analysis set (MS-PKAS)

The MS-PKAS will consist of all evaluable subjects who have received all 3 treatments during Visit 2 and Visit 3. The MS-PKAS includes all evaluable PK data appropriate for the evaluation of interest.

5.2.3 Use of analysis sets

The PS-FAS and MS-FAS populations will be used for both of efficacy and safety evaluation. MS-PKAS will be used for PK evaluations.

5.3 Definition of baseline

Baseline measurement is defined as the latest measurement prior to first dose of IMP. For each PK calculation will the pre-dose value be used as baseline.

5.4 Descriptive statistics

In general, all data collected will be presented with descriptive statistics. Descriptive statistics will include at least the number of subjects, mean, standard deviation (SD), median, minimum, and maximum for continuous data. Frequency and percentage will be provided for categorical data. Tables with descriptive statistics will be divided by treatment and assessment time, where applicable. Subject data listings will be sorted by treatment, subject and timing of assessments. Descriptive statistics will be separate for PS-FAS and MS-FAS populations.

5.5 Significance level

All hypothesis testing will use a 5% significance level (α=0.05), besides the equivalence testing.

5.6 Multiple comparisons/multiplicity

No adjustment for multiple comparison/multiplicity will be performed. All significant findings will be reviewed for medical relevance.

5.7 Handling of dropouts, missing data, and outliers

Outliers will be included in descriptive tables and listings and will not be handled separately in any analyses. No imputation of data will be performed.

5.8 Adjustment for covariates

No adjustments for covariates other than period, subject, and sequence are planned to be performed.

5.9 Multicentre studies

No adjustments for multicentre studies are planned to be performed.

5.10 Examination of subgroups

No examination of subgroups is planned to be performed.

5.11 Blind review

Not applicable.

6 SUBJECTS

6.1 Subject disposition

The subject disposition table, separate for PS-FAS and MS-FAS populations, will include the number of screened subjects, reasons for withdrawal prior to IMP, number of subjects for each IMP, reasons for withdrawal and number of completed subjects in the study. The table will also summarise the number of subjects in each study population. See tables and listings in the statistical output layout, section 14.

6.2 Baseline characteristics and demographics

The following baseline characteristics will be summarised:

- Gender
- Age
- Race/Ethnicity
- Medical history
- HIV
- Hepatitis

7 TREATMENT INFORMATION AND EXTENT OF EXPOSURE

Listings and descriptive statistics will be separate for PS-FAS and MS-FAS populations.

7.1 Active treatment

The number of subjects on each IMP will be tabulated with start time, stop time, morning bolus dose (ml), continuous infusion rate (ml/ h), total dose (mg and mg/kg B.W.) and duration of application that will be tabulated using listings and descriptive statistics.

7.2 Prior and concomitant medications

Prior and concomitant medication data will be listed and tabulated by Anatomical Therapeutic Chemical (ATC) code. Prior and concomitant medications will be coded according to the World Health Organization (WHO) ATC classification system.

8 STATISTICAL METHODOLOGY

Listings and descriptive statistics will be separate for PS-FAS and MS-FAS populations.

All parameters will be presented by treatment and assessment timepoint using descriptive statistics. Additional statistical analyses are specified below.

8.1 Primary endpoint(s) analysis

8.1.1 Definition of endpoint(s)

8.1.1.1 General pharmacokinetics

The PK analysis will be based on the PSAS and MSAS and performed by Sponsor. The PK parameters will be calculated for levodopa, carbidopa, and 3-OMD be assessed include, but are not limited to:

- C_{max} - The maximum observed concentration; obtained directly from the plasma concentration vs. time data
- t_{max} – The time of the maximum observed plasma concentration.
- C_{min} - The minimum (or trough) plasma concentration during the 2-16 h dosing interval, directly obtained from the experimental data of plasma concentration versus time, without interpolation
- $AUC_{0\text{-}16}$ - The area under the plasma concentration versus time curve, calculated from time 0 to 16 hours, computed using the log-linear trapezoidal rule (method of the lin-up log down trapezoidal rule).
- $AUC_{2\text{-}16}$ - The area under the plasma concentration versus time curve, calculated from time 2 to 16 hours, computed using the log-linear trapezoidal rule (method of the lin-up log down trapezoidal rule).
- $AUC_{0\text{-}2}$ - The area under the plasma concentration versus time curve, calculated from time 0 to 2 hours, computed using the log-linear trapezoidal rule (method of the lin-up log down trapezoidal rule). This represents the time period during the dosage interval when early onset of plasma concentrations is most representative.
- $AUC_{8\text{-}16}$ - The area under the plasma concentration versus time curve, calculated from time 8 to 16 hours, computed using the log-linear trapezoidal rule (method of the lin-up log down trapezoidal rule). This represents the time period during the dosage interval when apparent steady-state conditions of plasma concentration will be reached.
- (C_0) - .Pre-administration observed plasma concentration

- C_{last} – Last determinable plasma concentration
- $AUC_{0\text{-}last}$ – The area under the plasma concentration versus time curve, calculated from time 0 to the last quantifiable plasma concentration (C_{last}), computed using the log-linear trapezoidal rule (method of the lin-up log down trapezoidal rule).
- $t_{½}$ – Elimination half-life determined from the terminal slope of the log-linear curve
- $AUC_{0\text{-}inf}$ – The area under the plasma concentration versus time curve, calculated from time 0 to infinity, computed using the log-linear trapezoidal rule (method of the lin-up

log down trapezoidal rule) including the rest AUC from the last quantifiable sampling point up to infinity (calculated using C_{last} and the elimination slope).

- CL_{obs} - $AUC_{0\text{-}inf}$/Dose
- C_{av} – The average plasma concentration at the $steady - state = \frac{AUC_{8-16}}{8}$.
- PTF - The peak − trough fluctuation $= (C_{max} - C_{\min}) \cdot \frac{14}{AUC_{2-16}}$.

PK variables will be calculated based on the actual sampling times rather than the scheduled sampling times.

If there is a baseline plasma concentration of levodopa and carbidopa that is >LLOQ this concentration value will be subtracted from the actual plasma concentration value at baseline, and subsequent concentration values assuming an elimination of the substances that is in accordance with the subject's own elimination rate during the LCIG treatment (calculated from 16 h and up). This will be made until the so calculated subtraction value is insignificant (i.e. < LLOQ). No such baseline correction will be made for 3-OMD.

8.1.1.2 Statistical analysis

The statistical analysis will be based on the *MS-PKAS*, delivered by Sponsor.

This section refers to the primary objective #1 (endpoint 1.3) and secondary objective #2 (endpoint 2.2).

Statistical assessments of dosage normalised levodopa and carbidopa $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}16}$, $AUC_{0\text{-}2}$, $AUC_{2\text{-}16}$, and $AUC_{8\text{-}16}$ by analysis of variance (ANOVA) will be made on the logarithmic values, with back-transformation to nominal values of point estimates and confidence interval (CI). These variables will also be tested with dosage un-normalised values. The terms to be used in the ANOVA model will be sequence, patient within sequence, period, and formulation (i.v. or s.c. Infudopa and Duodopa; test and reference, respectively).

The statistical method for testing relative dosage normalised levodopa and carbidopa bioavailability will be based on the 90% CI for the ratio of the population means (test/reference). These statistical tests will also be done with dosage un-normalised values. The acceptance range for AUC ratio of the 90% CI for levodopa will be 0.80 to 1.25. These tests will be performed for Dose group 1 (i.v.) and Dose group 2 (s.c.) vs. Dose group 3 (Duodopa; reference) comparison, and for Dose group 1 (i.v. reference) vs. Dose group 2 (s.c.).

The CV or %SD for levodopa and carbidopa will be calculated for plasma concentration between 2 and 16 h by dividing the SD for each individual curve with the mean value of plasma concentration between 2 and 16 h. The mean value of plasma concentration will be calculated for each curve as $AUC_{2\text{-}16}$/14. Basic statistics for the CV will then be calculated per dose group. The one-sided 90% CI of the inter subject CV will be calculated for Dose group 1 (i.v.) and Dose group 2 (s.c.) vs. Dose group 3 (Duodopa; reference) comparison, and for Dose group 1 (i.v. reference) vs. Dose group 2 (s.c.). It will also be tested with paired t-tests if there are significant differences in inter-subject CV between treatments (i.v. vs. Duodopa, s.c. vs. i.v., and s.c. vs. Duodopa).

See tables and listings in statistical output layout, section 14.

8.1.2 Sensitivity analysis

No sensitivity analyses are planned to be performed.

8.1.3 Supplementary analyses

No supplementary analyses are planned to be performed.

8.2 Secondary endpoint(s) analysis

8.2.1 Definition of endpoint(s)

8.2.1.1 Adverse events

This section refers to secondary objective #2.1 (endpoint 2.1).

An overview of all AEs, including serious adverse events (SAEs), intensity, relationship to the IMP, and deaths will be presented by system organ class (SOC) and preferred term (PT).

Incidence of AEs and SAEs will be summarised by SOC and PT.

Time to onset of AE will be calculated from start of administration to start of AE. Duration of AE will be calculated from start of AE until end of AE. Descriptive statistics will be presented only if the number of AEs are ≥3.

For SOC ”General disorders and administration site conditions” and for each PT by treatment group will be presented AE counts and % of patients with AE for durations within the time intervals 0-0.5, >0.5-1, >1-17 h (end of infusion, including late stops), >17 h-2 d, >2-7, >7-14, >14-35, >35-50, >50 d. In addition, a corresponding presentation will be made for the time intervals 0-0.5 h, >0.5-17 h, and >17 h, including the range of observed durations.

For AE PT “Injection site hematoma” and “Injection site discoloration” and categories “present “or “absent” will be for each group given descriptive statistics for levodopa dose in mg, in mg/kg, B.W., and B.M.I.

All AE data will be listed by subject and include the verbatim term entered by the investigator.

See tables and listings in statistical output layout, section 14.

8.2.1.2 Safety laboratory

This section refers to secondary objective #2.1 (endpoint 2.1).

All safety laboratory will be summarised. Data will be presented with absolute and percent change from baseline at each treatment. Mean graphs for Base Excess, Total Ca2+, Ionised Ca2+, Mg2+ will be presented.

See tables and listings in statistical output layout, section 14.

8.2.1.3 Vital signs

This section refers to secondary objective #2.1 (endpoint 2.1).

Vital signs (sitting pulse and sitting blood pressure) will be summarised. Data will be presented with absolute and percent change from baseline at each treatment. Vital signs will also be presented in a spaghetti graph.

See tables and listings in statistical output layout, section 14.

8.2.1.4 Local tolerability

This section refers to secondary objective #2.1 (endpoint 2.1).

The local tolerability will be documented with photographs, which will be evaluated by a dermatologist. Pre-defined local tolerability AEs will be documented by the investigator, and pain, tenderness and pruritus with VAS by the subjects (including spaghetti plots). Local tolerability will be presented with descriptive statistics by treatment and change from baseline.

Draize scores of erythema and edema will be presented with absolute and percent change from baseline at each treatment, and frequency distribution of necrosis and eschar formation.

See tables and listings in statistical output layout, section 14.

8.2.1.5 TRS

This section refers to secondary objective #2.3 (endpoint 2.3.1).

A Treatment Response Scale (TRS) (Nyholm et al, 2005) will be used for a global assessment of clinical response. The TRS ranges from -3 (severe "off") to +3 ("on" with severe dyskinesia), where 0 is "on" without any dyskinesias.

The percentage will be calculated for the TRS ratings within the interval -1 to +2 that is, a clinically desirable, functional "on" state accepting mild parkinsonism and not more than moderate dyskinesia, and percentage of ratings within the intervals -3 to -2 (severe to moderate "off") and +3 ("on" with severe dyskinesia). Interrater reliability will be assessed using percentage agreement between the raters and κ (kappa) coefficients. Kappa coefficients between 0.60 and 0.80 are considered "good" and coefficients higher than 0.80 "very good."

See tables and listings in statistical output layout, section 14.

8.2.1.6 Parkinson's KinetiGraph

This section refers to secondary objective #2.3 (endpoint 2.3.2).

Parkinson Kinetigraph recordings will be obtained from the wrist on the subjects most disease affected side. Recordings will start in the morning of day 1 of each treatment visit and continue for up to 24h or until the subject leaves the trial site on day 2. The accelerometer data will be uploaded and proprietary algorithms (Global Kinetics Corporation, Melbourne, Australia) will be used to calculate the 25^{th}, 50^{th} and 75^{th} percentiles of a bradykinesia score (BK) and a dyskinesia score (DK) over the time-period 09-18 as well as +1h to +16h from pump start. Tremor episodes consisting of at least 10 seconds meeting the operational tremor criteria defined by Braybrook et al (2016) will be recorded and the percent of time with ongoing tremor between 9-18 as well as +1h to +16h after pump start will be calculated. The

interquartile ranges of BK and DK will be used to calculate a fluctuation score (FDS) for the measured time periods. Other outcomes will be median BK, DK, FDS scores as well as percent time with tremor in the normal daytime period (9-18) as well as the entire infusion period following the first hour after treatment start.

See tables and listings in statistical output layout, section 14.

8.2.1.7 PK

This section refers to primary objective #1 (endpoint 1.1 and 1.2) and secondary objective #2.3 (endpoint 2.3.3). For more detailed information se section 8.1.1.1, General pharmacokinetics.

Levodopa, carbidopa, and 3-OMD plasma profiles over time and PK parameter values will be presented using descriptive statistics and summarised by treatment. Individual spaghetti plots will be generated for the plasma concentration, both for logarithmic and linear scales. All PK data will be presented in a descriptive table by treatment.

See tables and listings in statistical output layout, section 14.

8.2.2 Sensitivity analysis

No sensitivity analyses are planned to be performed.

8.2.3 Supplementary analyses

No supplementary analyses are planned to be performed.

8.3 Tertiary/exploratory endpoint(s) analysis

Not applicable.

8.4 Discontinuation

Patients who discontinue from IMP treatment will be tabulated. The reason for discontinuation will be given. For discontinuation due to AE, the AEs will be given.

8.5 Other analyses

No other analyses are planned to be performed.

8.6 Interim analysis

There has been an interim analysis of first 5 subjects in the study (Clinical Study Interim Report 2019-01-15). There was a new interim analysis of PK and safety data of four completed subjects after the study was re-started. Four subjects were considered sufficient for the interim analysis for reasonable determination of mean values of numerical variables and frequencies of distribution of binominal variables, including reasonable estimates of confidence intervals. The following data were included in the interim analysis:

- Blood PK samples
- Inspection of local dermal area/scoring including photos
- Adverse events

A Board of the Interim Study Analysis met to discuss the results and conclude if the study should continue or not.

The possible outcomes the Board were evaluated, and the basis for the decisions was:

1. Are the plasma levels of levodopa following s.c. and i.v. too high or too low as compared to Duodopa at any time during the treatment, thereby necessitating a dosage adjustment?

Decision rules:

- If the deviation from Duodopa is of a magnitude that is deemed clinically important, appropriate changes in the dosing protocol in the study will be considered.

- If the deviation from Duodopa at steady-state is larger than established limits for bioequivalence (80% - 125%), the appropriate changes in the dosing protocol will be made.

2. Is the local and systemic tolerance acceptable?

Decision rule:

If adverse events have occurred that, according to the committee, can be attributed to the study drug and make it ethically unjustifiable to pursue the trial, the trial will be stopped. However, the trial can continue after the appropriate changes have been made if it can be convincingly demonstrated that changes in the protocol—e.g. a change of infusion rate, infusion system, an increase in the number of subcutaneous infusion sites or other feasible actions—will mitigate the risk for further adverse events.

In case the dosage regimen is changed, or other major change is made to the CSP an amendment must be submitted to MPA and EC.

Only descriptive statistics were performed. There was no statistical hypothesis testing.

The members of the Board of the Interim Study Analysis are presented in Appendix C in the CSP version 5.1.

9 CHANGES FROM THE CSP

- Define study populations, FAS and PKAS.

10 STATISTICAL DELIVERABLES

The following documents will be delivered:

- SAP
- Statistical analyses and descriptive tables

11 SOFTWARE

All statistical analyses will be performed using SAS Version 9.4 (SAS institute, Cary, NC).

Sponsor will use PKSolver, An add-in program for pharmacokinetic and pharmacodynamic data analysis in Microsoft Excel by Zhang et al. (2010), PMID: 20176408. Validation of the program was made for each installation into Excel, and at each daily run of analyses.

12 APPROVAL

Issued by:

_____ _____

Responsible Biostatistician — Date (dd-Mmm-yyyy)

CTC Representative

Approved by:

_____ _____

Date (dd-Mmm-yyyy)

Sponsor Representative

13 SUPPORTIVE DOCUMENTATION

13.1 Appendix 1 – list of abbreviations

Abbreviation of term	Explanation
AE	Adverse event
ATC	Anatomical-therapeutic-chemical
AUC	Area under the plasma concentration versus time curve
BK	Bradykinesia score
CF	Clean file
CRF	Case report form
CSP	Clinical study protocol
CV	Coefficient of variation
BMI	Body mass index
DK	Dyskinesia score
EC	Ethics Committee
FAS	Full analysis set
FDS	Fluctuation score
IMP	Investigational medicinal product
i.v.	Intravenous
LLOQ	Lower limit of quantification
MedDRA	Medical dictionary for regulatory affairs
MPA	Medicinal Products Agency
PK	Pharmacokinetic
PKAS	Pharmacokinetic analysis set
PKG	Parkinson's KinetiGraph
PT	Preferred term
PTT	Percent time with tremor
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis systems
s.c.	Subcutaneous
SD	Standard deviation

TRS	Treatment response scale
UPDRS	Unified Parkinson's disease rating scale
VAS	Visual analogue scale
WHO	World health organization

13.2 Appendix 2 – changes to protocol-planned analyses

14 STATISTICAL OUTPUT LAUOUT

Listings and descriptive statistics will be separate for PS-FAS and MS-FAS populations.

14.1 Template tables

Template tables includes in general how tables will be generated.

14.1.1 Descriptive statistic table – continuous variables

				Infudopa i.v.	Infudopa s.c.	LCIG	[Total]
Assessment (unit)	Result category	Assessment timepoint					
[Parameter 1] (unit)	Measured value	[Assessment timepoint 1]	N	x	x	x	x
			Mean (SD)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)
			Median (Min, Max)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)
			Geometric mean (CV%)	x.xxx (x.x)	x.xxx (x.x)	x.xxx (x.x)	x.xxx (x.x)
			95% CI	x.xxx; x.xxx	x.xxx; x.xxx	x.xxx; x.xxx	x.xxx; x.xxx
		[Assessment timepoint 2]	N	x	x	x	x
			Mean (SD)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)
			Median (Min, Max)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)
			Geometric mean (CV%)	x.xxx (x.x)	x.xxx (x.x)	x.xxx (x.x)	x.xxx (x.x)
			95% CI	x.xxx; x.xxx	x.xxx; x.xxx	x.xxx; x.xxx	x.xxx; x.xxx
	Absolute change from baseline	[Assessment timepoint 2]	N	x	x	x	x
			Mean (SD)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)
			Median (Min, Max)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)
			Geometric Mean (CV%)	x.xxx (x.x)	x.xxx (x.x)	x.xxx (x.x)	x.xxx (x.x)
			95% CI	x.xxx; x.xxx	x.xxx; x.xxx	x.xxx; x.xxx	x.xxx; x.xxx

Assessment (unit)	Result category	Assessment timepoint		Infudopa i.v.	Infudopa s.c.	LCIG	[Total]
			T-test p-value				x.xxxx
	Relative change from baseline (%)	[Assessment timepoint 2]	N	x	x	x	x
			Mean (SD)	x.x (x.x)	x.xxx (x.xxx)	x.xxx (x.xxx)	x.xxx (x.xxx)
			Median (Min, Max)	x.x (x, x)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)	x.xxx (x.xx, x.xx)
			Geometric Mean (CV%)	x.xxx (x.x)	x.xxx (x.x)	x.xxx (x.x)	x.xxx (x.x)
			95% CI	x.xxx; x.xxx	x.xxx; x.xxx	x.xxx; x.xxx	x.xxx; x.xxx
			T-test p-value				x.xxxx

Data based on [ANALYSIS SET]. Baseline at [Assessment timepoint 1]. ND: Not defined - no evaluable observations. NA: Not available - no non-missing observations. NC: Not calculated - number of non-missing observations less than 3
[STUDYID] [DOMAIN]: [PARAMETER CATEGORY], SAS program: descriptive_stat_tables.sas. Run by: [USERNAME], [USER EMAIL] [TIMESTAMP]

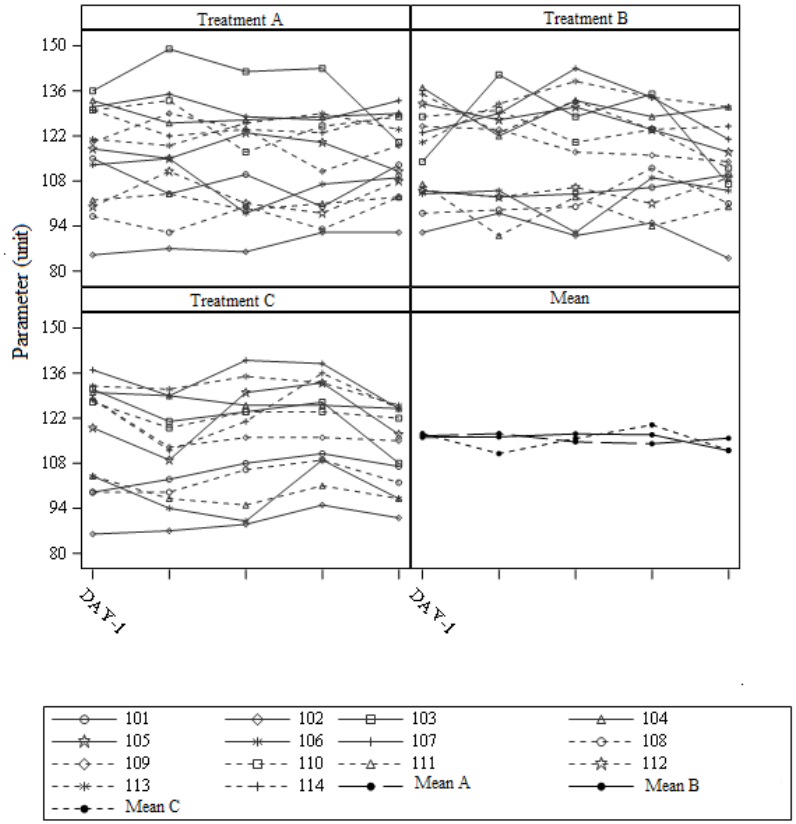
14.1.2 Descriptive statistic table – discrete variables

Assessment	Assessment timepoint	Result	Infudopa i.v.	Infudopa s.c.	LCIG	[Total]
[Parameter 1]	[Assessment timepoint 1]	[RESULT 1]	x(x.x%)/X	x(x.x%)/X	x(x.x%)/X	x(x.x%)/X
		[RESULT 2]	x(x.x%)/X	x(x.x%)/X	x(x.x%)/X	x(x.x%)/X
	[Assessment timepoint 2]	[RESULT 1]	x(x.x%)/X	x(x.x%)/X	x(x.x%)/X	x(x.x%)/X
		[RESULT 2]	x(x.x%)/X	x(x.x%)/X	x(x.x%)/X	x(x.x%)/X

[STUDYID] [DOMAIN]: [PARAMETER CATEGORY], SAS program: descriptive_stat_tables.sas. Run by: [USERNAME], [USER EMAIL] [TIMESTAMP]

14.2 Template figures

14.2.1 Spaghetti plot



Data based on [ANALYSIS SET].
[STUDYID] [DOMAIN]: [PARAMETER CATEGORY], SAS program: individual_figures.sas. Run by: [USERNAME], [USER EMAIL] [TIMESTAMP]

* mean optional

14.3 Tables

Table 14.1.1 Baseline characteristics and demographics (analysis set)

		Total (N=X)
Age (years)	n/nmiss	x/x
	Mean (SD)	x.x (x.x)
	Median (Min, Max)	x.x (x,x)
Body Mass Index (kg/m^2)	n/nmiss	x/x
	Mean (SD)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x, x.x)
Height (cm)	n/nmiss	x/x
	Mean (SD)	x.x (x.x)
	Median (Min, Max)	x.x (x,x)
Weight (kg)	n/nmiss	x/x
	Mean (SD)	x.xx (x.xx)
	Median (Min, Max)	x.xx (x.x,x.x)
Sex	Female	x (x.x%)
	Male	x (x.x%)
Ethnicity	Hispanic Or Latino	x (x.x%)
	Not Hispanic Or Latino	x (x.x%)
Race	American Indian Or Alaska Native	x (x.x%)
	Asian	x (x.x%)
	Black or African American	x (x.x%)
	Native Hawaiian or other Pacific Islander	x (x.x%)
	White	x (x.x%)

```
[STUDYID] Summarised demographics data.
Data based on the [analysis set].
SAS program: summary_demographics.sas. Run by: [USERNAME], [USER EMAIL] [TIMESTAMP]
```

Table 14.1.2 Subject disposition (all subjects)

	Total
Screened subjects	x
Withdrawn prior to [dose]	x
--- Withdrawal reason x	x
--- Withdrawal reason x	x
--- Withdrawal reason x	x
Included subjects	x
--- [Dose group 1]	x
--- [Dose group 2]	x
--- [Dose group 3]	x
Withdrawn subjects	x
--- Withdrawal reason x	x
--- Withdrawal reason x	x
--- Withdrawal reason x	x
Completed subjects	x
--- [Dose group 1]	x
--- [Dose group 2]	x
--- [Dose group 3]	x
Included in [FAS]	x
Included in [pop x]	x
Included in [pop x]	x
Subjects at [VISIT 1]	x
Subjects at [VISIT 2]	x
Subjects at [VISIT 3]	x
Subjects at [VISIT 4]	x

	Total
Subjects at [VISIT 5]	x

[STUDYID] Disposition, SAS program: disposition.sas. Run by: [USERNAME], [USER EMAIL] [TIMESTAMP]

Table 14.1.3.x Medical history events by system organ class and preferred term (analysis set) by treatment

System organ class Preferred term	Total N=X n(%)	m
Total	**x(x.x%)**	**x**
SOC 1s	**x(x.x%)**	**x**
SOC 1 PT 1	x(x.x%)	x
SOC 1 PT 2	x(x.x%)	x
SOC 1 PT 3	x(x.x%)	x
SOC 2	**x(x.x%)**	**x**
SOC 2 PT 1	x(x.x%)	x
SOC 2 PT 2	x(x.x%)	x

n, number of subjects; m, number of events
Percentages are based on the number of subjects in the treatment period included in the [analysis set]
[STUDYID] Medical history events by system organ class and preferred term, [analysis set], SAS program: mh_summary_by_soc_and_pt.sas. Run by: [USERNAME], [USER EMAIL] [TIMESTAMP]

Table 14.1.4. Concomitant medications by ATC levels 4 and 5 (analysis set) by treatment

ATC level 4 ATC level 5	Total N=X n(%)	m
Total	**x(x.x%)**	**X**
ATC 4	**x(x.x%)**	**X**
ATC 5	x(x.x%)	X

n, number of subjects; m, number of events;

Percentages are based on the number of subjects in the full analysis set

Table 14.1.5. Exposure of IMP (analysis set)

See appendix table – 14.1.1 Descriptive statistic table – continuous variables

Table 14.2.x.x Comparison between treatment for selected PK variables (analysis set)

PK variable	Test product	Reference product	90% CI lower bound	Ratio of geometric mean	90% CI upper bound	P-value	Inter subject CV (%)
Parameter (unit)	Xxx	xxx	x.xxx	x.xxxx	x.xxx	x.xxxx	xx
xxx	Xxx	xxx	x.xxx	x.xxxx	x.xxx	x.xxxx	xx
xxx	Xxx	xxx	x.xxx	x.xxxx	x.xxx	x.xxxx	xx

Data based on [ANALYSIS SET]
[STUDYID][TITLE],SAS program:[SAS PROGRAM]. Run by: [USERNAME], [USER EMAIL] [TIMESTAMP]

Table 14.3.x.x Overview of adverse events (analysis set)

	Infudopa i.v. N=X		Infudopa s.c. X=X		LCIG X=X		Total N=X	
	n(%)	m	n(%)	m	n(%)	m	n(%)	m
Any AE	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x
Any SAE	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x
Any AE leading to withdrawal	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x
Any AE leading to death	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x
Causality								
Possibly Related	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x
Probably Related	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x
Unlikely Related	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x
Severity								
Mild	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x
Moderate	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x
Severe	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x
Life-threatening	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x
Death	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x

n, number of subjects; m, number of events
Percentages are based on the number of subjects in the treatment period included in the [analysis set].
Adverse events that occurred during [ELEMENTS] are omitted from summary.
[STUDYID] Overview of adverse events, [analysis set], SAS program: ae_summary_tables.sas. Run by: [USERNAME], [USER EMAIL] [TIMESTAMP]

Table 14.3.x.x Adverse events by system organ class and preferred term (analysis set)

	Infudopa i.v. N=X		Infudopa s.c. N=X		LCIG N=X		Total N=X	
System organ class Preferred term	n(%)	m	n(%)	m	n(%)	m	n(%)	m
SOC 1s	**x(x.x%)**	**x**	**x(x.x%)**	**x**	**x(x.x%)**	**x**	**x(x.x%)**	**x**
SOC 1 PT 1	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x
SOC 1 PT 2	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x
SOC 1 PT 3	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x
SOC 2	**x(x.x%)**	**x**	**x(x.x%)**	**x**	**x(x.x%)**	**x**	**x(x.x%)**	**x**
SOC 2 PT 1	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x
SOC 2 PT 2	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x	x(x.x%)	x

n, number of subjects; m, number of events
Percentages are based on the number of subjects in the treatment period included in the [analysis set]
Adverse events that occurred during [ELEMENTS] are omitted from summary.
[STUDYID] Adverse events by system organ class and preferred term, [analysis set], SAS program: ae_summary_by_soc_and_pt.sas. Run by: [USERNAME], [USER EMAIL] [TIMESTAMP]

Table 14.3.x.x. Vital signs measurements (analysis set)

See appendix table – 14.1.1 Descriptive statistic table – continuous variables

Figure 14.3.x.x. Vital signs measurements (analysis set)

See appendix table – 14.2.1 Spaghetti plot

Table 14.3.x.x. Local tolerability measurements (analysis set)

See appendix table – 14.1.1 Descriptive statistic table – continuous variables

Table 14.3.x.x. Local tolerability interpretation (analysis set)

See appendix table – 14.1.2 Descriptive statistic table – discrete variables

Table 14.3.x.x. Treatment Response Scale (analysis set) by treatment

No template tables.

Table 14.3.x.x. Parkinson's KinetiGraph (analysis set) by treatment

No template tables.

Table 14.3.x.x. Plasma concentration (analysis set)

See appendix table – 14.1.2 Descriptive statistic table – discrete variables

Figure 14.3.x.x. Plasma concentration (analysis set)

See appendix table – 14.2.1 Spaghetti plot

Table 14.3.x.x. PK variables (analysis set)

See appendix table – 14.1.2 Descriptive statistic table – discrete variables

14.4 Listings

Listing 16.2.1.1. Discontinued subjects (All subjects)

Listing 16.2.2.1. Protocol deviations (All subjects)

Listing 16.2.3.1 Subjects excluded from PKAS (All subjects)

Listing 16.2.3.2 Population definitions (All subjects)

Listing 16.2.3.3. Non-eligible subjects (All subjects)

Listing 16.2.4.1. Demography (analysis set)

Listing 16.2.4.2 Medical history (analysis set)

Listing 16.2.5. Prior and concomitant medications (analysis set)

Listing 16.2.6.x. Plasma concentration (analysis set)

Listing 16.2.7. x. PK parameters (analysis set)

Listing 16.2.8.1. Adverse events, part 1 (analysis set)

Listing 16.2.8.2. Adverse events, part 2 (analysis set)

Listing 16.2.8.3. Serious adverse events, part 1 (analysis set)

Listing 16.2.8.4. Serious adverse events, part 2 (analysis set)

Listing 16.2.8.5. Serious adverse events, seriousness criteria (analysis set)

Listing 16.2.9. x. Local tolerability (analysis set)

Listing 16.2.9. x. Laboratory assessments (analysis set)

Listing 16.2.10. x. Vital signs (analysis set)

Listing 16.2.11.x. ECG (analysis set)

Listing 16.2.12. x. Physical examinations (analysis set)

Listing 16.2.13.x. Treatment Response Scale (analysis set)

Listing 16.2.14.x. Video recordings (analysis set)

Listing 16.2.15.x. Parkinson's KinetiGraph variables (analysis set)

Listing 16.2.16.x. VAS (analysis set)

Listing 16.2.17.x. Food intake (analysis set)

Listing 16.2.18. x. Disposition (All subjects)

Listing 16.2.19. x. Subject visits (All subjects)

Listing 16.2.20. x. Subject elements (All subjects, SDTM names)