CLINICAL STUDY PROTOCOL

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

Study code:	3112005
Short study title:	COMDOS 1
Study design:	An open, randomised study with crossover design
Phase:	I
Standard:	GCP
EudraCT number:	2016-003779-23
Principal Investigator:	Denis Strugala, Dr. med.
Sponsor:	Orion Corporation Orion Pharma Orionintie 1, FI-02200 Espoo, Finland
Date:	2 December 2016

Sponsor approvals:

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Clinical Study Director:	Aila Holopainen, electronically signed by Tiina Koivisto
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SYNOPSIS

Sponsor: Orion Corporation Orion Pharma
Finished product: Not applicable
Active pharmaceutical ingredients: ODM-104, levodopa, carbidopa
Study title: A dose-finding study for levodopa, carbidopa and ODM-104 test formulations after repeated administration in healthy males
Study code: 3112005
Investigator: The principal investigator is Denis Strugala, Dr. med.
Study centres: This study will be conducted in a single centre in Germany.
Development phase: I
Objectives: **Primary:** The primary objective is to compare pharmacokinetics (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 modified release (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. **Secondary:** The secondary objectives are to determine the PK properties of 3-O-methyldopa (3-OMD), carbidopa and ODM-104 in plasma after repeated administration of the different combinations.
Methodology: This is a phase I, open, repeated dose, randomised PK study in healthy males. 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 8 days. The total duration of the study will be approximately 10-15 weeks for each subject.
Number of subjects: The planned number of subjects is 56 (14 in each parallel group with crossover design).
Diagnosis and main criteria for inclusion: Written informed consent obtained, good general health ascertained by detailed medical history and physical examinations, males between 18-65 years of age, body mass index (BMI) between 19-30 kg/m^2, weight at least 55 kg, regular intestinal transit (no recent history of recurrent constipation, diarrhoea or other intestinal problems, and no history of major gastrointestinal surgery).
Test products, dose and mode of administration: Formulations for oral administration: • ODM-104 capsules in 50 mg and 100 mg strengths • Levodopa MR capsules in 50 mg, 100 mg and 150 mg strengths • Carbidopa capsules in 12.5 mg, 25 mg and 65 mg strengths Doses: Group 1 • 50 mg of MR levodopa + 12.5 mg of carbidopa • 50 mg of MR levodopa + 65 mg of carbidopa • 50 mg of MR levodopa + 65 mg of carbidopa + 50 mg of ODM-104 • 50 mg of MR levodopa + 65 mg of carbidopa + 100 mg of ODM-104 Group 2 • 100 mg of MR levodopa + 25 mg of carbidopa • 100 mg of MR levodopa + 65 mg of carbidopa • 100 mg of MR levodopa + 65 mg of carbidopa + 50 mg of ODM-104 • 100 mg of MR levodopa + 65 mg of carbidopa + 100 mg of ODM-104 Group 3 • 150 mg of MR levodopa + 37.5 mg of carbidopa • 150 mg of MR levodopa + 65 mg of carbidopa • 150 mg of MR levodopa + 65 mg of carbidopa + 50 mg of ODM-104

- 150 mg of MR levodopa + 65 mg of carbidopa + 100 mg of ODM-104

Group 4

- 100 mg of MR levodopa + 65 mg of carbidopa
- 100 mg of MR levodopa + 25 mg of carbidopa + 100 mg of ODM-104
- 100 mg of MR levodopa + 65 mg of carbidopa + 100 mg of ODM-104

Comparator products, dose and mode of administration:

Formulation: Sinemet 25 mg/100 mg immediate release (IR) tablets containing 100 mg of levodopa and 25 mg of carbidopa for oral administration.

Dose:

Group 4

- 100 mg of IR levodopa + 25 mg of carbidopa (Sinemet®)

Frequency/duration of treatment:

Carbidopa and ODM-104 (in treatment periods including ODM-104) will be taken 4 times a day, every 3.5 h, for 6 days. On day 7, levodopa will be taken at the same time with carbidopa, with or without ODM-104, 4 times a day, every 3.5 h.

Bioanalytical method: Concentrations of levodopa, carbidopa, 3-OMD and ODM-104 in plasma will be determined using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods.

Variables and methods of assessments:

The primary variable for the evaluation of PK of levodopa is the area under the concentration-time curve from time 0 to the 24 h PK sample (AUC_{0-24}). 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. Other crossover comparisons will be performed and considered as secondary.

The secondary PK variable is the observed concentration at the end of each dosing interval ($C_{min,tau}$), which is used to describe minimum concentration during the dosing intervals. The ratio of the maximum observed concentration (C_{max}) in a dosing interval and the observed concentration at the end of the dosing interval, $C_{max}/C_{min,tau}$, 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 other variables.

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).

Statistical methods:

PK parameters will be analysed after logarithmic transformation and 90% confidence intervals (CIs) for the geometric means. The conclusions regarding possible differences between different study treatments will be based on both overall evaluation of levodopa concentration-time profiles and formal statistical analyses of PK parameters.

Primary pharmacokinetic evaluation

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 random effect. Sensitivity analysis adjusted for subject weight and age will be performed. The primary conclusions will be based on the per-protocol (PP) population.

Secondary pharmacokinetic evaluation

Statistical evaluation of the secondary PK variable will be done using similar methods to the primary variable. Statistical model for $C_{min,tau}$ will include treatment, period, dosing interval and treatment by dosing interval interaction as fixed effects and subject by period interaction as random effect.

Other pharmacokinetic evaluations

PK variables for the evaluation of PK of levodopa, carbidopa, 3-OMD and ODM-104 will be summarised by treatment using descriptive statistics. Selected PK variables will be analysed using similar models and sensitivity analysis to the primary and secondary PK variables. Drug concentrations will be tabulated by time and treatment with descriptive statistics.

Safety evaluation

AEs and serious adverse events (SAEs) will be summarised by treatment using subject and event counts. Clinical safety variables and their changes from baseline will be evaluated using descriptive statistics. 12-lead ECG abnormalities will be tabulated and the intra-subject differences between visits will be evaluated. Laboratory safety variables will be evaluated using descriptive statistics for the actual values and their changes from baseline. Physical examination and C-SSRS findings will be tabulated.

ABBREVIATIONS AND DEFINITION OF TERMS

3-ODM	3-O-methyldopa
AADC	Aromatic l-amino acid decarboxylase
AE	Adverse event
AUC	Area under the concentration-time curve
BMI	Body mass index
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
C_{max}	Maximum concentration in plasma
C_{min}	Minimum concentration in plasma
$C_{min,tau}$	Observed concentration at the end of each dosing interval
COMT	Catechol-O-methyl transferase
eCRF	electronic case report form
CRO	Contract research organisation
C-SSRS	Columbia-Suicide Severity Rating Scale
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic data capture
GCP	Good clinical practice
GMP	Good manufacturing practice
HR	Heart rate
IC	Informed consent
IR	Immediate release
mITT	Modified intention-to-treat
MR	Modified release
PD	Parkinson's disease
PG	Pharmacogenomic(s)

PK	Pharmacokinetic(s)
PP	Per-protocol
PTF	Peak-trough fluctuation
SAE	Serious adverse event
λ_z	Terminal elimination rate constant
t_{max}	Time to reach maximum concentration in plasma
ULN	Upper limit of normal

Note on usage of terms:

Orion Corporation Orion Pharma is hereafter in this document called “Orion”.

The term ‘investigator’ in the text of the protocol refers to the principal investigator or co-investigator.

1. INTRODUCTION

1.1 Background

Levodopa, the dopamine precursor, still remains the most efficacious pharmacotherapeutic treatment for Parkinson's disease (PD). The current concept of continuous dopaminergic stimulation suggests that a more stable plasma concentration of a given antiparkinsonian drug throughout the day will result in better daily treatment responses in terms of fewer motor fluctuations, lesser OFF-time (time when PD signs and symptoms return before the next dose of levodopa) and fewer motor complications such as dyskinesia (Nyholm D et al., 2004; Stocchi F et al., 2005).

The major pathway for the metabolism of levodopa is its decarboxylation to dopamine by aromatic l-amino acid decarboxylase (AADC). An inhibitor of AADC, such as carbidopa, is routinely co-administered with levodopa to improve its bioavailability. When AADC is inhibited, levodopa is increasingly metabolised to 3-O-methyldopa (3-OMD) by catechol-O-methyl transferase (COMT). In man, the greatest activity of COMT is found in the liver, kidney and gastrointestinal tract. Addition of a COMT inhibitor, such as entacapone, to levodopa/AADC inhibitor therapy, therefore, provides a further refinement in delivering levodopa into the brain. Increased plasma levodopa concentrations can be achieved by combining entacapone with levodopa/carbidopa therapy (Nutt JG et al., 1994; Paija O et al., 2005), although daily variability in levodopa plasma levels during frequent dosing cannot be avoided (Kuoppamaki M et al., 2009). It also appears that after multiple daily doses of levodopa/carbidopa and entacapone, the plasma levodopa levels tend to increase towards the end of the day (Paija O et al., 2005).

ODM-104 is a new generation, mainly peripherally acting COMT inhibitor aimed at the treatment of PD in combination with levodopa and an AADC inhibitor. In experimental animals, ODM-104 has been shown to be metabolically more stable and its elimination longer than that of entacapone. It also provides longer-lasting COMT inhibition in peripheral tissues than entacapone. When co-administered with levodopa/carbidopa in rats, it increases the bioavailability of levodopa. In parkinsonian rat models, ODM-104 has been shown to be superior to entacapone in increasing levodopa-induced rotational behaviour (studies 11000118 and 11000230). In healthy human subjects, single doses of ODM-104 have been shown to more potently inhibit COMT activity in erythrocytes than entacapone at similar doses, and to modify levodopa pharmacokinetics (PK) following repeated dosing. Single doses up to 800 mg and repeated doses up to 200 mg 4 times a day, combined with levodopa and carbidopa, for 7 days have been well tolerated (study 3112001).

A modified release (MR) test formulation of levodopa will be further evaluated in this study. Compared with commercially available immediate release (IR) tablets of levodopa preparation (Sinemet®), more stable plasma levodopa profiles during repeated dosing were achieved with the MR levodopa formulation when administered 4 times a day with 65 mg of carbidopa and 100 mg of ODM-104, while still maintaining adequate daily area under the time-concentration curve (AUC) of levodopa (study 3112002). In clinical practice, such a levodopa profile is expected to result in better symptom control throughout the day in PD patients with end-of-dose motor fluctuations.

This PK study in healthy subjects aims to confirm carbidopa and ODM-104 dose selection in the MR levodopa combination with different levodopa strengths for the foreseen clinical studies. Levodopa PK from the test combinations will be compared with a marketed levodopa/carbidopa product.

1.2 Rationale of the study

The rationale of this study is to justify the planned carbidopa and ODM-104 doses for the foreseen phase III program. The aim is to investigate levodopa PK during repeated daily dosing with a MR formulation of 50, 100 and 150 mg of levodopa combined with 2 carbidopa strengths (standard 1 to 4 carbidopa to levodopa ratio or fixed 65 mg) and 50 or 100 mg of ODM-104 in healthy male subjects. The combinations will also be compared with the currently used marketed levodopa carbidopa IR formulation (Sinemet). The rationale for comparing the above combination treatments is to confirm carbidopa and ODM-104 dose selection for regulatory purposes in the USA without formal phase II dose finding studies with clinical endpoints. Adding marketed levodopa/carbidopa formulation in the comparison was requested by the FDA and will be used as a comparator in phase III.

PK variables such as AUC, maximum concentration (C_{max}), time to reach maximum concentration (t_{max}) and minimum concentration (C_{min}) will be determined. In addition, fluctuation of levodopa concentrations during the dosing intervals will be assessed. The primary focus will be on levodopa PK as the symptomatic effect of the combination in the treatment of PD is mediated through levodopa, and as carbidopa and ODM-104 do not have any therapeutic efficacy on their own.

Based on previous studies with levodopa, sex seems to have an effect on levodopa's PK. In order to decrease variation and consequently to receive explicit results, only male subjects will be included into this study.

Test formulations instead of final formulations are used in this study to enable all relevant comparisons. For example, study treatment 100 mg of MR levodopa + 65 mg of carbidopa is not possible with final formulation where ODM-104 is also involved. A PK bridge between test formulations and final formulations will be proved with later studies.

1.2.1 Rationale of the study design

A crossover design was chosen for this study in order to reduce the impact of inter-individual variability on levodopa PK parameters. This design has been previously used successfully in similar PK studies. Open-label study drug administration is regarded appropriate, because the primary study variables are PK parameters derived from drug concentrations in plasma. Administration of carbidopa and COMT inhibitor for 6 days before levodopa administration will ensure clinically adequate AADC and COMT inhibition when assessing levodopa PK on day 7. There will be a wash-out period of at least 4 days between the study treatment administrations. The length of the wash-out period is considered sufficient for the elimination of levodopa, carbidopa and ODM-104.

1.2.2 Rationale for selected doses

The maximum doses of carbidopa (up to 65 mg) and ODM-104 (100 mg) chosen to be used in this study have been generally well tolerated in previous PK studies in healthy men (studies

3112001, 3112002 and 3112003). This has been the case also with repeated dosing of 100 mg of levodopa (4 times a day) with different carbidopa doses and COMT inhibitors. Inclusion criteria and screening assessments have been defined to exclude subjects that are thought to be at higher risk of different adverse effects due to the administered treatments. Levodopa concentrations in plasma after standard doses are proportional to body weight, and in order to avoid nausea, the minimum subject weight has been set to 55 kg.

1.3 Benefit-risk assessment

Healthy subjects in this study will not receive any direct health-related benefit from administration of levodopa, carbidopa and ODM-104. However, the study subjects will receive general information on their current health by laboratory tests, electrocardiograms (ECGs), physical examination including blood pressure (BP) and heart rate (HR) measurements.

Levodopa, carbidopa and ODM-104 have been generally well tolerated and safe in previous PK studies (studies 3112001, 3112002 and 3112003) and in an ongoing study (3112004) in patients with PD; however, they are known to cause different symptoms in some subjects. Headache, nausea, nasopharyngitis, flatulence, vomiting, increased blood creatine phosphokinase, constipation and dizziness were reported relatively frequently in previous PK studies with ODM-104. In addition, isolated cases of cardiac conduction abnormalities and mild increases in liver transaminases were reported. No serious adverse events (SAEs) have been reported in previous phase I studies on ODM-104. Based on these findings as well as the nonclinical data on ODM-104, the events of increase in liver tests, cardiac arrhythmias and gastrointestinal irritation are considered as important potential risks for ODM-104. These risks are subject to close monitoring during the clinical program.

Carbidopa single dose used in the test treatments is higher than those in many levodopa treatments on the market with 4 to 1 levodopa to carbidopa ratio. However, the dosing frequency is 4 times a day and the total daily dose of carbidopa will not exceed the daily dose of the approved levodopa products in this study. Higher carbidopa dose has been used in combination with levodopa and ODM-104 in the previous PK studies and in the ongoing study in patients. In the present study subjects remain in the research institute for the whole duration of the dosing period. Samples for laboratory tests and ECG monitoring are applied to exclude subjects with abnormalities from entering the study and after treatment initiation to be discontinued if specified abnormalities emerge. Signs of nausea, gastrointestinal and other symptoms will be followed clinically daily and if intolerable, treatment will be discontinued.

Blood sampling may cause local pain and haematoma as well as fainting in isolated cases. In addition, ECG electrodes attached to the skin may cause irritation.

In summary, the benefit-risk assessment remains positive for studying ODM-104 in combination with levodopa and carbidopa.

2. STUDY OBJECTIVES

2.1 Primary objective

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.

2.2 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.

3. OVERALL STUDY DESIGN AND PLAN

3.1 Type of study

This is a phase I, open, repeated dose, randomised PK study in healthy males. The study will be conducted at 1 centre.

3.2 Study design

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 8 days. The total duration of the study will be approximately 10-15 weeks for each study subject.

The study design is presented in Figure 1 and the study treatments for the 4 groups are presented in Table 1.

Figure 1. Study design

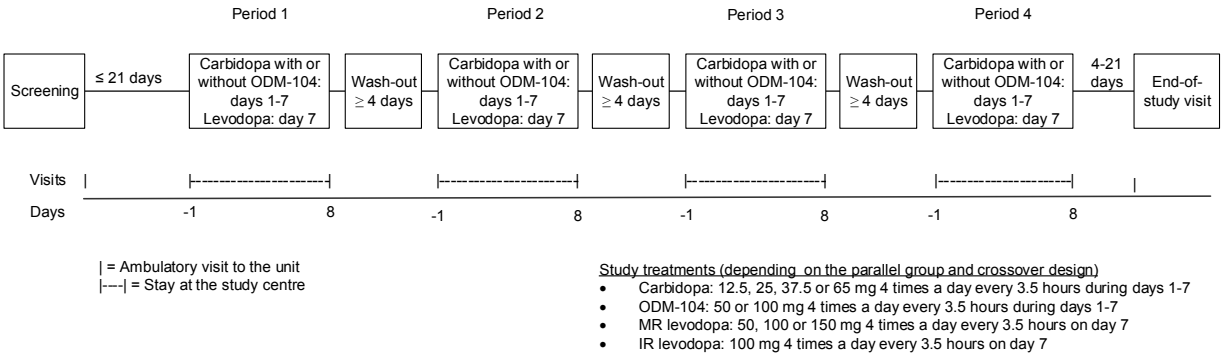

Table 1. Summary of study treatments

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

4. SELECTION OF STUDY POPULATION

4.1 Number of subjects

The planned number of subjects is 56 (14 in each parallel group with crossover design).

4.2 Inclusion criteria

Subjects must meet all of the following criteria to be included into the study:

1. Written informed consent (IC) obtained.
2. Good general health ascertained by detailed medical history and physical examinations.
3. Males between 18-65 years of age inclusive at screening.
4. Body mass index (BMI) between 19-30 kg/m^2 (BMI = weight/height^2) inclusive at screening.
5. Weight at least 55 kg inclusive at screening.
6. Regular intestinal transit (no recent history of recurrent constipation, diarrhoea, or other intestinal problems, and no history of major gastrointestinal surgery).

7. Subject with a partner of childbearing potential agrees to use adequate contraception from the first dose of study treatment until 90 days after the last dose of study treatment. Adequate methods of contraception include: Hormonal contraceptives, barrier methods (condom, diaphragm, cervical cap, etc.) in combination with a spermicide, intrauterine device and sexual abstinence.
8. Subject agrees to not donate sperm from the first dose of study treatment until 90 days after the last dose of study treatment.

4.3 Exclusion criteria

Subjects will not be included into this study if they meet any of the following criteria:

1. Evidence of clinically significant cardiovascular, renal, hepatic, haematological, gastrointestinal, pulmonary, metabolic, endocrine, neurological or psychiatric disease or cancer (except local non-melanoma skin cancer) within the previous 2 years.
2. Any condition requiring regular concomitant treatment (including vitamins and herbal products) or likely to need any concomitant treatment during the study. As an exception, paracetamol for occasional pain is allowed.
3. Any clinically significant abnormal laboratory value or ECG (such as prolonged QTcF >450 ms or QRS >120 ms) that in the opinion of the investigator could interfere with the interpretation of study results or cause a health risk for the subject if he takes part in the study.
4. Known hypersensitivity to the active substances or the excipients of the drugs.
5. History of vasovagal collapses or vagal reactions with unexplained reason within the previous 2 years or a tendency for vasovagal reactions during blood sampling.
6. HR < 50 bpm or > 90 bpm in the supine position after 5 min rest at the screening visit.
7. At the screening visit:
   - systolic BP < 100 mmHg or > 140 mmHg in the supine position after 5 min rest
   - diastolic BP < 50 mmHg or > 90 mmHg in the supine position after 5 min rest.
8. Creatinine > 1.5 x upper limit of normal (ULN) and alanine aminotransferase or aspartate aminotransferase >1.25 x ULN at screening.
9. History of anaphylactic/anaphylactoid reactions.
10. Strong tendency to motion sickness.
11. Recent or current (suspected) drug abuse.
12. Recent or current alcohol abuse; regular drinking of more than 21 units per week (1 unit = 4 cl spirits or equivalent).
13. Current use of nicotine-containing products more than 5 cigarettes (or equivalent)/day and/or inability to refrain from the use of nicotine-containing products for 48 h before

the first dose in each period until collection of the 24 h PK sample in the morning of day 8.

14. Use of caffeine-containing beverages more than 600 mg of caffeine/day and/or inability to refrain from using caffeine-containing beverages 24 h before the first levodopa administration on the PK day (day 7) until collection of the 24 h PK sample in the morning of day 8.
15. Blood donation or loss of a significant amount of blood (> 500 ml) within 90 days before the first study treatment administration.
16. Participation in another investigational drug study or administration of another investigational drug within 60 days before the first study treatment administration.
17. Veins unsuitable for repeated venipuncture or cannulation.
18. Predictable poor compliance or inability to communicate well with the study centre personnel.
19. Inability to participate in all treatment periods.

4.4 Information collected on screening failures

For subjects screened but not included in the study, the following electronic case report forms (eCRFs) will be completed: date of the screening visit, IC, demography (sex, year of birth, age and racial group), criteria causing the exclusion, decision of entry, adverse events (AEs) related to study assessments and SAEs.

4.5 Removal of subjects from treatment or assessment

Study subjects are free to discontinue the study at any time without providing a reason. However, the investigator should try to identify the reason and document it on the eCRF.

A subject must discontinue the study treatment if the investigator or the sponsor considers the discontinuation to be medically necessary or in the best interest of the subject.

A subject must discontinue the study treatment for example for the following reasons:

- Personal reason
- AE requiring discontinuation of the study treatment, as judged by the investigator:
  - Intolerable dopaminergic AEs such as prolonged moderate or severe vomiting with massive fluid loss and consequent circulatory disorders
  - Intolerable gastrointestinal AEs such as prolonged moderate or severe diarrhoea with massive fluid loss and consequent circulatory disorders
  - Abnormal 12-lead ECG finding of clinical relevance:
    - increase in QTc of >60 ms from baseline
    - increase in QRS of >25% from baseline

- 2nd or 3rd degree atrioventricular block
- sustained (>30 s) cardiac arrhythmias (supraventricular or ventricular tachycardia, atrial fibrillation and/or flutter)
- any symptomatic arrhythmia (except isolated extrasystoles)

– Increase in alanine aminotransferase, aspartate aminotransferase or alkaline phosphatase to >3 x ULN

– Other AE (e.g. fainting or profound weakness) requiring discontinuation of the study treatment

- Lost to follow-up
- Protocol deviation that could affect the outcome of the study, as judged by the investigator
- Other reason (e.g. impossibility to obtain blood samples)

Irrespective of the reason for discontinuation, the subject should be invited to end-of-study assessments as soon as possible. As long as the subject consents, all relevant assessments, at least those of safety, should be performed, preferably according to the schedule for the end-of-study assessments.

The study monitor should be notified about premature discontinuations within 24 h in the event of discontinuation due to an SAE (see section 6.4.1.3) or within 7 days in the event of discontinuation due to another reason.

The sponsor will decide if study subjects who prematurely discontinue will be replaced. Discontinued study subjects are not allowed to re-enter the study.

5. STUDY TREATMENTS

Manufacturing, packaging, and labelling of the study treatments will comply with good manufacturing practice (GMP) regulations (Annex 13 of EU guide to GMP).

5.1 Investigational medicinal products

5.1.1 Test products

5.1.1.1 ODM-104 capsules

ODM-104 capsules in 50 mg and 100 mg strengths are provided in size 0 hard gelatine capsules for oral administration. The colour of the capsules is Swedish orange. ODM-104 capsules are manufactured by Patheon UK Limited, the United Kingdom.

The capsules are stored below 30°C

5.1.1.2 Levodopa 50 mg, 100 mg and 150 mg capsules (Levodopa 50 mg, 100 mg and 150 mg A CAP)

Levodopa MR capsules in 50 mg, 100 mg and 150 mg strengths will be provided in size 0 hard gelatin capsules for oral administration. The colour of the capsules is white. Levodopa capsules are manufactured by Glatt GmbH, Germany.

The capsules are stored below 30°C.

5.1.1.3 Carbidopa capsules

Carbidopa capsules in 12.5 mg, 25 mg and 65 mg strengths will be provided for oral administration. Carbidopa 12.5 mg and 25 mg will be in size 3 hard gelatine white capsules and carbidopa 65 mg will be in size 0 hard gelatine dark green capsules. Carbidopa capsules are manufactured by Orion Corporation, Finland.

The capsules are stored below 30°C.

5.2 Comparator product

5.2.1 Sinemet® 25 mg/100 mg tablet

Sinemet 25 mg/100 mg IR tablets contain 100 mg of levodopa and 25 mg of carbidopa for oral administration. Sinemet 25 mg/100 mg tablets are manufactured by Merck, Sharp & Dohme B.V.

The tablets are stored below 30ºC.

5.3 Selection and timing of doses

Overall, MR levodopa strength will be 50, 100 or 150 mg, carbidopa strength will be 12.5, 25 or 65 mg and ODM-104 strength will be 0, 50 mg or 100 mg. Sinemet contains 100 mg of IR levodopa and 25 mg of carbidopa.

The strength of levodopa, carbidopa and ODM-104 will depend on the parallel group (Groups 1-4) the study subject has been assigned to. The doses during the 4 treatment periods are presented in Table 1 in section 3.2.

In all parallel groups, depending on the treatment period, carbidopa with or without ODM-104 will be taken 4 times a day during the days 1-6. On day 7 (PK sampling day), carbidopa with or without ODM-104 will be taken at the same time with levodopa 4 times a day. The duration of treatment will be 7 days for carbidopa and ODM-104 and 1 day for levodopa. In one of the periods in Group 4, Sinemet will be taken on day 7 without ODM-104 and on days 1-6, only carbidopa 25 mg will be administered.

The selected strengths and dosing regimens are based on previous PK studies in healthy subjects conducted during ODM-104 development program and other levodopa programs.

Carbidopa and ODM-104 (in treatment periods including ODM-104) will be taken 4 times a day – first dose, 3.5 h, 7 h and 10.5 h doses, for 6 days. The study treatments should be taken

at the same time every day to provide even concentrations of the active ingredients. The recommended study treatment intake times on days 1-6 are 8:00, 11:30, 15:00 and 18:30 h.

Subjects will arrive at the study centre in the evening before day 1 (day -1) and stay at the study centre until the 24 h PK blood sample has been drawn in the morning of day 8. Subjects will take all study treatments at the study centre.

In the evening of day 6, subjects will start fasting for at least 10 h (from around 22:00 h on day 6) before the first morning dose (0 h) at approximately 8:00 h on day 7. Drinking of water is permitted until 1 h before dosing.

The recommended study treatment intake times on day 7 are the same as those on the previous 6 days: 8:00, 11:30, 15:00 and 18:30 h. Study treatments will be ingested with 200 ml of water. Study subjects should maintain an upright position (sitting or standing) for at least 1 h after the study treatment administration and as much as possible during the day until 24:00 h.

On day 7, 150 ml of water will be given 2 h after each dosing. If extra water is needed, the extra amount of consumed water and time of drinking will be recorded on the eCRF. A standard breakfast will be served 1 h, a standard lunch 4.5 h, a standard snack 8 h, a standard dinner 11.5 h and a light night snack 14 h after the first morning dose. If the standard meals are not eaten completely, this will be recorded on the eCRF. Meals should be eaten within 30 min. Meals on days 1-6 will be served at about the same time as on day 7. However, drinking of water is not restricted and there is no 30 min time limit for eating a meal.

Subjects will remain housed in the unit until the morning of day 8, i.e. 24 h after the first dose of levodopa on the previous day.

5.4 Method of assigning study subjects to treatment groups

All subjects screened will be assigned a screening number. To ensure random allocation of the study treatment sequences, all subjects to be randomised into the study will receive the treatment sequence that corresponds to the next consecutive randomisation number in the study. At the study site, subjects will be assigned with next consecutive subject number before first treatment administration. The treatment sequence will be allocated to this subject number when his entry into the first treatment period of the study is confirmed using the dedicated eCRF. The subject is considered randomised at the time when eCRF provides the treatment sequence allocated to the subject.

In case a discontinued subject will be replaced, the replacing subject will receive the same treatment sequence as the subject he is replacing. If replacement subjects will be enrolled, these will be randomised to go through all 4 treatment periods.

In practise, the first subject who made a registration for the study fulfilling all inclusion criteria and none of the exclusion criteria will be dosed first, the next subject will be dosed second and so on. However, precedence will be given to subjects who participate in a study at the site for the first time and for subjects who served as “stand by” during a preceding study. Randomisation will be carried out on the day of the first treatment administration.

The study will be randomised consisting of 4 parallel groups (Groups 1-4). All groups will have a crossover design with 4 treatment periods, each lasting for 8 days.

Randomisation will be performed across all the groups, i.e. the subject entering the study may be randomised to any of the treatment sequences presented in Table 2.

Table 2. Example of the treatment sequences

Group	Sequence	Group	Sequence
1	B1 / C1 / A1 / D1	3	D3 / C3 / B3 / A3
	A1 / B1 / D1 / C1		B3 / D3 / A3 / C3
	D1 / A1 / C1 / B1		A3 / B3 / C3 / D3
	C1 / D1 / B1 / A1		C3 / A3 / D3 / B3
2	C2 / B2 / D2 / A2	4	A4 / D4 / C4 / B4
	D2 / C2 / A2 / B2		C4 / A4 / B4 / D4
	A2 / D2 / B2 / C2		B4 / C4 / D4 / A4
	B2 / A2 / C2 / D2		D4 / B4 / A4 / C4

See Table 1 for definitions of A1-D4

5.5 Blinding

This is an open-label study.

5.6 Emergency procedures

The investigator is responsible for ensuring adequate medical expertise and facilities to handle possible emergency situations during the study. Emergencies will be treated according to the decision of the physician in charge or the investigator when available.

5.7 Prior and concomitant treatments

Concomitant treatments including herbal products, vitamins and dietary supplements are not allowed during the study (within 2 weeks or 5 half-lives of the drug, whichever is longer, before the first study treatment administration until the end-of-study visit). Paracetamol may be taken for the treatment of occasional pain.

In case any concomitant treatment is required during the study, the study subject needs to discontinue the study due to a protocol deviation, if the investigator or sponsor considers that the concomitant treatment could affect the outcome of the study (see section 4.5). The decision will be based on the time the concomitant treatment was taken and the pharmacology and PK of the concomitant treatment.

All concomitant treatments during the study, including the post-treatment period, must be recorded on the eCRF. No other investigational treatment is allowed to be used concomitantly with the study treatment. The study subject must not participate concurrently in any other clinical drug study or have been administered another investigational drug within 60 days before the first study treatment administration.

5.8 Restrictions

Intake of grapefruit, grapefruit juice, bitter orange and bitter orange juice are prohibited during the study (from the screening visit until the end of study visit).

The use of coffee, black and green tea, energy drinks or any other caffeine-containing products is not allowed from 24 h before the first levodopa administration on the PK sampling day (day 7) until the last PK blood sample is taken on the following day. Only moderate consumption of caffeine-containing products is allowed on other study days.

Subjects will be instructed to abstain from consuming alcohol and nicotine-containing products for at least 48 h prior to first dosing in each period and during in-house stay.

If the subject practises intensive physical exercise, it should remain on a stable level during the study. Intensive physical exercise is not allowed from 48 h before first dosing in each period and during in-house stay.

Blood donation and administration of another investigational study treatment are not allowed during the study. Sauna bath is prohibited during in-house stay until 24 h after the last PK blood sample is taken.

See section 6.4.5 for restrictions regarding fasting before safety laboratory tests and section 5.3 regarding fasting and timing of meals related to dosing of study treatments.

See section 5.7 for restrictions regarding concomitant treatments.

5.9 Treatment compliance and exposure

All study treatment intakes will be performed in accordance with the specifications of the investigator and under the supervision of study centre personnel. This includes checking the oral and buccal cavity.

Levodopa, carbidopa and ODM-104 concentrations in plasma will indicate that each subject has ingested the study treatments. Any deviation from the treatment regimen must be documented on the eCRF.

The investigator or other study centre personnel is responsible for study drug accountability during the study. The investigator must maintain accurate records demonstrating the date and amount of drug received, to whom and by whom dispensed (drug dispensing list) and accounts of drugs accidentally or deliberately destroyed. At the end of the study, all original containers, whether empty or containing unused products, will be returned to the sponsor for disposal.

5.10 Availability of investigational medicinal product after termination of study

There is no option to continue study treatment once the study subject has completed or discontinued the study.

6. STUDY PROCEDURES AND ASSESSMENTS

6.1 Study procedures

Table 3 lists all study procedures and indicates with an ‘x’ during which visit a particular procedure is performed.

Table 3. Schedule of study events

Protocol activities	Screening	Treatment period						End-of-study
	≤21 days before first dose	Day -1	Day 1	Days 2-5	Day 6	Day 7	Day 8	4-21 days from last dose
IC[1]								
Physical examination	X							X
Demography and substance use	X							
Use of nicotine	X	X						
Weight and BMI	X							X
Height	X							
Vital signs: BP and HR	X	X	X[2]		X[3]	X[4]		X
12-lead ECG	X	X	X[2,5]		X[6]	X[7]		X
Laboratory assessments								
• Haematology and clinical chemistry	X		X[2,8]			X[8]		X[9]
• Urinalysis	X		X[2]			X		X
• Serology	X							
Alcohol breath test	X	X						
Urine drug abuse test	X	X						
C-SSRS	X					X		
Decision of entry	X							
Study treatments, 4 times a day								
Carbidopa			X					
ODM-104			X[10]					
Levodopa						X		
Blood samples for PK						X	X	
Blood sample for PG			X[11]					
Medical history and current medical conditions	Continuously							
AEs	Continuously							
Concomitant treatments	Continuously							

[1] IC for the main study before any screening activities; for the optional PG IC, see footnote 11

[2] On day 1: 0-2 h before the first dose

Vital signs in supine position after 5 min rest:

[3] On day 6: 1-2 h after the 7 h dose

[4] On day 7: 0-2 h before the first dose and at 1-2 h after the 7 h dose

12-lead ECG in supine position after 5 min rest

[5] On day 1: 0-2 h before the first dose - 3 recordings within 5 min, 1-2 min interval between the measurements

[6] On day 6: 1-2 h after the 7 h dose

[7] On day 7: 0-2 h before the first dose and 1-2 h after the 7 h dose

[8] Selected laboratory tests before the first dose of the day

[9] The same laboratory tests as at the screening visit except thyroid stimulating hormone and albumin

[10] Only in treatment periods including ODM-104

[11] PG (optional): The sample is taken once from subjects who have signed the PG IC

C-SSRS = Columbia-Suicide Severity Rating Scale; PG = pharmacogenomics

6.1.1 Procedures during the screening period

Screening procedures will start after receiving approval from the ethics committee (EC) and competent authority (CA).

A prospective subject will receive both written and verbal information about the study and will have an opportunity to ask questions and sufficient time to decide whether or not to participate in the study. A signed and dated written IC for the main study will be obtained prior to any screening activities (see section 11.3). A separate pharmacogenomic (PG) IC will be obtained from subjects who agree to take part in the optional study-related exploratory PG study (see section 6.3).

The screening visit will take place within 21 days before the first study treatment administration.

The following procedures will be performed at the screening visit:

- Physical examination will be performed.
- Demographic data (sex, year of birth, age and racial group), substance use (use of nicotine, alcohol and caffeine, and drug abuse) and weight, height and BMI will be recorded.
- Medical history, current medical conditions and concomitant treatments will be recorded.
- AEs will be recorded.
- BP and HR will be recorded in the supine position after at least 5 min rest.
- 12-lead ECG will be recorded in the supine position after at least 5 min rest.
- Alcohol breath testing will be performed.
- Blood samples for haematology, clinical chemistry and serology will be collected after fasting for at least 10 h; see section 6.4.5 for details.
- Urine drug abuse testing will be performed.
- Urinalysis will be performed.
- Columbia-Suicide Severity Rating Scale (C-SSRS) will be performed.
- Subjects will be instructed to call the study centre when they experience AE or need to take concomitant treatment after the screening visit until the end-of-study visit when they are not in-house.

For practical reasons, the procedures outlined above may be performed on 2 separate occasions, for example, the physical examination may be performed a couple of days later than the other procedures.

A subject will be entered into the study if all of the inclusion criteria and none of the exclusion criteria are met and will be randomised to one of the treatment sequences before starting study treatments.

6.1.2 Procedures during the treatment periods

6.1.2.1 Days -1 and 1

Subjects will arrive at the study centre in the evening before day 1 (day -1) and stay at the study centre until the 24 h PK blood sample has been collected in the morning of day 8.

The following procedures will be performed on day -1:

- Alcohol breath and urine drug abuse tests will be performed before the first study treatment administration. Use of nicotine-containing products within the previous week will be enquired.
- BP and HR will be recorded in the supine position after at least 5 min rest.
- 12-lead ECG will be recorded in the supine position after at least 5 min rest.

The following procedures will be performed on day 1:

- BP and HR will be recorded in the supine position after at least 5 min rest 0-2 h before the first morning dose.
- 12-lead ECG will be recorded in the supine position after at least 5 min rest 0-2 h before the first dose. 3 recordings will be performed within 5 min (1-2 min interval between the measurements).
- Blood samples for selected haematology and clinical chemistry tests will be collected before the first dose; see section 6.4.5.
- Urinalysis will be performed before the first dose.
- Subjects will take carbidopa and ODM-104 (in study periods including ODM-104) as described in section 5.3.
- Meals will be served as described in section 5.3.
- Current medical conditions and concomitant treatments will be recorded.
- AEs will be recorded.

6.1.2.2 Days 2-5

The following procedures on days 2-5 will be performed:

- Subjects will take carbidopa and ODM-104 (on study periods including ODM-104) similar to day 1 and as described in section 5.3.
- Meals will be served as described in section 5.3.
- AEs, current medical conditions and concomitant treatments will be recorded.

6.1.2.3 Day 6

The following procedures on day 6 will be performed:

- Subjects will take carbidopa and ODM-104 (on study periods including ODM-104) similar to day 1 and as described in section 5.3.
- HR and BP will be recorded in the supine position after at least 5 min rest 1-2 h after the 7 h dose.
- 12-lead ECG will be recorded in the supine position after at least 5 min rest 1-2 h after the 7 h dose.
- Meals will be served as described in section 5.3.
- Current medical conditions and concomitant treatments will be recorded.
- AEs will be recorded.

6.1.2.4 Day 7

Subjects will fast from 22:00 h (10 h) on day 6 until breakfast on day 7, except that drinking of water is permitted up to 1 h before dose.

- BP and HR will be recorded in the supine position after at least 5 min rest 0-2 h before the first dose and 1-2 h after the 7 h dose.
- 12-lead ECG will be recorded in the supine position after at least 5 min rest 0-2 h before the first dose and 1-2 h after the 7 h dose.
- Blood samples for selected haematology and clinical chemistry tests will be collected before the first dose; see section 6.4.5 for details.
- Urinalysis will be performed.
- C-SSRS will be performed.
- Subjects will take the first dose (levodopa, carbidopa and possible ODM-104) approximately at 8:00 h after the pre-dose PK blood sampling. All study treatments will be taken precisely at the planned time points, including time points coinciding with PK blood sampling; see section 5.3 for details.
- Blood samples for PK assessments will be collected; see section 6.2.1 for details.
- Meals will be served as described in section 5.3.
- AEs, current medical conditions and concomitant treatments will be recorded.

6.1.2.5 Day 8

- Blood sample for 24-h PK assessments will be collected in the morning of day 8; see section 6.2.1 for details.
- Subjects will be instructed to call the study centre when they experience any AE or need to take any concomitant treatment until the end-of-study visit when the subjects are not in-house.
- Subjects can leave the study centre after the 24 h PK blood sample has been collected.

6.1.3 Procedures during the end-of-study visit

The end-of-study visit will take place 4-21 days after the last study treatment dose. The following procedures will be performed at the end-of-study visit:

- Physical examination will be performed. Weight will be measured and BMI recorded.
- BP and HR will be recorded in the supine position after at least 5 min rest.
- 12-lead ECG will be recorded in the supine position after at least 5 min rest.
- Blood samples for haematology and clinical chemistry tests will be collected. The same haematology and clinical chemistry tests as at the screening visit except thyroid stimulating hormone and albumin will be determined; see section 6.4.5 for details.
- Urinalysis will be performed.
- AEs, current medical conditions and concomitant treatments will be recorded.

6.2 Pharmacokinetic assessments

6.2.1 Blood sampling

Peripheral venous blood samples will be drawn for the determination of concentrations of levodopa, carbidopa, 3-OMD and ODM-104 in plasma. For blood sampling, a forearm vein will be cannulated. Blood samples will be drawn before the drug administration (0 h) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 15, 16 and 24 h after the drug administration. At time points 3.5, 7 and 10.5 h, the study treatment will be administered and the blood sample drawn at a same time. However, exact timing of study treatment administration will be prioritised, e.g. in case of problems in blood sampling.

Before the start of the study, detailed instructions for collecting, handling, storing and shipping of the plasma samples will be provided to the study centre. Maximum volume of blood collected in the study is provided in the subject information.

6.2.2 Determination of drug concentrations

The concentrations of levodopa, carbidopa, 3-OMD and ODM-104 in plasma will be determined with validated LC-MS/MS methods. Metabolites of ODM-104 will be determined, if indicated necessary by the PK results of the study. Bioanalytical details and criteria for acceptance of the results will be described in the bioanalytical plans and reported in bioanalytical reports.

6.2.3 Calculation of pharmacokinetic variables

Table 4 lists the PK parameters which will be derived from the concentration-time data of levodopa, carbidopa, 3-OMD and ODM-104.

Table 4. 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

C_{max} The maximum observed concentration of the concentration-time curve

$C_{max,tau}$ The maximum observed concentration for each dosing interval

t_{max} The time to reach the maximum observed concentration

$t_{max,tau}$ The time to reach the maximum observed concentration for each dosing interval

$C_{min,tau}$ The observed concentration at the end of each dosing interval i.e. concentration at 3.5 h, 7 h, 10.5 h and 14 h

$C_{min,tau,actual}$ The observed minimum plasma concentration after each dose before the concentration starts to rise due to the following dose. For the 4th dosing interval, the plasma concentration at time 16 h will be used as the minimum plasma concentration.

AUC_{tau} The area under the concentration-time curve calculated with linear trapezoidal rule for each dosing interval

AUC_{0-16} The area under the concentration-time curve calculated with linear trapezoidal rule from time 0 to the 16 h PK sample

AUC_{0-24} The area under the concentration-time curve calculated with linear trapezoidal rule from time 0 to the 24 h PK sample

AUC_{∞} The area under the concentration-time curve from time 0 to infinity, AUC_{∞} will be determined by adding area under the concentration-time curve from time 0 to the last sample with a quantifiable concentration (AUC_t) to the extrapolated area that will be

	determined by dividing the last quantifiable concentration by λ_z
$t_{½}$	The terminal elimination half-life that is calculated with the equation ln 2 / λ_z
λ_z	The terminal elimination rate constant from the log-linear portion of the concentration-time curve after the last (10.5 h) dose
$C_{max}/C_{min,tau}$	Ratio of the maximum observed concentration in each dosing interval and the observed concentration at the end of each dosing interval
$C_{max}/C_{min,tau,actual}$	Ratio of the maximum observed concentration in each dosing interval and the observed minimum plasma concentration after each dose before the concentration starts to rise due to the following dose. For the 4th dosing interval the plasma concentration at time 16 h was used as the minimum plasma concentration
$C_{max}/C(16h)$	Ratio of the maximum observed concentration from time 0 to 16 h and the observed concentration at time 16 h
PTF_{tau}	Peak-trough fluctuation for each dosing interval, calculated by ($C_{max,tau}$-$C_{min,tau}$) x100/$C_{av,tau}$, where the average concentration, $C_{av,tau}$ = AUC_{tau}/duration of dose interval
PTF_{0-16}	Peak-trough fluctuation, calculated by (C_{max}-C_{min}) x100/C_{av}, where the average concentration, C_{av} = AUC_{0-16}/16 h

The PK parameters will be calculated with non-compartmental methods using Phoenix™ WinNonlin® Build 6.3.0.395 or a later software version (Certara L.P., USA). The actual time of sampling will be used in the calculation of PK parameters. Possible outlying concentrations excluded from the PK analysis will be reported and justified in the study report.

6.3 Pharmacogenomic variables

A blood sample for DNA extraction will be collected once between the day 1 of the first study period and the end-of-study visit from those subjects who agree to take part in the optional study-related exploratory PG study. A separate IC is required from the subject participating in this PG study. DNA from these subjects will be stored in the sponsor's sample repository until analysis.

The objective of exploratory DNA analysis is to investigate possible factors that may give supportive information related to the absorption, distribution, metabolism, excretion, pharmacodynamics and safety of ODM-104, its metabolites or other drug treatments given in this study.

Instructions for the collection, handling, storage and transportation of samples will be provided before the start of the study.

6.4 Safety assessments

6.4.1 Adverse events

6.4.1.1 Definitions

An AE is any untoward medical occurrence in a study subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE

can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. The definition also covers medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

Thus, an AE may be an appearance or worsening of any undesirable sign or symptom, any worsening of the current medical conditions or onset of a new disease, compared with the previous observations or a clinically significant adverse change in a laboratory variable or other diagnostic finding (e.g. ECG).

An SAE is any untoward medical occurrences that at any dose

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect, or
- is an important medical event jeopardizing the patient or requiring intervention to prevent serious outcome (examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; development of drug dependency or drug abuse; overdose or interaction)

Other significant AEs are AEs (other than those meeting the definition of serious) that are of clinical importance and lead to:

- a diagnostic or therapeutic intervention
- discontinuation of the investigational medicinal product
- reduction of its dose
- significant additional concomitant treatment, or
- marked haematological and other laboratory abnormalities

6.4.1.2 Assessment of adverse events

All AEs must be elicited, documented and reported by the investigator to the sponsor from the time that a study subject signs the IC form until the end-of-study visit, i.e. 4-21 days after the last dose of study treatment.

SAEs and other significant AEs should be followed up until resolved or until the event is considered a chronic or stable outcome, or both.

AE may be notified to the investigator by the study subject or observed by the investigator clinically, or be an adverse change in laboratory assessment results. The investigator will

evaluate the subject's AEs at each visit by asking a standard question such as "Since you were last asked, have you felt unwell or different from the usual in any way?"

The investigator will assess and record the causality and severity of the AEs. Causality should be assessed in relation to the investigational medicinal product (see criteria for causality and severity below).

Causality criteria:

Related: The temporal relationship of the AE/SAE onset to the administration of the investigational medicinal product makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the AE/SAE.

Not related: The temporal relationship of the AE/SAE onset to the administration of the investigational medicinal product makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the AE/SAE.

Severity criteria:

Mild: Discomfort noticed, but it does not affect normal activity.

Moderate: Discomfort sufficient to reduce or affect normal daily activity.

Severe: Incapacitating with inability to work or perform normal daily activity.

From the time that a study subject candidate signs the IC form, newly appearing diagnosed diseases will be recorded on the AE eCRF.

Investigators must report all AEs to the sponsor on a specific AE eCRF irrespective of their assessment of the causal relationship of the investigational medicinal product to the event.

SAEs are by definition AEs and should be elicited in the same way, and also reported on the AE eCRF.

6.4.1.3 Reporting of serious adverse events by the investigator

The investigator must report all SAEs within 24 h of becoming aware of an SAE. SAEs must be reported within 24 h regardless of the time that may have elapsed since the time the event occurred and regardless of the causal relationship of investigational medicinal product to the event.

All SAEs should be reported on an electronic SAE form, which should be completed by the investigator or other relevant study centre personnel and signed by the investigator. Optionally, if the investigator is not able to complete the SAE form electronically, the paper version of the SAE form can be completed and sent by e-mail or faxed to Orion Drug Safety. The SAE reporting contact information can be found on the SAE form and will be filed in the investigator's study file.

If the initial report is reported by phone or e-mail to the study monitor or other contract research organisation (CRO) personnel and the study centre personnel are unable to fill in the SAE form within 24 h, a paper SAE form will be initiated by the person receiving the report.

The investigator must report the SAE on the SAE eCRF as soon as possible. In addition, SAEs should be reported on the AE eCRF.

The minimum criteria for SAE reporting are: the event or outcome meets the SAE definition, the event happens to an identifiable study subject, and the event is reported by an identifiable and qualified reporter (usually an investigator or other qualified study centre personnel)

A follow-up report to an SAE should be prepared if any relevant change in the condition of the study subject occurs after the initial report. The follow-up report should be documented as an update to the initial report.

SAEs that occur after the end-of-study visit (4-21 days after the last dose of study treatment), should be reported on the SAE form, if the investigator feels that there is a reasonable possibility for the event to have been caused by the study subject's participation in the study.

6.4.1.4 Reporting of serious adverse events to competent authorities and ethics committees

The sponsor is responsible for expediting all suspected unexpected serious adverse reactions (SUSARs) as well as other safety issues requiring expedited reporting to the relevant authorities within applicable timelines.

Notification of the ECs about all relevant events (SUSARs, other relevant safety information) will be performed by the CRO as a delegate of the sponsor.

The expectedness evaluation is required for regulatory reporting and it is performed by the sponsor. The expectedness in this study is evaluated against the Reference safety information section in the current ODM-104 Investigator's brochure (days 1-7, groups 1-4) and the Sinemet UK Summary of Product Characteristics (SmPC) (day 7, group 4).

6.4.2 Special situations

The special situations with study treatment are defined as:

- medication error
- overdose
- abuse
- misuse
- interaction

These special situations with study treatment are reported on the Special situations with study treatment eCRF even if there is no accompanying AE. All clinical manifestations in relation to these special situations will be reported as AEs or SAEs at the same time using the corresponding section of the eCRF.

6.4.3 Pregnancy during the study

Whenever it becomes known that a female partner of a subject becomes pregnant during the exposure to study treatments, the outcome of the pregnancy, delivery, postpartum recovery and

the clinical condition of the offspring during the neonatal period should be reported, subject to the partner's consent. A pregnancy follow-up form will be provided to the investigator for completion after the sponsor has received the initial report.

Any case of pregnancy during a clinical study should be reported by the investigator in the same way as an SAE.

6.4.4 Clinical safety assessments

HR, PB and 12-lead ECG will be recorded in the supine position after at least 5 min rest. The time points at which HR, BP and 12-lead ECG are recorded ECG are presented in Table 3.

12-lead ECG will be recorded 3 times within 5 min (1-2 min interval between the measurements) on day 1 pre-dose. The mean of 3 separate 12-lead ECG recordings will be considered as a baseline.

All 12-lead ECG data collected will be stored. Decision on whether or not to analyse all data will be made during or after the study. If additional ECG analysis will be performed, the results may be reported in a separate report.

A physical examination will be performed by the investigator at screening and end-of-study.

6.4.5 Laboratory safety assessments

The following laboratory tests will be taken at the screening visit after at least 10 h of fasting:

Haematology:

- Haemoglobin
- Haematocrit
- Erythrocytes
- Thrombocytes
- Mean corpuscular volume
- Mean corpuscular haemoglobin
- Mean corpuscular haemoglobin concentration
- Leucocytes
- Differential count (lymphocytes, monocytes, eosinophils, neutrophils, basophils)

Clinical chemistry:

- Albumin
- Creatinine
- Alkaline phosphatase
- Alanine aminotransferase

- Aspartate aminotransferase
- Creatine kinase
- Gamma-glutamyl transferase
- Glucose
- Magnesium
- Sodium
- Potassium
- Calcium (albumin corrected)
- C-reactive protein
- Thyroid stimulating hormone
- Total bilirubin

Urinalysis:

- Stick-test: pH, leucocytes[1], nitrites[1], protein, blood[1], glucose ([1] in case of findings, a microscopy examination of urine sediment will be performed)

Serology:

- Human immunodeficiency virus antigen/antibody
- Hepatitis C virus antibodies
- Hepatitis B-surface antigen

Selected laboratory tests

The following selected laboratory tests will be performed on days 1 and 7 in each treatment period, before the first dose:

Haematology:

- Haemoglobin
- Haematocrit
- Erythrocytes
- Thrombocytes
- Mean corpuscular volume
- Mean corpuscular haemoglobin
- Mean corpuscular haemoglobin concentration
- Leucocytes

- Differential count (lymphocytes, monocytes, eosinophils, neutrophils, basophils)

Clinical chemistry:

- Creatine kinase
- Creatinine
- Alkaline phosphatase
- Aspartate aminotransferase
- Gamma-glutamyl transpeptidase
- Alanine aminotransferase
- Total bilirubin
- Sodium
- Potassium
- Magnesium
- C-reactive protein

Urinalysis

- Stick-test: pH, leucocytes[1], nitrites[1], protein, blood[1], glucose ([1]in case of findings, a microscopy examination of urine sediment will be performed)

End-of-study laboratory tests

The same laboratory tests as at the screening visit, except determination of thyroid stimulating hormone and albumin, serology tests, urine test for drug abuse and alcohol breath test will be performed.

Alcohol and drug abuse tests during the study

An alcohol breath test will be performed at the screening visit and on admission in each treatment period.

A urine drug abuse test will be performed at the screening visit and on admission in each treatment period.

The reference ranges of the local laboratories will be recorded on the eCRFs by the sponsor. The investigator's assessment of clinical relevance will be documented on the eCRFs.

In case there are clinically relevant findings, control assessments may be performed according to the judgement of the investigator.

Instructions for the collection, handling, storage and transportation of samples will be provided before the start of the study.

7. DATA COLLECTION AND MANAGEMENT

The investigators and study centre personnel will prepare and maintain accurate source data for each study subject about clinical findings specified in the protocol. Source data include e.g. subject records and laboratory results. The data from source documents will be recorded into an electronic data capture (EDC) system, Medidata Rave (Medidata Inc), using eCRFs at the study centre. Externally produced data, if any, will be uploaded directly into the EDC system or transferred to the sponsor at agreed time intervals. All data on the eCRFs must be verifiable in the source data unless eCRF data are declared as source data.

Investigators and other relevant study centre personnel will be trained to use the eCRFs. After completion of training, they are provided with user names and authorised access to enter and correct data on the eCRFs.

Electronic queries about missing, misleading, incomplete or illogical data will appear in the EDC system. An audit trail within the system will track all changes/corrections made. The investigator has to confirm the content of the eCRF with an electronic signature.

Individual data fields in the EDC system may be locked on an ongoing basis during the study. The fields may be unlocked if further updates are needed. When all data have been entered and all queries resolved, the whole database will be locked. Only authorised and well-documented updates to the study data are possible after the database lock.

Further details regarding data collection and management are presented in the data management plan.

8. STATISTICAL METHODS

8.1 Statistical hypotheses

The primary variable for the evaluation of PK of levodopa is $AUC_{0\text{-}24}$. 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. 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.

H0: $AUC_{0\text{-}24,\ levodopa/carbidopa/ODM\text{-}104} = AUC_{0\text{-}24,\ levodopa/carbidopa}$

H0: $AUC_{0\text{-}24,\ levodopa/carbidopa/ODM\text{-}104} \neq AUC_{0\text{-}24,\ levodopa/carbidopa}$

8.2 Estimation of sample size

The sample size estimation is based on earlier ODM-104 phase I study 3112003. Sample size is estimated using the $AUC_{0\text{-}24}$. 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% ($AUC_{0\text{-}24}$ 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 Analysis of variance (ANOVA) with a 0.1 two-sided significance level. To allow drop outs 14 subjects per group and 56 subjects in total will be randomised into this study with 4-treatment, 4-period William's crossover design. This will provide adequate power for the primary comparison.

Replacement subjects may be enrolled (see section 4.5).

8.3 Analysis populations

The datasets derived from individual study subjects will be classified into following 3 classes prior to database lock and before carrying out any statistical analyses:

- Modified intention-to-treat (mITT) population: all randomised subjects who have received at least 1 dose of study treatment.
- Per-protocol (PP) population: Subjects who have completed the study according to the protocol without major protocol deviations.
- Safety population is the same as the mITT population.

8.4 Statistical analyses

Statistical analyses are described in more detail in the statistical analysis plan.

8.4.1 Demographic and other baseline characteristics

All relevant demographic and baseline characteristics will be summarised using descriptive statistics. The number and reasons for discontinuations will be listed and tabulated by treatment groups.

8.4.2 Treatment compliance and extent of exposure

The number of exposed subjects, the number of administered study treatments and the duration of study treatment exposure will be tabulated with descriptive statistics.

8.4.3 Pharmacokinetic analysis

The primary variable for the evaluation of PK of levodopa is AUC_{0-24} to describe the total levodopa exposure. The secondary PK variable is $C_{min,tau}$, which is used to describe minimum concentration during the dosing intervals. The ratio of the C_{max} in a dosing interval and the observed concentration at the end of the dosing interval, $C_{max}/C_{min,tau}$, 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 other variables.

PK parameters will be analysed after logarithmic transformation and 90% confidence intervals (CIs) for the geometric means will be calculated.

The conclusions regarding possible differences between different study treatments will be based on both overall evaluation of levodopa concentration-time profiles and formal statistical analyses of PK parameters.

Primary pharmacokinetic evaluation

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 random effect. Sensitivity analysis adjusted for subject weight and age will be performed.

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

The primary conclusions will be based on the PP population.

Secondary pharmacokinetic evaluation

Statistical evaluation for secondary PK variable will be done using similar methods as for primary variable. Statistical model for $C_{min,tau}$ will include treatment, period, dosing interval, and treatment by dosing interval interaction as fixed effect and subject by period interaction as random effect.

Other pharmacokinetic evaluations

The other PK variables for the evaluation of PK of levodopa, carbidopa, 3-OMD and ODM-104 are presented in Table 4. All PK variables will be summarised by treatment using descriptive statistics. Selected PK variables will be analysed using similar models and sensitivity analysis to the primary and secondary PK variables. Drug concentrations will be tabulated by time and treatment with descriptive statistics.

8.4.4 Pharmacogenomic analysis

In the context of this study, genetic polymorphisms may be analysed in relation to significant variation or specific scientific questions in PK or safety variables of levodopa, carbidopa or ODM-104. If such analysis is decided to be performed, a substudy will be designed and the results will be reported in a separate report.

8.4.5 Safety analysis

An authorised person will code AEs, medical history and concomitant diseases using standard coding dictionaries.

8.4.5.1 Analysis of adverse events

AEs will be classified by system organ classes and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). The number and proportion of subjects reporting each AE and the number of events will be presented in a frequency table. The following AE data will be summarised: overview of AEs, severity of AEs and causality to the study treatment. SAEs, AEs leading to premature discontinuation of study treatment and other significant AEs will be evaluated case by case.

AEs occurring before and after the initiation of study treatment will be reported separately.

8.4.5.2 Clinical safety analysis

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.

8.4.5.3 Laboratory safety analysis

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.

8.4.5.4 Analysis of prior and concomitant treatments

Prior and concomitant treatments will be coded using the anatomical therapeutic chemical (ATC) classification system. The number and percentage of subjects using concomitant treatments will be summarised by a pharmacological subgroup and chemical substance.

8.5 Interim analyses

No interim analysis is planned for this study.

9. DATA QUALITY ASSURANCE

9.1 Training

An initiation meeting will be arranged for the investigators and other relevant study centre personnel. This meeting will include a review of the protocol, eCRF completion and study procedures.

The investigators will ensure that appropriate training relevant to the study is given to the medical, nursing and other personnel involved in the study. The investigators will also ensure that any information relevant to the conduct of the study is forwarded to other relevant study centre personnel.

9.2 Case report forms

Electronic queries about missing, misleading, incomplete or illogical data will appear in the EDC system. An audit trail within the system will track all changes/corrections made. The investigator has to confirm the content of the eCRF with an electronic signature.

9.3 Monitoring, audits and inspections

The study monitor will visit the study centre regularly as agreed by the investigator and the sponsor. The study monitor will ensure that the study complies with good clinical practice (GCP) and applicable regulatory requirements and that the protocol is followed in all aspects, including the randomisation procedure, accurate recording of results, reporting of AEs, drug accountability and record keeping. Furthermore, it will be verified that the clinical facilities remain appropriate, and that the eCRFs correspond with source data. Further details regarding monitoring are presented in the monitoring manual.

The study may be audited by independent representative(s) of the sponsor or inspected by the CAs. For these purposes, the study monitor, auditors and inspectors will be allowed direct access to source data of the study subjects, original laboratory data etc., as far as they are related to the study.

It is essential that the investigator and other relevant members of the study centre team are available during the monitoring visits, audits and inspections, and that they devote sufficient time to these processes.

9.4 Laboratories and other vendors

All blood and urine samples will be worked up and analysed in the CRO's clinical laboratory. ECGs will be recorded and analysed in the clinic of the CRO.

Details regarding laboratory safety assessments and ECG analyses are presented in separate instructions. Quality certificates are required from all safety laboratories.

Bioanalytics will be performed using validated methods.

10. FURTHER REQUIREMENTS AND GENERAL INFORMATION

10.1 Investigators and study administrative structure

10.1.1 Investigators

Should the principal investigator transfer one of his/her responsibilities to other members of the study centre team, he/she must have this documented.

In the event of changes in key study centre team members, the responsible investigator must ensure that the successor is fully informed and capable of following the procedures.

A curriculum vitae in English must be obtained from all investigators who sign the protocol, and from other relevant persons.

10.1.2 Data and safety monitoring board

No data and safety monitoring board will be established for this study.

10.2 Insurance

The sponsor will provide clinical trial liability insurance for study subjects according to local regulations.

10.3 Retention of records

The investigator agrees to keep the following documentation in the investigator's study file: study subject records, including a subject screening log, a subject identification list, all original signed IC forms, a copy of eCRFs and records of drug dispensing.

The study files will be stored in the respective archives for 15 years, after which the sponsor will be contacted and the possibility of future archiving will be mutually agreed upon.

10.4 Completion of the study

The study is estimated to start in February 2017 (first subject first visit) and end when the last subject's last visit takes place.

Upon completion of the study, all unresolved issues will be clarified and remaining study treatments and other study materials will be collected.

The sponsor reserves the right to prematurely terminate the study for valid scientific or administrative reasons. After such a decision, the investigator must contact all participating study subjects within 7 days, and invite them for an end-of-study visit. All eCRFs must be completed up to the end-of-study visit.

10.5 Reports, publications and communication of results

Orion wishes to collaborate with the investigator to publish the results as timely as possible, without compromising accuracy or industrial property rights. The preparation, submission and authorship for publications containing the study results shall be in accordance with a process determined by mutual written agreement among the sponsor and participating institutions, and in accordance with international criteria for authorship; see International Committee of Medical Journal Editors recommendations, available at http://www.icmje.org.

Orion remains the exclusive owner of the study data defined by the protocol.

This study will be registered in one of the acceptable registries before the enrolment of the first subject.

11. ETHICS

11.1 Ethics committee

The study protocol, subject information sheet, IC form, and all other necessary documents will be submitted to an independent EC for review according to local regulations.

A favourable opinion will be obtained from the EC for the study, as well as any amendment(s), and communication of study-related safety issues as requested by the EC. The investigator should file all correspondence with the EC in the investigator's study file. Relevant copies of this correspondence should be forwarded to the sponsor.

11.2 Ethical conduct of the study

The study will be conducted in accordance with the Declaration of Helsinki guiding physicians in biomedical research involving human subjects.

The study shall not be initiated before favourable opinion from the EC and approval from the CA has been obtained for the protocol.

The study will be conducted in compliance with the protocol, GCP (ICH/135/95) and applicable regulatory requirements. A substantial amendment shall not be implemented until the protocol amendment has received a favourable opinion from the EC and approval from the CA. Only in case of the need to eliminate an immediate hazard(s) to study subjects, the investigator may implement deviation from the protocol without prior favourable opinion from the EC and approval from the CA for the protocol amendment.

11.3 Subject information and informed consent

The investigator will ensure that each subject is fully informed about the objectives and procedures of the study. The investigator will also explain any possible risks with participating in the study and answer all questions regarding the study. The subject will be given sufficient time to make a decision regarding participation in the study.

Subjects will be informed of their right to discontinue the study at any time without their medical care or legal rights being affected. Subjects will also be informed that representatives of the sponsor or CA may inspect relevant parts of their medical records and study data.

The investigator will obtain a signed and dated consent from each subject before any study related procedures are performed. One original of the signed and dated IC will be given to the subject. A second original will be retained in the investigator's study file. The investigator should confirm the receipt of every IC by entering the date of the consent both on the subject's eCRF and also on the subject screening log and identification list.

11.4 Subject data protection

Information collected during the course of the study will be stored in a database and used in the further development of study treatments and thereafter for as long as the information is relevant to patient care. The use includes the transfer of data to CAs in the European Union, the United States or other countries for the purpose of obtaining and maintaining marketing authorisations. All information is handled confidentially and according to local laws and regulations.

The study subjects can be identified in the eCRFs only by study subject number, sex, year of birth, age and racial group.

The confidentiality of PG data will be protected according to local laws and regulations.

12. REFERENCE LIST

Kuoppamaki M et al. (2009) Comparison of pharmacokinetic profile of levodopa throughout the day between levodopa/carbidopa/entacapone and levodopa/carbidopa when administered four or five times daily. Eur J Clin Pharmacol 65(5):443-55.

Nutt JG et al. (1994) Effect of peripheral catechol-O-methyltransferase inhibition on the pharmacokinetics and pharmacodynamics of levodopa in parkinsonian patients. Neurology 44(5):913-9.

Nyholm D et al. (2004) Levodopa infusion therapy in Parkinson disease: state of the art in 2004. Clin Neuropharmacol 27(5):245-56.

Paija O et al. (2005) Entacapone increases levodopa exposure and reduces plasma levodopa variability when used with Sinemet CR. Clin Neuropharmacol 28(3):115-9.

Stocchi F et al. (2005) Intermittent vs continuous levodopa administration in patients with advanced Parkinson disease: a clinical and pharmacokinetic study. Arch Neurol 62(6):905-10.

13. APPENDICES

Appendix 1. Investigator signature

3112005 Clinical study protocol

Written by: Chotai Priteesh

Date dd.mm.yyyy (UTC)	Justification	Electronically signed by
02.12.2016 13:31:27	Approved	Vahteristo Mikko (mikvah)
02.12.2016 13:33:52	Approved	Ellmen Juha (juhael)
02.12.2016 14:27:24	Approved	Koivisto Tiina a (tiikoi)
02.12.2016 15:19:56	Approved	Tuunainen Johanna (johmak)