STATISTICAL ANALYSIS PLAN

A DOSE-FINDING STUDY FOR LEVODOPA, CARBIDOPA AND ODM-104 TEST FORMULATIONS AFTER REPEATED ADMINISTRATION IN HEALTHY MALES

3112005
COMDOS 1

Phase I study

Standard: GCP

The statistical analysis plan is approved and valid from the date of the last e-signature on the last page

Clinical Study Director: Aila Holopainen
Study Statistician: Mikko Vahteristo
Development Leader: Juha Ellmén

Statistical analysis plan written by: Mikko Vahteristo

Sponsor: ORION PHARMA

Confidential

Table of contents

1 Abbreviations

AE	Adverse event
AUC	Area under the concentration-time curve
BMI	Body mass index
BP	Blood pressure
C_{max}	Peak concentration in plasma
C_{min}	Minimum observed concentration
CV	Coefficient of variation
ECG	Electrocardiogram
HR	Heart rate
IR	Immediate release
ITT	Intention-to-treat
MR	Modified release
PD	Parkinson's disease
PG	Pharmacogenomic(s)
PK	Pharmacokinetic(s)
PP	Per-protocol
SAE	Serious adverse event
$t_{½}$	Terminal elimination half-life
t_{max}	Time to reach peak concentration in plasma

2 General remarks

The purpose of this document is to describe the statistical methodology for this clinical study, including also plans of populations to be used and the plans how the results will be presented.

3 Overall study design and plan

This is a phase I, open, repeated dose, randomised PK study in healthy males. The study will be conducted at one centre.

The study will consist of 4 parallel groups (Groups 1-4). All groups will have a crossover design with 4 treatment periods, each lasting for 7 days. The total duration of the study will be approximately 10-15 weeks for each study subject.

4 Study objectives

4.1 Primary objective

The primary objective is to compare PK of levodopa after repeated administration as follows (Groups 1-4):

Group 1:

- A1=50 mg of MR levodopa + 12.5 mg of carbidopa
- B1=50 mg of MR levodopa + 65 mg of carbidopa
- C1=50 mg of MR levodopa + 65 mg of carbidopa + 50 mg of ODM-104
- D1=50 mg of MR levodopa + 65 mg of carbidopa + 100 mg of ODM-104

Group 2:

- A2=100 mg of MR levodopa + 25 mg of carbidopa
- B2=100 mg of MR levodopa + 65 mg of carbidopa
- C2=100 mg of MR levodopa + 65 mg of carbidopa + 50 mg of ODM-104
- D2=100 mg of MR levodopa + 65 mg of carbidopa + 100 mg of ODM-104

Group 3:

- A3=150 mg of MR levodopa + 37.5 mg of carbidopa
- B3=150 mg of MR levodopa + 65 mg of carbidopa
- C3=150 mg of MR levodopa + 65 mg of carbidopa + 50 mg of ODM-104
- D3=150 mg of MR levodopa + 65 mg of carbidopa + 100 mg of ODM-104

Group 4:

- A4=100 mg of IR levodopa + 25 mg of carbidopa (Sinemet®)
- B4=100 mg of MR levodopa + 65 mg of carbidopa
- C4=100 mg of MR levodopa + 25 mg of carbidopa + 100 mg of ODM-104
- D4=100 mg of MR levodopa + 65 mg of carbidopa + 100 mg of ODM-104

The primary objective is to compare PK of 3 different strengths of levodopa after repeated administration in combination with carbidopa and ODM-104.

ODM-104 and carbidopa dose effects will be studied with the 3 MR levodopa strengths and compared with the standard levodopa formulation. Primary comparisons for each of the 4 treatment groups will be performed for levodopa PK between the treatments. The resulting PK data will be used to select the optimal combination of levodopa, carbidopa and ODM-104 for subsequent clinical studies.

4.2 Secondary objectives

The secondary objectives are to determine the PK properties of 3-OMD, carbidopa and ODM-104 in plasma after repeated administration of the different combinations.

5 Statistical hypotheses

The primary variable for the evaluation of PK of levodopa is AUC_{0-24} to describe the total levodopa exposure. Primary comparison will be made within levodopa dose level groups, between crossover treatment arms levodopa / 12.5, 25 or 37.5 mg of carbidopa and levodopa / 65 mg of carbidopa / 100 mg of ODM-104. I.e. comparisons A1 vs. D1, A2 vs. D2, A3 vs. D3, and A4 vs. D4 will be the primary ones.

Other crossover comparisons will be performed and considered as secondary. Parallel group comparisons may be performed. The conclusions on possible differences between treatments will be based on both overall evaluation of levodopa concentration-time profiles and formal statistical analyses of PK parameters.

H_0: $AUC_{0\text{-}24,\ \text{levodopa/carbidopa /ODM-104}} = AUC_{0\text{-}24,\ \text{levodopa/carbidopa}}$
H_1: $AUC_{0\text{-}24,\ \text{levodopa/carbidopa /ODM-104}} \neq AUC_{0\text{-}24,\ \text{levodopa/carbidopa}}$

6 Determination of sample size

The sample size estimation is based on earlier ODM-104 phase I study 3112003. Sample size is estimated using the AUC_{0-24}. Sample size estimation is based on the results from 12 subjects that completed treatment periods with levodopa 100 mg / carbidopa 25 mg / entacapone 200 mg and MR levodopa 100 mg / carbidopa 65 mg / ODM-104 100 mg. The latter treatment arm with ODM-104 and 65 mg of carbidopa increased exposure by 22% (AUC_{0-24} 14022.2 vs. 17092.6). Within subject variability is estimated to be 0.1386 (√MSE in logarithmic scale). It is assumed that MR levodopa 100 mg / carbidopa 65 mg / ODM-104 100 mg will increase exposure by 40% compared to MR levodopa 100 mg / carbidopa 25 mg.

When the sample size in each sequence is 3 (with a total sample size of 12), a crossover design will have 80% power to detect a difference in means of 0.336 assuming that the within subject variation is 0.139 using a crossover ANOVA with a 0.1 two-sided significance level. To allow drop outs 14 subjects per group and 56 subjects in total will be randomized into this study with 4-treatment, 4-period William's crossover design. This will provide adequate power for the primary comparison. In case there are premature discontinuations the sponsor will decide case-by-case whether replacement subjects will be entered into the study. Replacement subjects will be randomized to go through all 4 treatment periods. Discontinued study subjects are not allowed to re-enter the study.

7 General statistical considerations

7.1 Analysis populations

The datasets derived from individual study subjects will be classified into following three classes prior to database lock and before carrying out any statistical analyses:

- Modified intention-to-treat (mITT) population: all randomized subjects who have received at least one dose of study treatment. The difference between ITT and mITT is that subjects in mITT will be included to have the treatment actually administered. In ITT, subjects are included in the treatment they were intended to be administered.

- Per-protocol (PP) population: Subjects who have completed the study according to the protocol without major protocol violations.
- Dosing intervals, where subject experience emesis during the treatment period at Day 7 and following dosing intervals during the period, will be removed from analysis using PP population.
- Periods with PK parameters covering entire Day 7 (e.g. AUC∞) will be excluded from the PP population analysis entirely, in case of emesis.
- If the emesis is experienced at time point 14 hours or thereafter during the last dosing interval, the dosing interval and period will be included into the PP population
- Safety population is the same as the modified ITT population.

The role of each population is described in Table 1.

Table 1. Populations that will be used in tabulations and statistical analyses.

Primary efficacy variable	Secondary efficacy variables	Demographics Additional variables	Safety variables
PP	PP	mITT	Safety population
mITT	mITT		

7.2 Statistical issues

7.2.1 Significance level and confidence intervals

90% confidence intervals and p-values will be produced between different treatments. A two-sided significance level of 10% will be considered the level of statistical significance. Confidence intervals and p-values will be presented up to four decimal places.

7.2.2 Handling of dropouts or missing data

In general, missing data or partial data will not be imputed, and statistical analyses will be performed for observed cases only. Possible missing data will be included in statistical calculations via mixed models theory, where missing data can be utilized by setting the subject as random effect in the statistical model. Possible sensitivity analyses may be carried out to evaluate the robustness of the statistical results, that is, particularly the impact of potential outliers.

7.2.3 Handling of baseline values

Screening visit will be used as a baseline for all post baseline variables. If multiple values of a variable are recorded at screening:

- For safety laboratory measurements the last of these values will be used as baseline.
- For ECG the average of these values will be calculated and used as baseline.

7.2.4 Interim analyses and data monitoring

Interim analyses are not planned.

7.2.5 Multicentre studies

This is a single centre study.

7.2.6 Multiplicity

For the primary comparisons, there is only one primary comparison in each group, thus multiplicity correction is not needed. For secondary comparisons, where several treatments are included, all pairwise comparisons will be adjusted according to Tukey method.

7.2.7 Examination of subgroups

No subgroup analyses are planned.

7.2.8 Checking model assumptions

Assumptions for parametric testing will be checked by visual inspection of residuals. If the residuals do not follow normal distribution closely enough, non-parametric comparison methods (e.g. Kruskall-Wallis test for PK variables) or use of transformation will be considered.

7.2.9 Transformations

PK parameters (at least AUC and Cmax) will be analysed after logarithm transformation.

7.2.10 Handling of outliers and sensitivity analyses

If outliers are detected based on residual examination, a sensitivity analysis without the outliers may be performed to evaluate potential impact to the results.

7.2.11 Methods for handling multiple time points

PK parameters C_{max}, AUC, t_{max} and $t_{½}$ will be calculated and used in statistical comparisons. When modelling PK parameters that are calculated by dosing intervals, treatment by dosing interval interaction will be included in the statistical models.

7.2.12 Descriptive statistics

The following statistics will be provided for continuous variables: N, mean, SD, min, median and max. In PK variables also geometric mean and coefficient of variation (CV%) will be calculated. Because log-normal distribution, the formula $CV\% = 100 \times \sqrt{\exp(\sigma^2 - 1)}$, where σ^2 is MSE of the statistical analysis of log transformed data, will be used. For categorical variables frequency counts and percentages will be presented. All mean, median, standard deviation, and if feasible quartile values will be presented to one more decimal place than the raw values. Minimum and maximum will be presented to the same precision as the raw values.

All percentages will be rounded to one decimal place, with the exception of 0 and 100, which will be presented as integers.

8 Statistical analyses to be used in this study

8.1 Disposition of subjects

The number of subjects will be tabulated for the following populations:

- Screened
- Randomised
- Modified ITT
- PP
- Safety
- Discontinued study
- Completed study

The disposition and number and reasons for withdrawal and discontinuations will be listed and, if needed, tabulated by treatment sequence. Reasons for excluding subjects or subject periods from pharmacokinetic analyses will be listed. Data from subjects who failed at screening will be included only in the disposition tabulations and data listings.

8.2 Demographic and other baseline characteristics

Demographic and other baseline characteristics will be tabulated by treatment sequence. Medications taken by the subjects before, during, and after the study will be classified by ATC Level 3 and drug name, and will be tabulated and/or listed as appropriate. WHO – DD will be used for coding prior and concomitant medications. No statistical tests will be performed.

8.3 Extent of exposure and measurements of treatment compliance

Each study subject will receive the study treatments under observation of the site personnel. The exposure will be verified by measurement of drug concentrations. Any deviation from the planned compliance and exposure will be listed. Drug administration and plasma concentration data will be listed and tabulated by treatment. The number of subjects exposed to study treatments and the number of doses administered will be tabulated by treatments.

8.4 Analysis of pharmacokinetic variables

Table 2 lists the PK parameters which will be derived from the concentration-time data of levodopa, carbidopa, 3-OMD and, ODM-104.

Table 2. PK parameters to be calculated for levodopa, carbidopa, 3-OMD and ODM-104.

Parameter	Levodopa	Carbidopa	3-OMD	ODM-104
C_{max}	X[1]	X[1]	X[1]	X[1]
$C_{max,tau}$	X[1]			X

t_{max}	X	X	X	X
$t_{max,tau}$	X			X
$C_{min,tau}$	X[1]			X
$C_{min,tau,actual}$	X[1]			
AUC_{tau}	X[1]			X
AUC_{0-16}	X[1]			
AUC_{0-24}	X[1]	X[1]	X[1]	X[1]
AUC_{∞}	X			X
$t_{½}$	X			X
λ_z	X			X
$C_{max}/C_{min,tau}$	X[1]			
$C_{max}/C_{min,tau,actual}$	X[1]			
$C_{max}/C(16h)$	X[1]			
PTF_{tau}	X[1]			
PTF_{0-16h}	X[1]			

[1] Statistical analysis will be performed

8.4.1 Primary PK parameter

The primary PK variable for the evaluation of PK of levodopa is AUC0-24 to describe the total levodopa exposure. The primary PK variable will be summarised using descriptive statistics by treatment and analysed using a mixed linear model with 90% CI applicable for the crossover design. The statistical model will include treatment and period as fixed effects and subject as a random effect. Sensitivity analysis adjusted for subject weight and age will be performed.

The following SAS-code for the primary comparison will be applied:

```
proc mixed data=pkparam2 plots=all alpha=0.10;
 class subject trtpcd visit;
 model log_auc = trtpcd visit / ddfm=KR outp=Resid solution;
random subject;
lsmeans trtpcd / diff cl alpha=0.10;
ods output  tests3=testCross lsmeans=lsmeansCross
diffs=diffscross;
by group;
run;
```

The following SAS-code for the sensitivity analysis will be applied:

```
proc mixed data=pkparam2 plots=all alpha=0.10;
 class subject trtpcd visit;
 model log_auc = trtpcd visit weightkg age / ddfm=KR outp=Resid
solution;
random subject;
lsmeans trtpcd / diff cl alpha=0.10 adjust=tukey ADJDFE=ROW;
ods output  tests3=testCross2 lsmeans=lsmeansCross2
diffs=diffscross2;
by group;
run;
```

8.4.2 Secondary PK parameters

The secondary PK variable is $C_{min,tau}$, which is used to describe minimum concentration during the dosing intervals. Statistical evaluation for secondary PK variable will be done using similar methods as for primary variable, except the statistical model will include also the dosing interval as fixed effect.

The following SAS-code for the analysis will be applied:

```
proc mixed data=pkparam2 alpha=0.10;
 class subject trtpcd interval visit;
 model log_auc = trtpcd interval trtpcd*interval visit /
ddfm=KR outp=Resid solution;
 random subject*visit;
 lsmeans trtpcd trtpcd*interval / diff cl alpha=0.10
adjust=tukey ADJDFE=ROW;
 ods output  tests3=testCross lsmeans=lsmeansCross
diffs=diffscross;
 by group;
 run;
```

8.4.3 Additional variables

The ratio of the maximum observed concentration (Cmax) in a dosing interval and the observed concentration at the end of the dosing interval, Cmax/Cmin,tau, which is used to describe levodopa fluctuation during the dosing intervals and other PK variables of levodopa, 3-OMD, carbidopa and ODM-104 will be evaluated as additional variables.

Levodopa fluctuation ratios ($C_{max}/C_{min,tau}$, $C_{max}/C_{(16\ h)}$, PTF_{tau} and $PTF_{(0\text{-}16)}$, and $AUC_{0\text{-}24}$, C_{max} and $C_{min,tau}$ will be the main PK variables of interest.

Drug concentrations will be tabulated by time and treatment with descriptive statistics.

8.5 Evaluation and analysis of safety and tolerability

Safety will be evaluated by recording heart rate, systolic and diastolic blood pressure, 12-lead electrocardiogram (ECG), physical examination findings, laboratory safety assessments and

adverse events (AEs). Suicidality will be assessed with the Columbia-Suicide Severity Rating Scale (C-SSRS).

8.5.1 Adverse events

Adverse events (AEs) reported after administration of the study treatment will be classified by System organ classes (SOC) and preferred terms using the MedDRA dictionary.

The number and proportion (%) of subjects having each AE will be given by treatment group. The numbers will be additionally broken down by severity (mild, moderate, severe) and by the causality (related, not related).

All serious adverse events (SAEs) and other significant AEs will be evaluated case by case. Additionally, narrative descriptions will be included in the study report for all SAEs and certain other significant AEs.

8.5.2 Laboratory safety variables

Laboratory values and changes from baseline (screening value) in laboratory values will be summarised using descriptive statistics. The number and proportion of subjects with laboratory values outside the normal range will be summarised by visit for each laboratory analyte. Unscheduled laboratory measurements will not be used in tables. They will be included in the listings.

8.5.3 Vitals signs, physical findings, and other observations related to safety

Vital signs (systolic and diastolic BP and HR) at each visit and change from baseline (screening value) in each vital sign will be summarised using descriptive statistics. 12-lead ECG parameters at each time point and change from baseline (screening value) will be summarised using descriptive statistics. Physical examination and C-SSRS findings will be tabulated.

8.6 Additional analyses

8.7 Changes in the statistical plans from those presented in the clinical study protocol

8.8 Execution of statistical analyses

Statistical analyses will be performed by or under the supervision of the Department of Biostatistics and Support Functions of Orion Pharma.

8.9 Software

Statistical analyses, tables and subject data listings will be performed with SAS® for Windows version 9.4 (SAS Institute Inc., Cary, NC, USA).

9 Reference list

1. SAS, Institute Inc., Cary, NC, USA.

10 Appendices

10.1 List of tables, figures and graphs

14 Post-text tables and figures

14.1 Demographic data

Table 14.1.1	Disposition of subjects
Table 14.1.2.1	Reasons for excluding data from the statistical analyses of pharmacokinetic parameters
Table 14.1.2.2	Reasons for study discontinuation
Table 14.1.3	Demographic and other baseline characteristics
Table 14.1.4	Medical history and current medical conditions
Table 14.1.5.1	Prior treatments
Table 14.1.5.2	Concomitant treatments during study treatment periods
Table 14.1.5.3	Concomitant treatments after end of study treatment
Table 14.1.6	Extent of exposure

14.2 Pharmacokinetic data

Table 14.2.1.1	Levodopa concentration (ng/ml)
Table 14.2.1.2.1	AUCtau (h*ng/mL) of levodopa
Table 14.2.1.2.2	Statistical analysis for AUCtau of levodopa
Table 14.2.1.3.1	AUC0-24 (h*ng/mL) of levodopa
Table 14.2.1.3.2	Statistical analysis for AUC0-24 of levodopa
Table 14.2.1.4.1	AUC0-16 (h*ng/mL) of levodopa
Table 14.2.1.4.2	Statistical analysis for AUC0-16 of levodopa
Table 14.2.1.5	AUCinf (h*ng/mL) of levodopa
Table 14.2.1.6.1	Cmax,tau (ng/mL) of levodopa
Table 14.2.1.6.2	Statistical analysis for Cmax,tau of levodopa
Table 14.2.1.7.1	Cmax (ng/ml) of levodopa
Table 14.2.1.7.2	Statistical analysis for Cmax of levodopa
Table 14.2.1.8.1	Cmin,tau (ng/mL) of levodopa
Table 14.2.1.8.2	Statistical analysis for Cmin,tau (ng/mL) of levodopa
Table 14.2.1.8.3	Actual Cmin,tau (ng/mL) of levodopa
Table 14.2.1.8.4	Statistical analysis for actual Cmin,tau (ng/mL) of levodopa
Table 14.2.1.9.1	Cmax / Cmin ratio tau of levodopa
Table 14.2.1.9.2	Statistical analysis of Cmax / Cmin ratio tau of levodopa

Table 14.2.1.9.3	Actual Cmax / Cmin ratio tau of levodopa
Table 14.2.1.9.4	Statistical analysis of actual Cmax / Cmin ratio tau of levodopa
Table 14.2.1.10.1	Cmax / C(16h) of levodopa
Table 14.2.1.10.2	Statistical analysis of Cmax / C(16h) of levodopa
Table 14.2.1.11	tmax,tau (h) of levodopa
Table 14.2.1.12	tmax (h) of levodopa
Table 14.2.1.13	t1/2 (h) of levodopa
Table 14.2.1.14	Lambda z of levodopa
Table 14.2.1.15.1	PTFtau of levodopa
Table 14.2.1.15.2	Statistical analysis for PTFtau of levodopa
Table 14.2.1.16.1	PTF0-16 of levodopa
Table 14.2.1.16.2	Statistical analysis for PTF0-16 of levodopa
Table 14.2.2.1	Carbidopa concentrations (ng/ml)
Table 14.2.2.2.1	AUC0-24 (h*ng/mL) of Carbidopa
Table 14.2.2.2.2	Statistical analysis for AUC0-24 (h*ng/mL) of Carbidopa
Table 14.2.2.3.1	Cmax (ng/ml) of Carbidopa
Table 14.2.2.3.2	Statistical analysis for Cmax (ng/ml) of Carbidopa
Table 14.2.2.4	tmax (h) of Carbidopa
Table 14.2.3.1	3-ODM concentrations (ng/ml)
Table 14.2.3.2.1	AUC0-24 (h*ng/mL) of 3-ODM
Table 14.2.3.2.2	Statistical analysis for AUC0-24 (h*ng/mL) of 3-ODM
Table 14.2.3.3.1	Cmax (ng/ml) of 3-ODM
Table 14.2.3.3.2	Statistical analysis for Cmax (ng/ml) of 3-ODM
Table 14.2.3.4	tmax (h) of 3-ODM
Table 14.2.4.1	ODM-104 concentrations (ng/ml)
Table 14.2.4.2	AUC0tau (h*ng/mL) of ODM-104
Table 14.2.4.3	AUC0-24 (h*ng/mL) of ODM-104
Table 14.2.4.4	Statistical analysis of AUC0-24 (h*ng/mL) of ODM-104
Table 14.2.4.5	AUCinf (h*ng/mL) of ODM-104
Table 14.2.4.6	Cmax,tau (ng/ml) of ODM-104
Table 14.2.4.7	Cmax (ng/ml) of ODM-104
Table 14.2.4.8	Statistical analysis of Cmax (ng/ml) of ODM-104
Table 14.2.4.9	Cmin,tau (ng/ml) of ODM-104
Table 14.2.4.10	tmax,tau (h) of ODM-104
Table 14.2.4.11	tmax (h) of ODM-104
Table 14.2.4.12	t½ (h) of ODM-104
Table 14.2.4.13	Lambda z of ODM-104

14.3 Safety data

Table 14.3.1.1	Summary of adverse events during study treatment (subject and event count)
Table 14.3.1.2	Adverse events during study treatment (subject and event count)

Table 14.3.1.3	Adverse events during study treatment by severity (subject count)
Table 14.3.1.4	Adverse events related to study treatment (subject and event count)
Table 14.3.1.5	Adverse events during study treatment by severity and causality (event count)
Table 14.3.1.6	Adverse events before start of study treatment (subject and event count)
Table 14.3.1.7	Adverse events at the end of study (subject and event count)
Table 14.3.2.1	Summary listing of deaths, other serious and significant adverse events
Table 14.3.2.2	Listing of deaths
Table 14.3.2.3	Listing of serious adverse events
Table 14.3.2.4	Listing of adverse events leading to premature discontinuation
Table 14.3.2.5	Listing of other significant adverse events
Table 14.3.2.6	Listing of special situations
Table 14.3.3.1	Summary listing of narratives of deaths, other serious and significant adverse events
Table 14.3.4	Listing of significant abnormal laboratory values
Table 14.3.5.1.1	Haematology
Table 14.3.5.1.2	Changes from baseline in haematology
Table 14.3.5.1.3	Shift tables for haematology variables
Table 14.3.5.2.1	Chemistry
Table 14.3.5.2.2	Changes from baseline in chemistry
Table 14.3.5.2.3	Shift tables for chemistry variables
Table 14.3.5.3	Serology
Table 14.3.5.4.1	Urinalysis
Table 14.3.5.4.2	Shift tables for urinalysis variables - Safety population
Table 14.3.6.1.1	Supine heart rate (bpm)
Table 14.3.6.1.2	Changes from baseline in supine heart rate (bpm)
Table 14.3.6.2.1	Supine diastolic blood pressure (mmHg)
Table 14.3.6.2.2	Changes from baseline in supine diastolic blood pressure (mmHg)
Table 14.3.6.3.1	Supine systolic blood pressure (mmHg)
Table 14.3.6.3.2	Changes from baseline in supine systolic blood pressure (mmHg)
Table 14.3.7.1.1	Summary of 12-lead ECG findings
Table 14.3.7.1.2	Shift table for 12-lead ECG findings
Table 14.3.7.2.1	PR interval (ms)
Table 14.3.7.2.2	Changes from baseline in PR interval (ms)
Table 14.3.7.3.1	QRS interval (ms)
Table 14.3.7.3.2	Changes from baseline in QRS interval (ms)
Table 14.3.7.4.1	RR interval (ms)
Table 14.3.7.4.2	Changes from baseline in RR interval (ms)
Table 14.3.7.5.1	QT interval (ms)
Table 14.3.7.5.2	Changes from baseline in QT interval (ms)
Table 14.3.7.7.1	QTc [Fridericia] interval (ms)
Table 14.3.7.7.2	Changes from baseline in QTc [Fridericia] interval (ms)

Table 14.3.7.8.1	QT interval (categorical analyses)
Table 14.3.7.8.2	Changes from baseline in QT interval (categorical analyses)
Table 14.3.7.10.1	QTc [Fridericia] interval (categorical analyses)
Table 14.3.7.10.2	Changes from baseline in QTc [Fridericia] interval (categorical analyses)
Table 14.3.1.8	Physical examination
Table 14.3.1.9	Suicidality assessment by C-SSRS during treatment
Table 14.3.1.9.1	Suicidality assessment by C-SSRS - Screening

14.4 Figures

Figure 14.4.1.1	Mean ± (SEM) levodopa concentration profile
Figure 14.4.1.2	Individual levodopa concentration profiles
Figure 14.4.1.3	Individual levodopa concentration profiles by subject
Figure 14.4.2.1	Mean ± (SEM) carbidopa concentration profile
Figure 14.4.2.2	Individual carbidopa concentration profiles
Figure 14.4.2.3	Individual carbidopa concentration profiles by subject
Figure 14.4.3.1	Mean ± (SEM) 3-OMD concentration profile
Figure 14.4.3.2	Individual 3-OMD concentration profiles
Figure 14.4.3.3	Individual 3-OMD concentration profiles by subject
Figure 14.4.4.1	Mean ± (SEM) ODM-104 concentration profile
Figure 14.4.4.2	Individual ODM-104 concentration profiles
Figure 14.4.4.3	Individual ODM-104 concentration profiles by subject
Figure 14.4.5.1	Mean ± (SEM) heart rate - Supine
Figure 14.4.5.2	Mean ± (SEM) change of heart rate - Supine
Figure 14.4.5.3	Individual profiles of heart rate - Supine
Figure 14.4.6.1	Mean ± (SEM) systolic blood pressure - Supine
Figure 14.4.6.2	Mean ± (SEM) change of systolic blood pressure - Supine
Figure 14.4.6.3	Individual profiles of systolic blood pressure - Supine
Figure 14.4.7.1	Mean ± (SEM) diastolic blood pressure - Supine
Figure 14.4.7.2	Mean ± (SEM) change of diastolic blood pressure - Supine
Figure 14.4.7.3	Individual profiles of diastolic blood pressure - Supine
Figure 14.4.8.1	Mean ± (SEM) of PR interval
Figure 14.4.8.2	Mean ± (SEM) change of PR interval
Figure 14.4.8.3	Individual profiles of PR interval
Figure 14.4.9.1	Mean ± (SEM) of QRS interval
Figure 14.4.9.2	Mean ± (SEM) change of QRS interval
Figure 14.4.9.3	Individual profiles of QRS interval
Figure 14.4.10.1	Mean ± (SEM) of RR interval
Figure 14.4.10.2	Mean ± (SEM) change of RR interval
Figure 14.4.10.3	Individual profiles of RR interval

Figure 14.4.11.1	Mean ± (SEM) of QT interval
Figure 14.4.11.2	Mean ± (SEM) change of QT interval
Figure 14.4.11.3	Individual profiles of QT interval
Figure 14.4.12.1	Mean ± (SEM) of QTcB interval
Figure 14.4.12.2	Mean ± (SEM) change of QTcB interval
Figure 14.4.12.3	Individual profiles of QTcB interval
Figure 14.4.13.1	Mean ± (SEM) of QTcF interval
Figure 14.4.13.2	Mean ± (SEM) change of OTcF interval
Figure 14.4.13.3	Individual profiles of QTcF interval

10.2 List of subject data listings

16.2. SUBJECT DATA LISTINGS

The section headings are given in italics, and other headings are actual listings for data.

16.2.1 Discontinued subjects and disposition

16.2.1.1 Study discontinuations

16.2.1.2 Disposition of subjects

16.2.1.3 Study dates

16.2.2 Protocol deviations

16.2.2.1 Protocol deviations

16.2.3 Subjects and observations excluded from efficacy analyses/statistical analyses of pharmacokinetic parameters

16.2.3.1 Reasons for excluding observations from efficacy analyses/PK parameters

16.2.4 Demographic data

16.2.4.1 Demographic and other baseline characteristics

16.2.4.2 Medical history and current medical conditions

16.2.4.3 Concomitant treatments

16.2.5 Compliance data and/or drug concentration data

16.2.5.1 Concentration data of ODM-104

16.2.5.2 Concentration data of levodopa carbidopa and 3-OMD

16.2.6 Pharmacokinetic data

16.2.6.1 Study treatment administration and blood sampling times

16.2.6.2 Pharmacokinetic parameters of ODM-104

16.2.6.3 Pharmacokinetic parameters of levodopa

16.2.6.4 Pharmacokinetic parameters of carbidopa

16.2.6.5 Pharmacokinetic parameters of 3-OMD

16.2.7 Adverse events

16.2.7.1 Adverse events before start of study treatment

16.2.7.2 Adverse events after start of study treatment

16.2.8 Laboratory measurements

16.2.8.1 Laboratory measurements

16.2.9 Vital signs, physical findings and other observations related to safety

16.2.9.1 Vital signs

16.2.9.2 Physical examination

16.2.9.3 12-lead ECG

16.2.9.4 Suicidality assessments using C-SSRS

16.2.10.1 Water intake and meals

Note! In case no observation fulfils the listing criteria's, e.g. no discontinuations, an empty list is produced.

10.3 Table templates

Examples of tables.

STUDY 3112005 DRAFT Page: 1 (1)

Table 14.1.1 Disposition of subjects
Modified Intention to treat population

	Group 1 (N=XX)	Group 2 (N=XX)	Group 3 (N=XX)	Group 4 (N=XX)	Total (N=XX)
	n (%)	n (%)	n (%)	n (%)	n (%)
Screened					82
Randomised	XX (XXX)	XX (XXX)	XX (XXX)	XX (XXX)	XX (XXX)
Intent-to-treat population	XX (XXX)	XX (XXX)	XX (XXX)	XX (XXX)	XX (XXX)
Per-protocol population	XX (XXX)	XX (XXX)	XX (XXX)	XX (XXX)	XX (XXX)
Safety population	XX (XXX)	XX (XXX)	XX (XXX)	XX (XXX)	XX (XXX)
Completed study	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Discontinued study	X (XX.X)	X (X.X)	X (XX.X)	X (X.X)	X (XX.X)

Program: T_14_1_1_Disposition of subjects.sas Date: 23MAY17:08:17

Table 14.1.3 Demographic and other baseline characteristics
Modified Intention to treat population

		Group 1 (N=XX)	Group 2 (N=XX)	Group 3 (N=XX)	Group 4 (N=XX)	Total (N=XX)
		n (%)	n (%)	n (%)	n (%)	n (%)
Gender	MALE	XX (XXX)	XX (XXX)	XX (XXX)	XX (XXX)	XX (XXX)
Race	CAUCASIAN	XX (XXX)	XX (XX.X)	XX (XXX)	XX (XX.X)	XX (XX.X)
	ASIAN	X (X.X)	X (X.X)	X (X.X)	X (X.X)	X (X.X)
Age (years)	N	XX	XX	XX	XX	XX
	Mean	XX.X	XX.X	XX.X	XX.X	XX.X
	SD	XX.X	XX.X	XX.X	XX.X	XX.X
	Min	XX	XX	XX	XX	XX
	Median	XX.X	XX.X	XX.X	XX.X	XX.X
	Max	XX	XX	XX	XX	XX
Weight (kg)	N	XX	XX	XX	XX	XX
	Mean	XX.X	XX.X	XX.X	XX.X	XX.X
	SD	X.X	X.X	XX.X	XX.X	X.X
	Min	XX	XX	XX	XX	XX
	Median	XX.X	XX.X	XX.X	XX.X	XX.X
	Max	XX	XX	XXX	XX	XXX
Height (cm)	N	XX	XX	XX	XX	XX
	Mean	XXX.X	XXX.X	XXX.X	XXX.X	XXX.X
	SD	X.X	X.X	X.X	X.X	X.X
	Min	XXX	XXX	XXX	XXX	XXX
	Median	XXX.X	XXX.X	XXX.X	XXX.X	XXX.X
	Max	XXX	XXX	XXX	XXX	XXX

Table 14.2.1.2.1 AUCtau (h*ng/mL) of levodopa
Per protocol population

		A1 (N=XX)	B1 (N=XX)	C1 (N=XX)	D1 (N=XX)
AUC 0-3.5h	N	XX	XX	XX	XX
	Gmean	XXXX.XX	XXXX.XX	XXXX.XX	XXXX.XX
	Mean	XXXX.XX	XXXX.XX	XXXX.XX	XXXX.XX
	SD	XXX.XX	XXX.XX	XXX.XX	XXX.XX
	CV%	XX.XX	XX.XX	XX.XX	XX.XX
	Min	XXXX.X	XXXX.X	XXXX.X	XXX.X
	Median	XXXX.XX	XXXX.XX	XXXX.XX	XXXX.XX
	Max	XXXX.X	XXXX.X	XXXX.X	XXXX.X
AUC 3.5-7h	N	XX	XX	XX	XX
	Gmean	XXXX.XX	XXXX.XX	XXXX.XX	XXXX.XX
	Mean	XXXX.XX	XXXX.XX	XXXX.XX	XXXX.XX
	SD	XXXX.XX	XXX.XX	XXX.XX	XXX.XX
	CV%	XX.XX	XX.XX	XX.XX	XX.XX
	Min	XXXX.X	XXXX.X	XXXX.X	XXXX.X
	Median	XXXX.XX	XXXX.XX	XXXX.XX	XXXX.XX
	Max	XXXX.X	XXXX.X	XXXX.X	XXXX.X
AUC 7-10.5h	N	XX	XX	XX	XX
	Gmean	XXXX.XX	XXXX.XX	XXXX.XX	XXXX.XX
	Mean	XXXX.XX	XXXX.XX	XXXX.XX	XXXX.XX
	SD	XXXX.XX	XXX.XX	XXX.XX	XXX.XX
	CV%	XX.XX	XX.XX	XX.XX	XX.XX
	Min	XXXX.X	XXXX.X	XXXX.X	XXXX.X
	Median	XXXX.XX	XXXX.XX	XXXX.XX	XXXX.XX
	Max	XXXX.X	XXXX.X	XXXX.X	XXXX.X
AUC 10.5-14h	N	XX	XX	XX	XX
	Gmean	XXXX.XX	XXXX.XX	XXXX.XX	XXXX.XX
	Mean	XXXX.XX	XXXX.XX	XXXX.XX	XXXX.XX
	SD	XXX.XX	XXX.XX	XXX.XX	XXX.XX
	CV%	XX.XX	XX.XX	XX.XX	XX.XX
	Min	XXXX.X	XXXX.X	XXXX.X	XXXX.X
	Median	XXXX.XX	XXXX.XX	XXXX.XX	XXXX.XX
	Max	XXXX.X	XXXX.X	XXXX.X	XXXX.X

Program: T_14_2_1_2_1_Levodopa AUC_tau.sas Date: 23MAY17:08:38

Table 14.2.1.3.1 AUC0-24 (h*ng/mL) of levodopa
Per protocol population

		A1 (N=XX)	B1 (N=XX)	C1 (N=XX)	D1 (N=XX)
AUC0 24h	N	XX	XX	XX	XX
	Gmean	XXXXX.XX	XXXXX.XX	XXXXX.XX	XXXXX.XX
	Mean	XXXXX.XX	XXXXX.XX	XXXXX.XX	XXXXX.XX
	SD	XXXX.XX	XXXX.XX	XXXX.XX	XXXX.XX
	CV%	XX.XX	XX.XX	XX.XX	XX.XX
	Min	XXXX.X	XXXX.X	XXXX.X	XXXX.X
	Median	XXXXX.XX	XXXXX.XX	XXXXX.XX	XXXXX.XX
	Max	XXXXX.X	XXXXX.X	XXXXX.X	XXXXX.X

Program: T_14_2_1_3_1_Levodopa AUC0-24.sas Date: 23MAY17:08:40

Table 14.2.1.3.2 Statistical analysis for AUC0-24 of levodopa
Per protocol population

Analysis of variance

Effect			Estimate (Geometric Mean)	Stderr	90% Confidence Interval	P-value
Fixed Effects						
Formulation			.	.		X.XXXX
Period			.	.		X.XXXX
Least Square Means						
Formulation	A1		XXXXX.XXX	X.XXXX	(XXXXX.XX ,XXXXX.XX)	<.XXXX
Formulation	B1		XXXXX.XXX	X.XXXX	(XXXXX.XX ,XXXXX.XX)	<.XXXX
Formulation	C1		XXXXX.XXX	X.XXXX	(XXXXX.XX ,XXXXX.XX)	<.XXXX
Formulation	D1		XXXXX.XXX	X.XXXX	(XXXXX.XX ,XXXXX.XX)	<.XXXX
Differences in Least Square Means						
Formulation	A1	B1	X.XXXXXXX	X.XXXX	(X.XXXX , X.XXXX)	X.XXXX
Formulation	A1	C1	X.XXXXXXX	X.XXXX	(X.XXXX , X.XXXX)	X.XXXX
Formulation	A1	D1	X.XXXXXX	X.XXXX	(X.XXXX , X.XXXX)	X.XXXX
Formulation	B1	C1	X.XXXXXX	X.XXXX	(X.XXXX , X.XXXX)	X.XXXX
Formulation	B1	D1	X.XXXXXXX	X.XXXX	(X.XXXX , X.XXXX)	X.XXXX
Formulation	C1	D1	X.XXXXXXX	X.XXXX	(X.XXXX , X.XXXX)	X.XXXX

Table 14.3.1.1 Summary of adverse events during study treatment (subject and event count)
Safety population

		A1 (N=XX) n (%)	B1 (N=XX) n (%)	C1 (N=XX) n (%)	D1 (N=XX) n (%)
Subject count	AEs	X (XX.X)	X (XX.X)	X (XX.X)	X (XX.X)
	Related AEs	X (XX.X)	X (XX.X)	X (XX.X)	X (XX.X)
	AEs leading to discontinuation of study				
	Mild AEs	X (XX.X)	X (XX.X)	X (XX.X)	X (XX.X)
	Moderate AEs	X (XX.X)	X (XX.X)	X (XX.X)	X (XX.X)
	Severe AEs				
	SAEs				
Event count	AEs	XX	XX	XX	XX
	Related AEs	X	XX	XX	XX
	AEs leading to discontinuation of study				
	Mild AEs	X	XX	X	XX
	Moderate AEs	X	X	XX	X
	Severe AEs				
	SAEs				

Program: T_14_3_1_1_Summary of AEs.sas Date: 23MAY17:08:57

Table 14.3.1.2 Adverse events during study treatment (subject and event count)
Safety population

System Organ Class Preferred Term	B1 (N=XX) Subjects n (%)	Events n	C1 (N=XX) Subjects n (%)	Events n	A1 (N=XX) Subjects n (%)	Events n	D1 (N=XX) Subjects n (%)	Events n
Cardiac disorders								
Total	X (X.X)	X	X (X.X)	X				
Cardiovascular insufficiency			X (X.X)	X				
Palpitations	X (X.X)	X						
Gastrointestinal disorders								
Total	X (XX.X)	X	X (XX.X)	X	X (XX.X)	X		
Abdominal discomfort	X (X.X)	X	X (X.X)	X				
Abdominal pain			X (X.X)	X				
Abdominal pain lower					X (X.X)	X		
Diarrhoea	X (XX.X)	X	X (X.X)	X				
Flatulence			X (X.X)	X	X (X.X)	X		
Gingival bleeding	X (X.X)	X						
General disorders and administration site conditions								
Total							X (X.X)	X
Fatigue							X (X.X)	X
Infections and infestations								
Total	X (X.X)	X	X (X.X)	X	X (X.X)	X	X (X.X)	X
Gingivitis							X (X.X)	X
Nasopharyngitis	X (X.X)	X	X (X.X)	X	X (X.X)	X		
Injury, poisoning and procedural complications								
Total	X (X.X)	X			X (X.X)	X		
Muscle strain	X (X.X)	X						
Thermal burn					X (X.X)	X		

Table 14.3.5.1.1 Haematology
Safety population

Laboratory variable=B-Erythrocytes - 10E12/l

Treatment		N	Mean	SD	Minimum	Median	Maximum
-	Screening	XX	X.XXX	X.XXX	X.XX	X.XXX	X.XX
A1	Period 1	X	X.XXX	X.XXX	X.XX	X.XXX	X.XX
	Period 2	X	X.XXX	X.XXX	X.XX	X.XXX	X.XX
	Period 3	X	X.XXX	X.XXX	X.XX	X.XXX	X.XX
	Period 4	X	X.XXX	X.XXX	X.XX	X.XXX	X.XX
B1	Period 1	X	X.XXX	X.XXX	X.XX	X.XXX	X.XX
	Period 2	X	X.XXX	X.XXX	X.XX	X.XXX	X.XX
	Period 3	X	X.XXX	X.XXX	X.XX	X.XXX	X.XX
	Period 4	X	X.XXX	X.XXX	X.XX	X.XXX	X.XX
C1	Period 1	X	X.XXX	X.XXX	X.XX	X.XXX	X.XX
	Period 2	X	X.XXX	X.XXX	X.XX	X.XXX	X.XX
	Period 3	X	X.XXX	X.XXX	X.XX	X.XXX	X.XX
	Period 4	X	X.XXX	X.XXX	X.XX	X.XXX	X.XX
D1	Period 1	X	X.XXX	X.XXX	X.XX	X.XXX	X.XX
	Period 2	X	X.XXX	X.XXX	X.XX	X.XXX	X.XX
	Period 3	X	X.XXX	X.XXX	X.XX	X.XXX	X.XX
	Period 4	X	X.XXX	X.XXX	X.XX	X.XXX	X.XX
A2	Period 1	X	X.XXX	X.XXX	X.XX	X.XXX	X.XX
	Period 2	X	X.XXX	X.XXX	X.XX	X.XXX	X.XX
	Period 3	X	X.XXX	X.XXX	X.XX	X.XXX	X.XX
	Period 4	X	X.XXX	X.XXX	X.XX	X.XXX	X.XX

Table 14.3.7.2.2 Changes from baseline in PR interval (ms)
Safety population

Treatment		N	Mean	SD	Minimum	Median	Maximum
-	Screening	X	.	.	.	.	.
A1	Period 1 DAY -1	X	-X.XX	XX.XX	-XX.X	-X.XX	XX.X
	Period 1 DAY 1: 0-2 H BEFORE FIRST DOSE	X	.	.	.	.	.
	Period 1 DAY 6: 1-2 H AFTER 7 H DOSE	X	-X.XX	XX.XX	-XX.X	-X.XX	XX.X
	Period 1 DAY 7: 0-2 H BEFORE FIRST DOSE	X	X.XX	XX.XX	-X.X	X.XX	XX.X
	Period 1 DAY 7: 1-2 H AFTER 7 H DOSE	X	X.XX	X.XX	-X.X	-X.XX	XX.X
	Period 2 DAY -1	X	X.XX	X.XX	-X.X	X.XX	X.X
	Period 2 DAY 1: 0-2 H BEFORE FIRST DOSE	X	.	.	.	.	.
	Period 2 DAY 6: 1-2 H AFTER 7 H DOSE	X	-X.XX	XX.XX	-XX.X	-X.XX	XX.X
	Period 2 DAY 7: 0-2 H BEFORE FIRST DOSE	X	X.XX	X.XX	-X.X	X.XX	XX.X
	Period 2 DAY 7: 1-2 H AFTER 7 H DOSE	X	X.XX	X.XX	-X.X	X.XX	XX.X
	Period 3 DAY -1	X	-XX.XX	XX.XX	-XX.X	-XX.XX	-X.X
	Period 3 DAY 1: 0-2 H BEFORE FIRST DOSE	X	.	.	.	.	.
	Period 3 DAY 6: 1-2 H AFTER 7 H DOSE	X	-X.XX	X.XX	-XX.X	-X.XX	X.X
	Period 3 DAY 7: 0-2 H BEFORE FIRST DOSE	X	-X.XX	X.XX	-XX.X	X.XX	X.X
	Period 3 DAY 7: 1-2 H AFTER 7 H DOSE	X	-X.XX	XX.XX	-XX.X	-X.XX	X.X
	Period 4 DAY -1	X	X.XX	XX.XX	-X.X	-X.XX	XX.X
	Period 4 DAY 1: 0-2 H BEFORE FIRST DOSE	X	.	.	.	.	.
	Period 4 DAY 6: 1-2 H AFTER 7 H DOSE	X	X.XX	XX.XX	-XX.X	-X.XX	XX.X
	Period 4 DAY 7: 0-2 H BEFORE FIRST DOSE	X	-X.XX	X.XX	-XX.X	X.XX	X.X
	Period 4 DAY 7: 1-2 H AFTER 7 H DOSE	X	-X.XX	X.XX	-XX.X	X.XX	X.X

Screening value is considered as baseline

Program: T_14_3_7_2_2_Change from bl in PR interval.sas Date: 23MAY17:09:10

Table 14.3.1.9 Suicidality assessment by C-SSRS during treatment
Safety population

		A1 (N=13)	B1 (N=14)	C1 (N=14)	D1 (N=13)
		n (%)	n (%)	n (%)	n (%)
CSS02-Wish to be Dead	NO	XX (XXX)	XX (XXX)	XX (XXX)	XX (XXX)
CSS02-Non-Specific Suicidal Thought	NO	XX (XXX)	XX (XXX)	XX (XXX)	XX (XXX)
CSS02-Actual Attempt	NO	XX (XXX)	XX (XXX)	XX (XXX)	XX (XXX)
CSS02-Non-suicidal Self-injurious Behav	NO	XX (XXX)	XX (XXX)	XX (XXX)	XX (XXX)
CSS02-Interrupted Attempt	NO	XX (XXX)	XX (XXX)	XX (XXX)	XX (XXX)
	NA	X (X.X)	X (X.X)	X (X.X)	X (X.X)
CSS02-Aborted Attempt	NO	XX (XXX)	XX (XXX)	XX (XXX)	XX (XXX)
CSS02-Preparatory Acts/Behavior	NO	XX (XXX)	XX (XXX)	XX (XXX)	XX (XXX)
	NA	X (X.X)	X (X.X)	X (X.X)	X (X.X)
CSS02-Suicidal Behavior	NO	XX (XXX)	XX (XXX)	XX (XXX)	XX (XXX)
CSS02-Suicide	NO	XX (XXX)	XX (XXX)	XX (XXX)	XX (XXX)

Program: T_14_3_9_C-SSRS.sas Date: 23MAY17:09:14

3112005 Statistical Analysis Plan

Written by: Vahteristo Mikko

Date dd.mm.yyyy (UTC)	Justification	Electronically signed by
13.06.2017 07:21:31	Approved	Vahteristo Mikko (mikvah)
13.06.2017 07:46:02	Approved	Ellmen Juha (juhael)
14.06.2017 04:37:59	Approved	Holopainen Aila (ailaho)