Levodopa in early Parkinson's disease: the LEAP-study

A prospective double blind randomized delayed start multi-center trial

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form (General Assessment and Registration form) is the application form that is required for submission to the accredited Ethics Committee (ABR = Algemene Beoordeling en Registratie)
AE	Adverse Event
ALDS	AMC Linear Disability Scale
BDI-II	Beck Depression Inventory II
CCMO	Central Committee on Research Involving Human Subjects
COMT	Catechol-O-Methyl Transferase
CRF	Case Record Form
CRU	Clinical Research Unit
DA	Dopamine receptor Agonist
EudraCT	European drug regulatory affairs Clinical Trials GCP Good Clinical Practice
EQ-5D	EuroQol-5D
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
LLD	Local Logistics Database
IB	Investigator's Brochure
IMPD	Investigational Medicinal Product Dossier
MAO-B	Monoamine Oxidase-B
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
MMSE	Mini Mental State Examination
PD	Parkinson's Disease
PDI	Peripheral Decarboxylase Inhibitor
PDQ-39	Parkinson's Disease Questionnaire-39
PIN	Personal Identification Number
(S)AE	Serious Adverse Event
SPC	Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)
SUSAR	Suspected Unexpected Serious Adverse Reaction
UPDRS	Unified Parkinson's Disease Rating Scale
WMO	Medical Research Involving Human Subjects Act (Wet Medisch-wetenschappelijk Onderzoek met Mensen

1. SUMMARY

Rationale: At present there is no cure for Parkinson's disease (PD). The mainstay of the treatment consists of dopamine replacement either with the dopamine precursor levodopa — plus a peripheral decarboxylase inhibitor — or with directly acting dopamine receptor agonists. There is considerable debate about when and how to initiate pharmacological therapy. Currently, CBO-guidelines indicate to start symptomatic treatment in PD only when functional health is hindered. The results of recent studies suggest that early treatment with levodopa might have a — thus far unrecognized — delayed beneficial effect on PD symptoms.

Objective: To investigate whether early treatment with levodopa has a delayed beneficial effect on PD symptoms and functional health, and improves the ability to (maintain) work, reduces the use of (informal) care, caregiver burden, and costs. Additionally, cost-effectiveness and cost-utility of early levodopa treatment will be assessed.

Study design: The study is a prospective, randomized delayed-start, double blind and placebo-controlled multi-center trial.

Study population: 446 newly diagnosed PD patients without impaired functional health.

Intervention: 40 weeks treatment with levodopa/carbidopa 100/25 mg TID (including 2 weeks of dose escalation) or 40 weeks placebo TID (phase 1). Following phase 1, all patients will receive levodopa/carbidopa 100/25 mg TID for 40 weeks, including 2 weeks of dose escalation for the placebo-group (phase 2).

Main study outcome measures: There are 8 specified Assessment Visits: at baseline and at 4, 22, 40, 44, 56, 68, and 80 weeks. Outcome measures are the Unified Parkinson's Disease rating scale (UPDRS), the AMC Linear disability Scale (ALDS), side effects, perceived quality of life (Parkinson's Disease Questionnaire-39, (PDQ-39)), the EuroQol-5D (EQ-5D), ability to (maintain) work, the use of (informal) care, caregiver burden, and costs.

Keywords

Parkinson's disease; levodopa; randomized delayed start trial; disease modifying; clinical outcome; cost-effectiveness analysis; cost-utility analysis.

2. INTRODUCTION AND RATIONALE

2.1 Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disease affecting the motor, autonomic, cognitive, and sensory systems. The motor symptoms are characterized by the progression of tremor, rigidity, bradykinesia, and postural instability. In the Netherlands, 50,000 people suffer from PD. Above the age of 65 years; the prevalence of PD is 1.6% (1). PD is one of the diseases with the largest impact on functional health and perceived quality of life, right after dementia and esophageal cancer (2). In younger PD patients, social functioning and the ability to work are impaired. Caring for a family member with PD is a long and stressful process, which imposes heavy demands on the emotional, physical, and financial resources of the caregiver (3).

At present there is no cure for PD. The core symptoms are caused by the degeneration of dopamine producing neurons. The mainstay of the treatment consists of dopamine replacement either with the dopamine precursor levodopa — plus a peripheral decarboxylase inhibitor (PDI) — or with directly acting dopamine receptor agonists (DA). There is considerable debate about when and how to initiate pharmacological therapy (4). Currently, CBO-guidelines indicate to start symptomatic treatment in PD only when functioning in daily life is hindered.

For over 40 years levodopa is used to treat PD. Levodopa is inexpensive and very efficacious (5; 6). Nevertheless, many neurologists tend to delay initiation and timely adjustments of levodopa for several reasons — with in some patients the acceptance of severe disability and unnecessary loss of functional health. One reason is the concern that levodopa is toxic. To date however, this has never been supported by the results of clinical studies. Another reason is the concern for the induction of side effects such as dyskinesias. Sooner or later however, almost all patients need levodopa and although the use of DA delays the onset of dyskinesias, these benefits disappear when levodopa therapy is started. More importantly, the motor symptoms of PD improve more with levodopa as compared to DA (7; 8).

2.2 Delayed effects of symptomatic treatment of Parkinson's disease

The following physiological effects of the pharmacological treatment of PD can be envisioned. First, there are the direct effects on symptoms (direct symptomatic). These effects are related to the plasma and brain levels of the drug (*e.g.*, the antiparkinson effect of

levodopa takes effect when the concentration of the drug exceeds a certain threshold). Secondly, there are long-term effects (disease-modifying). Theoretically, these can be subdivided in effects on the survival of neurons (neuroprotection) and functional effects. Anyway, long-term beneficial functional effects may postpone disability and improve patients' quality of life.

In the "Earlier versus Later Levodopa Therapy in Parkinson's disease study" (ELLDOPA-study) (6), 361 patients were randomized to receive levodopa in three different doses or placebo for 40 weeks. After two weeks of withdrawal, the levodopa-treated groups scored on average six or more points less on the UPDRS compared to the placebo-group — a lower score means less severe disease. These results suggest that levodopa has a prolonged beneficial — and clinically important — effect on PD symptoms. The consecutive assessments within the first 40 weeks of the ELLDOPA-study show that the differences between the treatment arms increase over time, indicating that the beneficial effect of levodopa augments over time. This is in agreement with a prolonged beneficial effect that lasts for several months or longer. Interestingly, the data of the ELLDOPA-study suggest that the effect is stronger with higher doses of levodopa.

In another study, 163 patients with early PD were treated with levodopa and benserazide, combined with either selegiline, a monoamine oxidase B-inhibitor (MAO-B-inhibitor), or placebo in a five-year treatment schedule followed by a one-month washout of selegiline (9). During washout, there was no trend towards worsening among patients previously treated with selegeline, *i.e.*, they continued to function better than the controls.

In the "Rasagiline monotherapy in early Parkinson's disease"-trial (TEMPO-study) (10), patients with early-stage PD were randomly assigned to the MAO-B-inhibitor rasagiline — 1 or 2 mg per day — for 1 year or placebo for 26 weeks followed by 26 weeks rasagiline 2 mg per day. Subjects treated with 1 and 2 mg rasagiline per day for 12 months showed less functional decline than subjects whose treatment was delayed for 6 months. The results of the TEMPO-study suggest a disease modifying effect of rasagiline. The ADAGIO-study also had a delayed start design, but 36 instead of 26 weeks for each treatment-phase. The results showed a beneficial delayed effect for the 1 mg per day group, but no beneficial effect for the delayed start 2 mg per day group (11). Given the negative findings for the 2-mg dose, there is no definite conclusion regarding the disease-modifying effect of rasagiline at a dose of 1 mg per day.

The PRamipexole On Underlying Disease (PROUD) study assessed early versus delayed pramipexole treatment in early PD. The study has not been published yet. 535 untreated PD patients were randomized to double-blind placebo or pramipexole (1.5 mg per day) for 6-9 months, and continued with pramipexole for up to 15 months. The results of the PROUD-study do not support a disease-modifying effect of pramipexole.

The results of the ELLDOPA study indicate that levodopa may have a delayed beneficial effect in addition to the direct symptomatic effect. Whether this is an effect on the survival of neurons (*i.e.*, neuroprotection) or a functional effect (*e.g.*, effects on compensatory mechanisms in early PD) is not clear. The mechanism of action of rasagiline is through inhibition of MAO-B leading to slower catabolism of endogenous dopamine. The data regarding the possible disease modifying effects of rasagiline are conflicting. Pramipexole is a DA and exerts its effect by stimulating dopamine receptors directly. Pramipexole has a dopamine receptor affinity profile which is different from the profile of (endogenous) dopamine (12). Hypothetically, the presynaptic striatal effects of pramipexol may even reduce the amount of striatal dopamine and therefore the results of the PROUD study do not enfeeble the hypothesis that levodopa has a disease modifying effect. To summarize, data regarding the possible delayed effects of other symptomatic treatments than levodopa are not conclusive.

2.3 Hypothesis

Levodopa has a large direct symptomatic effect and may have a clinically relevant delayed beneficial effect.

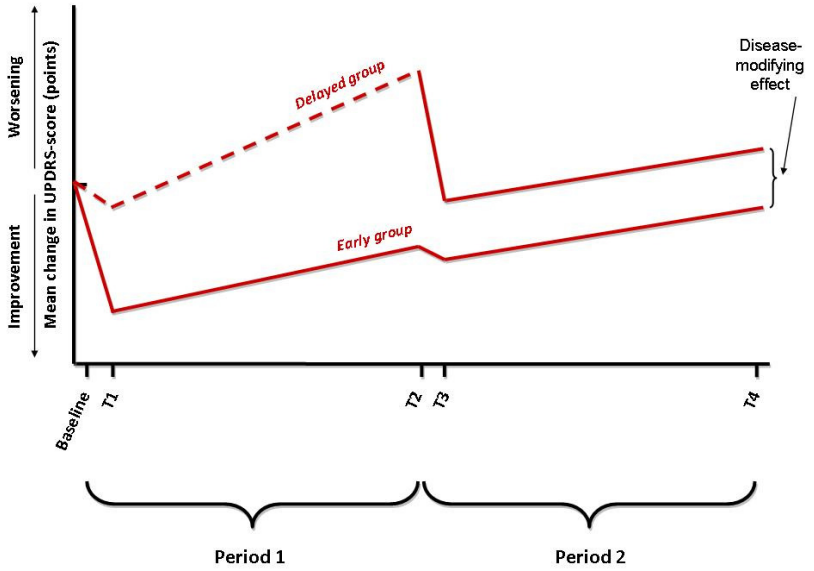
3. OBJECTIVES

Our aim is to investigate whether the early start of levodopa has a delayed beneficial effect on PD symptoms and functional health, subsequently improves patient's quality of life and the ability to (maintain) work, reduces the use of (informal) care, caregiver burden, and costs. We will also assess cost-effectiveness and cost-utility of early levodopa treatment.

4. STUDY DESIGN

The study is a randomized, double blind, placebo-controlled multi-center clinical trial. To differentiate between the direct symptomatic effect and the delayed, disease modifying effects of levodopa, we will use a randomized delayed start design (Figure 1).

Figure 1. Delayed start design



Studies with a delayed-start design investigate two agents: active treatment (A, solid line) and placebo treatment (P, dashed line). The study consists of two phases. In phase 1, patients are randomly assigned at baseline (time point 0) to A or P and receive a study agent from time point 0 to T2. Data in time period 0 to T1 usually reflect transitory responses to initiation of study agents and are often not used in the analysis. Time period T1 to T2 is used to collect data to evaluate the effect of the agent on symptoms and a possible indication of a disease-modifying effect.

In phase 2 (time point T2 to T4), all patients receive active-treatment A. Data from time period T2 to T3 may reflect transitory responses and are usually not used in the analysis. Time period T3 to T4 is used to collect data to evaluate disease-modifying effects of the agent. The difference between the P–A and A–A curves at time point T4 is used to evaluate the disease-modifying effect, and the difference in the slopes of P–A and A–A from time period T3 to T4 is used to test whether the disease-modifying effect is maintained in phase 2.

5. STUDY POPULATION

5.1 Population

In general, patients with PD in the Netherlands are diagnosed and treated by a neurologist. Patients will be recruited from community and academic hospitals. We approached all hospitals in the Netherlands and asked for participation in the study. To date, 63 neurology clinics have signed the “intent for participation” statement (Appendix I).

5.2 Inclusion criteria

The inclusion criteria are:

- idiopathic PD (13) with bradykinesia and at least two of the following signs:
    - resting tremor;
    - rigidity;
    - asymmetry.
- newly diagnosed PD within the past two years;
- age 30 years and over;
- a life expectancy of more than two years;
- no limitations in functional health for which the patient needs PD-medication.

5.3 Exclusion criteria

The exclusion criteria are:

- tremor as most prominent symptom, such as (13):
    - a severe resting tremor that is present (almost) continuously;
    - tremor of medium to large amplitude which results in functional disability (such as interfering with feeding)
- previous treatment with PD-medication, *e.g.,* levodopa, DA, MAO-B-inhibitor, catechol-O-methyl transferase-inhibitor (COMT-inhibitor), or amantadine;
- cognitive impairments, *i.e.,* Mini Mental State Examination (MMSE) of 23 points or lower (14);
- more than 28 points on the Beck Depression Scale II (BDI-II) (15);
- diagnosis of depression by a psychiatrist in the last year;
- history of psychosis;
- the presence of signs indicating atypical or secondary parkinsonism such as:
    - the use of drugs that may cause parkinsonism (*e.g.*, metoclopramide, cinarizine, anti-psychotics, natrium-valproate, lithium, amiodarone);

- metabolic disorders (*e.g.,* Wilson's disease);
- encephalitis;
- vascular parkinsonism;
- repeated head-trauma.

- untreated closed-angle glaucoma;
- alcohol abuse;
- pregnancy
- legally incompetent adults;
- inability to provide written informed consent.

5.4 Sample size calculation

Calculation

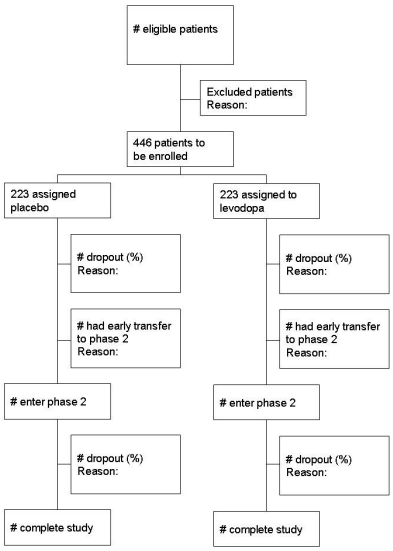
The final outcome assessment takes place at 80 weeks, which includes active treatment in both trial arms during the last 40 weeks. In view of a recent well-designed study, we consider a difference of 4 points on the total UPDRS as clinically relevant (16). We assume a mean baseline UPDRS score of 28 points with a standard deviation of 13 points, based on the results of the ELLDOPA-study (6). At the final outcome assessment at 80 weeks, we anticipate a mean UPDRS score in the early treatment group of 31 points (worsening of 3 points during follow-up) and a mean UPDRS score in the delayed group of 35 points (worsening of 7 points).

A sample size of 167 in each group will have 80% power to detect a difference in mean follow-up scores of 4 points — the difference between the early group of 31 points and the delayed group mean of 35 points — assuming that the common standard deviation is 13, and using a two group t-test with a 0.05 two-sided significance level. Assuming a withdrawal rate of 25 percent, we plan to include 223 patients per treatment arm, which means 446 patients in total (Figure 2).

Motivation for expected withdrawal rate

In the ELLDOPA-study a dropout rate of 22.2 percent was reported in the placebo-group (6). After 80 weeks, the ADAGIO-study reported a total dropout rate of 24.4 percent in the 1 mg delayed start group and 19.2 percent in the 2 mg delayed start group. Based on these results, a total withdrawal rate of 25 per cent is considered realistic.

Figure 2. Flow chart



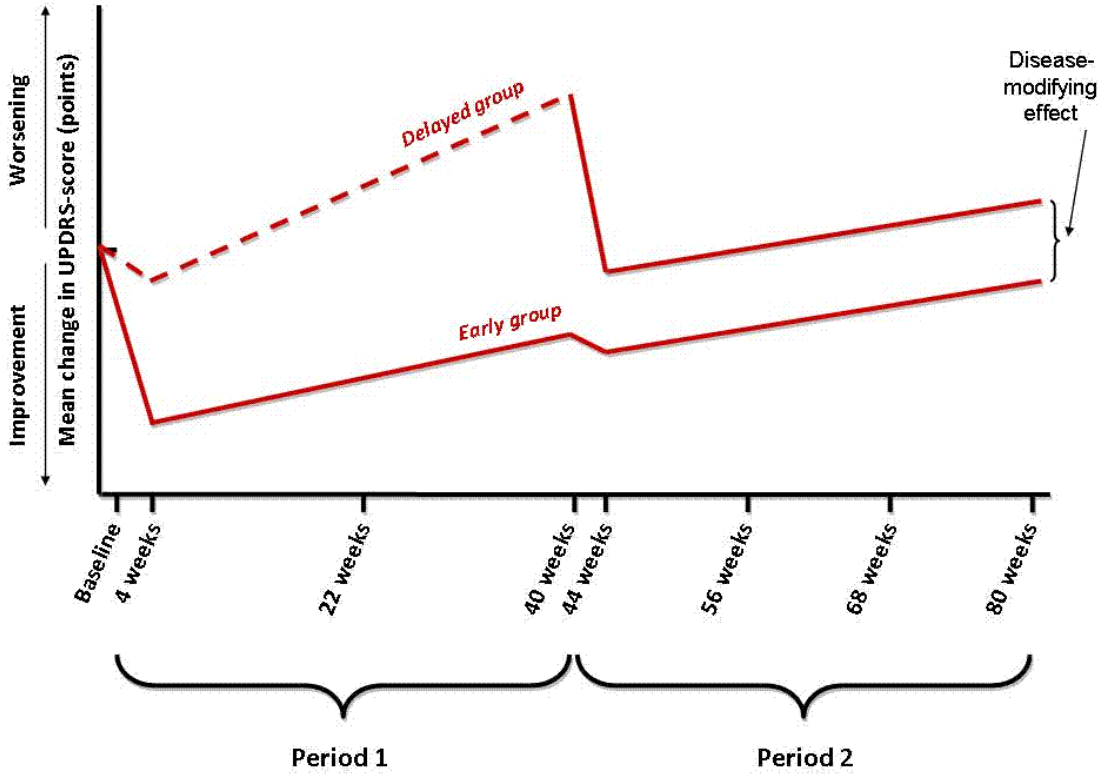
6. TREATMENT OF SUBJECTS

6.1 Investigational treatment

Patients will be randomized to 40 weeks treatment with levodopa/carbidopa (early group) or to 40 weeks placebo (delayed group). This phase is called Phase 1 (Figure 3). After this, all patients will receive 40 weeks levodopa/carbidopa (Phase 2). Carbidopa is the PDI incorporated in the tablet.

There are eight specified assessment visits: at baseline, and after four weeks, 22 weeks, 40 weeks, 44 weeks, 56 weeks, 68 weeks, and 80 weeks (respectively Visits 1, 2, 3, 4, 5, 6, 7 and 8). A minimum of 8 Visits is needed to investigate progression of symptoms during Phase 1 and Phase 2.

Figure 3. Current study design



The patients in the early treatment group will take levodopa/carbidopa capsules according to the starting-schedule during the first two weeks (Table 1). In week 3 to 40, they will take levodopa/carbidopa 100/25 mg tablets TID (phase 1). In week 41 and 42, they will take

levodopa/carbidopa 100/25 mg capsules TID. The remaining 38 weeks (week 43 to week 80) the levodopa/carbidopa 100/25 mg tablets will be prescribed by the treating neurologist and obtained from regular pharmacies (phase 2).

The patients in the delayed start group will take placebo capsules TID during the first 2 weeks. Subsequently during week 3 to 40, they will take placebo tablets TID. Week 41 and 42, they will take levodopa/carbidopa capsules according to the starting-schedule (Table 1). During week 43 to week 80, the levodopa/carbidopa 100/25 mg tablets will be prescribed by the treating neurologist and obtained from regular pharmacies (phase 2).

Because the treating neurologists will prescribe regular Levodopa/carbidopa 100/25 mg tablets TID for the last 38 weeks (week 43 to week 80), the study-costs are kept lower. Besides, after 40 weeks most patients would need regular anti-Parkinson medications if they did not participate in the study

During the first 2 weeks of phase 1 (week 1 and 2) and during the first 2 weeks of phase 2 (week 41 and 42) the study medication will be distributed in capsules. During week 3 to 40 (phase 1), patients will take tablets.
The levodopa/carbidopa tablets and placebo tablets will be identical in appearance, smell, and taste. The levodopa/carbidopa 50/12.5 mg capsules, the levodopa/carbidopa 100/25 mg capsules, and the placebo capsules will be identical in appearance, smell, and taste. If possible, changes in PD-medication will be avoided during the course of the study.

Table 1. Treatment schedule

		Early group			Delayed group		
		Morning	Noon	Evening	Morning	Noon	Evening
Phase 1	Week 1 (capsules)	50/12.5	Placebo	50/12.5	Placebo	Placebo	Placebo
	Week 2 (capsules)	100/25	50/12.5	50/12.5	Placebo	Placebo	Placebo
	Weeks 3 to 40 (tablets)	100/25	100/25	100/25	Placebo	Placebo	Placebo
Phase 2	Week 41 (capsules)	100/25	100/25	100/25	50/12.5	Placebo	50/12.5
	Week 42 (capsules)	100/25	100/25	100/25	100/25	50/12.5	50/12.5
	Week 43 to 80 (tablets*)	100/25	100/25	100/25	100/25	100/25	100/25

Doses are written as levodopa/carbidopa mg.

* The treating neurologist will prescribe the medication.

Motivation for interventions

We chose a study period of 80 weeks to distinguish short-term and long-term effects of levodopa. The study period is in agreement with the study periods of similar studies.

Eight assessments are needed to compare estimates of slope (the change in UPDRS points per week) between the early group and the delayed group for phase 1 and phase 2, *i.e.*, to assess the short-term and delayed effects of levodopa.

6.2 Use of co-intervention

Patients will not receive other PD medication than the study medication, such as DA's, MAO-B-inhibitors, and COMT-inhibitors.

6.3 Escape medication

If a patient needs additional treatment during phase 1, the patient will proceed to phase 2. For a patient that was assigned to the early group this means no change in treatment. For patients assigned to the delayed group this implies starting levodopa/carbidopa treatment. Patients who subsequently require additional therapy will not be withdrawn from the study. The treating neurologist decides if a patient needs more treatment.

7. INVESTIGATIONAL MEDICINAL PRODUCT

Clinical experience with levodopa has been widely reported for over 40 years. There are 2 placebo-controlled studies with levodopa (5; 6). Levodopa treatment has been compared with DA in a number of randomized clinical trials and, less rigorously, with other anti-parkinsonian treatments — such as anti-cholinergic drugs, amantadine, and MAO-B-inhibitors. A systematic review of the available trials suggests that levodopa is more efficacious than comparators that were tested for symptomatic monotherapy of PD (7; 8).

7.1 Name and description of investigational medicinal product

See Summary of Product Characteristics (SPC) for levodopa/carbidopa 50/12.5 mg capsules (page 1-10) and levodopa/carbidopa 100/25 mg capsules and tablets (page 1-11). For the description of placebo capsules (matching levodopa/carbidopa 50/12.5 mg and 100/25 mg capsules) and placebo tablets (matching levodopa/carbidopa 100/25 mg tablet) see the Investigational Medicinal Product Dossier (IMPD) (Appendix II and III).

7.2 Summary of findings from non-clinical and clinical studies

See SPC for levodopa/carbidopa 50/12.5 mg capsules (page 7-8) and levodopa/carbidopa 100/25 mg capsules and tablets (page 8-9). For description of placebo capsules (matching levodopa/carbidopa 50/12.5 mg and 100/25 mg capsule) and placebo tablet (matching levodopa/carbidopa 100/25 mg tablet) see the IMPD (Appendix II and III).

7.3 Summary of known and potential risks and benefits

See SPC for levodopa/carbidopa 50/12,5 mg capsules (page 6-7) and levodopa/carbidopa 100/25 mg capsules and tablets (page 6-8). For description of placebo capsules (matching levodopa/carbidopa 50/12.5 mg and 100/25 mg capsules) and placebo tablets (matching levodopa/carbidopa 100/25 mg tablet) see the IMPD (Appendix II and III).

7.4 Description and justification of route of administration and dosage

Patients will take the study medication orally TID. This has been a safe route of administration for over 40 years and has the lowest burden for the patient compared to other ways of administrating the medication, because patients can use the medication at home.

We chose the daily levodopa/carbidopa dose of 300/75 mg as a trade-off between high doses, with more risks for side effects, and low doses, *i.e.*, less effective doses. A typical starting dose is for example levodopa/carbidopa 50/12.5 mg BID. In regular practice — after

therapy is initiated — levodopa/PDI may be titrated upward over several weeks to 400/100 to 800/200 mg daily, divided into three or four doses (17). In the ELLDOPA-study, three levodopa doses were tested and compared with placebo; 300 mg per day was the middle daily dose (6).

7.5 Dosages, dosage modifications and method of administration

The following tablets will be used (during week 3 to 40, phase 1):

- Levodopa/carbidopa 100/25 mg (via ACE Pharmaceuticals);
- matching placebo identical in appearance, smell, and taste (via ACE Pharmaceuticals).

The following capsules will be used (during week 1 and 2 [phase 1] and week 41 and 42 [phase 2]):

- Levodopa/carbidopa 50/12.5 mg (via ACE Pharmaceuticals);
- Levodopa/carbidopa 100/25 mg via ACE Pharmaceuticals);
- matching placebo identical in appearance, smell, and taste (via ACE Pharmaceuticals).

From week 42 onward the treating physician will prescribe regular levodopa/carbidopa 100/25 mg, which the patient will obtain from his own pharmacy.

The patients in the early treatment group will take levodopa/carbidopa capsules according to the starting-schedule during the first two weeks (Table 1). In week 3 to 40, they will take levodopa/carbidopa 100/25 mg tablets TID (phase 1). In week 41 and 42, they will take levodopa/carbidopa 100/25 mg capsules TID. The remaining 38 weeks (week 43 to week 80) the levodopa/carbidopa 100/25 mg tablets will be prescribed by the treating neurologist and obtained from regular pharmacies (phase 2).

The patients in the delayed start group will take placebo capsules TID during the first 2 weeks. Subsequently during week 3 to 40, they will take placebo tablets TID. Week 41 and 42, they will take levodopa/carbidopa capsules according to the starting-schedule (Table 1). During week 43 to week 80, the levodopa/carbidopa 100/25 mg tablets will be prescribed by the treating neurologist and obtained from regular pharmacies (phase 2).

Because the treating neurologists will prescribe regular Levodopa/carbidopa 100/25 mg tablets TID for the last 38 weeks (week 43 to week 80), the study-costs are kept lower. Besides, after 40 weeks most patients would need regular anti-Parkinson medications if they did not participate in the study

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7.6 Preparation and labelling of Investigational Medicinal Product

For the IMPD of levodopa/carbidopa 50/12.5 mg capsules, levodopa/carbidopa 100/25 mg capsules, placebo capsules, levodopa/carbidopa 100/25 mg tablets, and placebo tablets, see Appendices II, III, IV and V. Labelling will be performed according to the Good Manufacturing Practice (GMP) guidelines. For the description of the labelling-procedures, see Appendix VI.

7.7 Drug accountability

After randomisation, an e-mail is automatically generated and sent to ACE Pharmaceuticals. This E-mail contains the following information:

- Randomization number;
- Name, address and telephone number of the neurologist and research nurse that initiated the randomisation;
- Name and address of the concerning hospital;
- Name, address and telephone number of the local investigator of the concerning hospital;
- Name, address and telephone number of the patient.

ACE Pharmaceuticals will allocate the randomized patient to a medication number that corresponds with the treatment group, early- or delayed group and is responsible for manufacturing, packaging, labelling and shipment of the study medication.

Randomization data are kept strictly confidential and accessible only to authorised persons at ACE Pharmaceuticals until the time of unblinding. Code-breaking sheets for emergency use will be kept in a hospital safe.

8. METHODS

8.1 Study parameters

8.1.1 Main study endpoint

The primary clinical outcome measure is the difference in the mean total UPDRS scores between the early and delayed groups at 80 weeks.

The UPDRS consists of the following four parts (18):

I. Non-motor experiences of daily living (6 items);
II. Motor experiences of daily living (20 items);
III. Motor examination (33 items);
IV. Motor complications (6 items).

A higher score denotes more severe PD symptoms: the best score is 0 and the worst score 176.

8.1.2 Secondary study endpoints

Secondary outcomes are:

(I) The progression of symptoms between Visit 2 and Visit 4 (phase 1) and between Visit 5 and Visit 8 (phase 2) measured with the UPDRS (Figure 3);

Progression in Phase 1

Superiority of the UPDRS slope during phase 1 of the early group as compared to the delayed group.

Progression in Phase 2

Non-inferiority of the UPDRS slope in phase 2 of the early group as compared to the delayed group.

(II) Disability measured with the ALDS (19);

The difference between the early group and the delayed group in median change scores (change score = difference between baseline and 80 weeks assessment score) of the ALDS-score. The ALDS is a flexible and feasible instrument to assess the level of disability in patients with newly diagnosed PD.

(III) Number of patients that need additional medication for PD;

(IV) Number of patients that proceed early to phase 2;

(V) Number of patients withdrawn from the study or lost to follow up;

(VI) Levodopa induced motor response fluctuation;

The frequency, severity, nature, and duration of any levodopa induced motor response fluctuation throughout the course of the study.

(VII) (Serious) adverse events;
The frequency, severity, nature, and duration of any adverse event throughout the course of the study

(VIII) Perceived quality of life measured with the PDQ-39 (20);

(IX) The utility measure in the cost-utility analysis measured with the EQ-5D (21);

(X) Working status and absence from paid work measured with a standardized questionnaire (22);

(XI) Caregiver burden (23);

(XII) Resource utilization outside of the participating hospitals through a standardized questionnaire

8.2 Randomization, blinding and treatment allocation

After inclusion, the patient will be randomized by the web-based database. The server of the website will operate from the Academic Medical Center. Eligible patients will be randomized by a computer in a 1:1 ratio to the early group or the delayed group in a double-blind design. Untill the computerized randomization is fully operational, patients will be randomized by the research nurse in the AMC or, in her absence, by C.V.M. Verschuur or R.M.A. de Bie.
Randomization will be stratified by type of hospital (University Medical Center versus Non-University Medical Center), age (below 65 years or 65 years and older), and disease duration (shorter than 0.5 year or 0.5 year and longer), using variable permuted blocks. Code-breaking sheets for emergency use will be kept in a hospital safe.
Study personnel, research nurses, neurologists, and the patients are blinded to the treatment allocation at all times. All data will be entered in the central database before the treatment codes are broken. Indications to break the randomization code are not predefined.

8.3 Study procedures

When the neurologist evaluates a patient for eligibility, he will check the inclusion and exclusion criteria. The neurologist will introduce the study to the patient, inform the patient, and ask the patient permission to be contacted by a research nurse. If the patient is eligible and agrees, the neurologist will inform the research nurse at the AMC. The research nurse in the AMC will register the patient in the Local Logistics Database (LLD), after which the local research nurse will be informed automatically. The neurologist will provide the patient with written information about the study and with the Informed Consent Form (Appendix VII).
Within three days, a research nurse will contact the patient by phone to answer any questions about the study. Patients will be given as much time as needed to decide if they want to participate. If necessary, an appointment will be made to answer any questions at the

hospital where the patient was seen by the neurologist who made the diagnosis and introduced the study. If the patient agrees to participate, the first appointment will be made (Visit 1) at the hospital where the patient was seen by the neurologist who made the diagnosis and introduced the study.
At the start of Visit 1, the patient signs the informed consent form before continuation of the assessments. At the end of Visit 1, the research nurse will randomize the patient by the central website based computer program. The patient will be assigned to the early group or to the delayed group. Because of geographical reasons, each main study center will station a research nurse — of which some part-time; *i.e.*, AMC Amsterdam, Leiden UMC, UMC Groningen, UMC Nijmegen, and Atrium MC Heerlen. From each main study center, the study logistics of on average 12 other hospitals can be performed. Because the logistics are complex and the assessments are cumbersome, it is vital that research nurses perform these to facilitate inclusion and to assure proper follow-up assessments.
All research nurses will be trained and examined in performing all aspects of the Visits, *i.e.* explaining the study and using the questionnaires. Every six months, the research nurses will follow additional training to keep their expertise up to date and to minimize intra-rater and inter-rater variability.

During Visit 1 (baseline), patients will undergo documentation of MMSE, BDI-II, UPDRS, ALDS, PDQ-39, EQ-5D, resource utilization and labor participation and caregiver burden through a standardized questionnaire, and current medication (Table 2). The additional baseline characteristics that will be recorded are the first symptom of PD (*e.g.*, tremor, bradykinesia) and the date of first manifestation of PD.
At Visits 2, 3, 4, 5, 6, 7 and 8, patients will undergo documentation of UPDRS, ALDS, and side effects through a standardized questionnaire. Patient compliance will be monitored at every study Visit except Visit 1 (baseline) by counting the empty packages and remaining capsules (week 1-2 and week 41-42) or remaining tablets (week 3-40 and week 43-80). Therefore, patients must bring the unused medication and empty packages at every study visit.

At Visits 3, 4, 6, 7 and 8 patients will also undergo documentation of PDQ-39, EQ-5D, resource utilization and labor participation and caregiver burden through a standardized questionnaire.

At baseline, three 7 mL EDTA blood samples will be drawn and stored for future genetic research; e.g., to evaluate possible genetic modifiers of response to medication.

Table 2. Assessment schedule

	Inclusie	Baseline	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
In- and exclusioncriteria	X								
Baseline characteristics		X							
MMSE		X							X
Medication		X	X	X	X	X	X	X	X
BDI-II		X			X				X
UPDRS		X	X	X	X	X	X	X	X
ALDS		X	X	X	X	X	X	X	X
Side effects questionnaire			X	X	X	X	X	X	X
Compliance			X	X	X	X	X	X	X
PDQ-39				X	X		X	X	X
EQ-5D		X		X	X		X	X	X
Resource utilization and labor participation		X		X	X		X	X	X
Caregiver burden		X		X	X		X	X	X

X = assessment, white = no assessment

8.4 Withdrawal of individual subjects

If patients wish to do so, they can leave the study at any time for any reason without consequences. The investigator can decide to withdraw a subject from the study if the treating neurologist points out urgent medical reasons, which make it necessary to withdraw the patient from the study. The datasets from withdrawn patients will be kept in the study database to facilitate analysis according to the intention-to-treat principle. Criteria for withdrawal are not predefined.

8.5 Follow-up of subjects withdrawn from treatment

If a patient violates the study medication protocol this will be registered. All further study procedures and measurements will be conducted according to the study protocol.

8.6 Premature termination of the study

Reasons for premature termination of the study are not specified.

9. SAFETY REPORTING

9.1 Section 10 WMO events

Consistent with section 10 - subsection 1 of the Medical Research Involving Human Subjects Act (WMO), the investigator will inform the subjects and the reviewing accredited Medical research ethics committee (METC) if anything occurs, that implies that the disadvantages of participation are significantly greater than foreseen. Inclusion will be suspended pending further review by the METC. All subjects are kept up to date by the investigator.

9.2 Adverse and serious adverse events

Adverse events are defined as any undesirable experience occurring to a subject during the study, irrespective of a possible relationship with the investigational drug, i.e. levodopa/carbidopa. All adverse event reported by the subjects or observed by the treating physicians will be recorded.

A serious adverse event (SAE) is any event that:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization
- results in persistent or significant disability or incapacity.

If an SAE occurs, the principal investigator will be notified by email or telephone within 24 hours. Using the Central Committee on Research Involving Human Subjects (CCMO) module 'ToetsingOnline', all SAEs will be reported to the CCMO and central METC. The reporting will occur within 15 days after the investigator has first received information on the SAE. For fatal or life-threatening cases a preliminary report will be offered within 7 days followed by a complete report within 8 days.

9.3 Suspected unexpected serious adverse reactions (SUSAR)

Adverse reactions are all untoward and unintended responses to the investigational product related to any dose administered. Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information, *i.e.*, the summary of the product characteristics.

Using the CCMO module 'ToetsingOnline', all SUSARs that could have consequences for the safety of the subjects involved in the LEAP-study will be reported to the CCMO and central METC. The reporting will occur within 15 days after the investigator has first

received information on the SAE. For fatal or life-threatening cases a preliminary report will be offered within 7 days followed by a complete report within 8 days.

The remaining SUSARs are recorded in an overview list (line listing) that will be submitted once every 6 months to the METC. This line listing provides an overview of all SUSARs concerning the trial medication, accompanied by a brief report highlighting the main points of concern.

9.4 Annual safety report

In addition to the expedited reporting of SUSARs, the investigator will submit a safety report once a year to the central METC and the competent authority until the follow-up of the last patients is completed. This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse events, ordered by organ system;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and a descriptive report on the efficacy and harmfulness of the medicine under investigation.

9.5 Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

9.6 Safety Monitoring

Because this study is a low-risk study, there will be no safety monitoring.

10. STATISTICS

10.1 Clinical evaluation

Data will be analyzed according to the intention-to-treat principle. The main analysis of this trial consists of a comparison between the trial treatment groups of the primary outcome after 80 weeks. First, the follow-up difference of mean UPDRS scores between the treatments arms will be crudely analyzed using a two-group t-test. Second, the UPDRS follow-up scores will be further investigated using analysis of covariance (ANCOVA), taking into account patients' UPDRS baseline values.

With regard to the comparisons of the secondary outcomes, progression of symptoms during phases 1 and 2, we plan two separate analyses. For phase 1, we will use measurements 2 (4 weeks), 3 (22 weeks) and 4 (40 weeks) to estimate the difference in slopes between the two treatment groups using a random effects model to account for the repeated measures within patients. A more progressive course (steeper upward slope) in the placebo group during phase 1 can reflect direct symptomatic effects or disease-modifying effects of levodopa. This will be further explored by examining the slopes of phase 2. Equal steepness of the slope during phase 2 indicates that the (assumed) effect found in phase 1 is a true disease-modifying effect. Therefore, we will use measurements 5 (44 weeks), 6 (56 weeks), 7 (68 weeks), and 8 (80 weeks) to test equality of progression in phase 2 with a non-inferiority test on the difference between the slopes of the two treatment arms using a non-inferiority margin of 0.055 UPDRS points difference in increase per week. For phase 2, we will also use a random effects model.

As pointed out before, the main outcome in this study will be the comparison between treatment arms on UPDRS scores after the total study period of 80 weeks, since this outcome relates to clinical practice. The comparisons of slopes in the secondary analyses serve only to differentiate between the different types of treatment effects. Here we pre-specify the possible inference made on these secondary analyses:

1) if a faster progression is found in the placebo group during phase 1 and the non-inferiority assumption assuming equal progression is met in phase 2, this will be indicative of a true disease-modifying effect;

2) if a faster progression is found in the placebo group during phase 1, but non-inferiority of slopes during phase 2 is not demonstrated, than the results are indicative of only direct symptomatic effects.

With regard to the comparisons of the other secondary outcomes (disability, number of patients that need additional medication for PD, levodopa induced response fluctuation, side effects, quality of life, ability to (maintain) work, use of (informal) care, and caregiver burden),

we will use the appropriate parametric and nonparametric statistics. In all analyses statistical uncertainties will be expressed in 95% confidence intervals.

10.2 Economic evaluation

10.2.1 General considerations

The economic evaluation of early levodopa treatment will be performed as a cost-effectiveness and cost-utility analysis from a societal perspective with the costs per unit on the UPDRS and the costs per quality adjusted life-year as the primary outcomes respectively.

The primary outcome of the cost-effectiveness analysis is closely related to the primary clinical outcome, the UPDRS, which is frequently used in clinical trials for PD to assess treatment efficacy. The cost-utility analysis is considered mandatory to enable health policy makers allocating scarce health care resources across disease populations, across interventions, and across health sectors, based on explicit efficiency criteria. It is expected that early levodopa treatment compared with delayed treatment is associated with moderately higher initial health care costs, but also with improved quality of life and increased ability to work during the follow-up period. It is yet unclear if the net effect of these expected consequences renders early levodopa treatment an affordable therapy in early PD.

Incremental cost-effectiveness and cost-utility ratios will be calculated for the extra costs per unit decrease in UPDRS score and the extra costs per additional quality of life years respectively. Sampling variability will be accounted for following bias-corrected and accelerated non-parametric bootstrapping. Cost-effectiveness planes and cost-effectiveness acceptability curves will be reported. Subgroup analyses by age and by level of co-morbidity will be performed. Younger patients (below 55 years of age) tend to develop motor complications more easily, while older patients or highly co-morbid patients may be more susceptible to short-term side effects. One-way and multi-way sensitivity analyses will be performed for the discount rate (0%, 3%, 4% and 5%), the length of the friction period (3-6 months), and choice of UK rather than Dutch tariffs of time trade-off ratings of health states (all, see below).

The time horizon in the study will initially extend to 80 weeks from randomization. With a time horizon of more than a year, time preferences come into play and have to be accounted for by discounting future benefits and costs. Discounting will be done against 4%.

As stated, the time horizon initially will be 80 weeks. However, it is well conceivable that differential consequences for early versus delayed levodopa treatment extend beyond that period. Following recent international recommendations (23) we propose an add-on mathematical modeling study to derive long-run estimates for a lifetime horizon. In this

mathematical modeling study, equations will be formulated that reflect the disease progression by deterioration of UPDRS score over time and that relate this deterioration to quality of life and costs. Estimates of model parameters will be derived from literature data and own data (*i.e.*, CARPA-cohort) on natural disease course and life expectancy.

10.2.2 Cost analysis

From the societal perspective the economic evaluation will include the direct medical as well as the direct and indirect non-medical costs of care. Direct medical costs result from the use of health care resources including levodopa treatment, out-patient and inpatient hospital treatment and diagnosis, out-of-hospital treatment by the family physician, psychologist, physiotherapist, and the like. Reimbursable (walking) aids or home adaptations (safe stairs) supplied by municipal agencies will be taken into account as well, if opportune. Direct non-medical costs reflect the non-reimbursable out-of-pocket expenses by patients related to the disease, for example travel to and from health care providers, private household assistance, over-the-counter medication, and non-reimbursable aids and adaptations at home. Also, non-reimbursable expenditures by informal caregivers will be monitored. Indirect non-medical costs are associated with loss of productivity due to inability to work. Both, absence from work as well as lost productivity while at work, will be registered during follow-up in the subgroup of patients below the age of 65.

The utilization of healthcare will be registered as part of the data collection for the trial (web based case record forms). Resource utilization outside of the participating hospitals will be documented by self-administered questionnaires that will be sent to patients along with the other study questionnaires. Patients will report the use of health services, including visits to the general practitioner or other healthcare providers. Working status and absence from paid work will be documented using a standardized questionnaire. Patients' primary caregiver, if present, will be asked to complete a survey on caregiver burden. For measurement frequency see the paragraph concerning outcome parameters.

The most recent national guidelines for unit costing in health care research will be applied (24). The friction cost method will be applied in case of costs of production loss and based on the most recent friction period. Costs will be price-indexed for the base year 2011. Yearly consumer price indices will be used to standardize unit costs estimated in different calendar years.

Costs will be calculated for individual patients by multiplying actual (health care) resource use and unit costs. Mean costs per patient over the period of the trial will be calculated.

10.2.3 Patient outcome analysis

Parkinson's disease may seriously affect a person's quality of life due to the physical symptoms and the psychological impact of having to cope with a progressive disease. Treatment with levodopa is highly effective in reducing and preventing symptoms. Long-term treatment however should be closely monitored for side effects and few patients may even exhibit side effects on the short-term. Clearly, the evaluation of levodopa treatment should include an assessment of the health burden in early PD. To this end, the disease specific PDQ-39 will be used to assess the quality of life as perceived by the patients (see clinical outcome parameters). The PDQ-39 contains 39 items representing four dimensions — Parkinson and systemic symptoms, social and emotional functioning. In addition, the EQ-5D will be applied as the utility measure in the cost-utility analysis. The EQ-5D contains five items: mobility, self-care, usual activities, pain/complaints, and mood (anxiety/depression). Each item has three response options: no problems, some problems, or serious problems. The EQ-5D scoring profile can be converted into a utility score based on general population based tariffs of time trade-off ratings of health states. Initially, available Dutch tariffs (25) will be applied, while widely used UK tariffs (26) will be applied in the sensitivity analysis (see above). The EQ-5D has been validated in PD patients, strongly correlates with clinical scales, and is more sensitive in this patient group than the well-known, also generic Short Form-36 (SF-36) (21). For measurement frequency, see the paragraph concerning outcome parameters.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The LEAP-study will be conducted according to the principles of the Declaration of Helsinki (version of 2008) and in accordance with WMO and other guidelines, regulations and Acts. Study monitoring and data management, will be performed in accordance with the International Conference on Harmonisation - Good Clinical Practice (GCP) guidelines. Technicians and data managers of the AMC Clinical Research Unit (CRU) will perform central data management, using Oracle Clinical. Internet-based remote data capture will be used for entering, managing and validating data from the investigative sites. Oracle Clinical was designed to meet industry regulations, including Food and Drug Association (FDA) 21CFR Part 11 Rule (1997), ICH; Good Clinical Practice: Consolidated Guideline (1997), and FDA Guidance for Industry “Computerized Systems Used In Clinical Trials” (1999). The approval of the ethics committees of the participating centers will be sought. The patients will receive written information about the study and they need to give their informed consent. Before the start of the study, it will be registered at a trial register (http://www.controlled-trials.com; ISRCTN Register).

The Investigator will permit independent monitoring. Monitors will have access to all CRF’s and subjects’ medical records which are relevant to this trial. The purpose of monitoring is to oversee the progress of the clinical trial and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, GCP-guidelines and the applicable regulatory requirements.

11.2 Recruitment and consent

When the neurologist evaluates a patient for eligibility, he will check the in- and exclusion criteria. The neurologist will introduce the study to the patient, inform the patient, and ask the patient permission to be contacted by a research nurse. If the patient is eligible and agrees, the neurologist will inform the research nurse at the AMC. The research nurse in the AMC will register the patient in the Local Logistics Database (LLD), after which the the local research nurse will be informed automatically. The neurologist will provide the patient with written information about the study and with the Informed Consent Form (Appendix VII).

Within three days, a research nurse will contact the patient by phone to answer any questions about the study. Patients will be given as much time as needed to decide if they want to participate. If necessary, an appointment will be made to answer any questions at the hospital where the patient was seen by the neurologist who made the diagnosis and introduced the study. If the patient agrees to participate, the first appointment will be made

(Visit 1) at the hospital where the patient was seen by the neurologist who made the diagnosis and introduced the study.

11.3 Benefits and risks assessment, group relatedness

For over 40 years levodopa is used to treat PD: it is inexpensive and very efficacious (5; 6). Nevertheless, many neurologists tend to delay initiation and timely adjustments of levodopa — with in some patients the acceptance of severe disability — for several reasons. One reason is the concern that levodopa is toxic. To date however, this has never been supported by the results of clinical studies. Another reason is the concern for the induction of side effects such as dyskinesias. Sooner or later however, almost all patients need levodopa and although the use of dopamine-agonists delays the onset of dyskinesias, these benefits disappear when levodopa therapy is started. More importantly, the motor symptoms of PD improve more with levodopa as compared to DA (7; 8). The dose used in this study is considered to be relatively low. Side effects of levodopa are dose-dependent.

Furthermore, if this trial confirms a delayed beneficial effect of early treatment with levodopa — in addition to the direct effect — on PD symptoms and functional health, and improves the ability to (maintain) work, reduces the use of (informal) care, caregiver burden, and costs, patients need to be treated with levodopa as soon as the diagnosis is made. Therefore we consider the risks and burden for the patient to be well in proportion to the potential value for the enrolled patients.

11.4 Compensation for injury

The sponsor/investigator has liability insurance, which is in accordance with article 7 subsections 6 of the WMO.

The sponsor (also) has insurance, which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,- (i.e., four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,- (i.e., three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,- (i.e., five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as ‘verrichter’ in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

12. ADMINISTRATIVE ASPECTS AND PUBLICATION

12.1 Handling and storage of data

The investigator will set up a Trial Master File at the beginning of the study. The list of essential documents will be in accordance with the GCP-guidelines. The essential documents that make up the file will be stored in a secure but accessible manner. All essential documents will be legible and accurate. The participating centers will keep copies of relevant documents, including essential center-specific documents.

12.2 Handling and storage of documents

When the neurologist evaluates a patient for eligibility, he will check the inclusion and exclusion criteria. The neurologist will introduce the study to the patient, inform the patient, and ask the patient permission to be contacted by a research nurse. If the patient is eligible and agrees, the neurologist will register the patient in the LLD and inform the local research nurse. The neurologist will provide the patient with written information about the study and with the Informed Consent Form (Appendix VII).
After inclusion, the patient will be randomized by the web-based database. The server of the website will operate from the Academic Medical Center. For each randomized patient a digital Case Record Form (CRF) will be completed. The CRF consists of a sequential set of instructions with provision for data recording. All randomized patients are identified by a Patient Identification Number (PIN) in combination with a center number. Trial personnel will not pass names outside the local hospital, except for the automatically generated E-mail for ACE-pharmaceuticals. a the time of inclusion. The local investigator will ensure that patients' anonymity is maintained. On screening forms, digital or paper CRF's or other documents submitted to the coordinating center, patients will only be identified by a PIN in combination with a center number. The subject identification code list will be safeguarded by the investigator.

Central data management will be performed in Oracle Clinical by technicians and data managers of the AMC Clinic Research Unit. Internet-based remote data capture will be used for entering, managing and validating data from the investigative sites. Oracle Clinical is designed to meet industry regulations, including:

- FDA 21CFR Part 11 Rule (March 20, 1997),
- ICH; Good Clinical Practice: Consolidated Guideline (May 9, 1997)
- FDA Guidance for Industry "Computerized Systems Used In Clinical Trials" (May 10, 1999)

12.3 Amendments

Amendments are changes made to the researchprotocol after a favourable opinion by the accredited METC has been given.

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.
Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the investigator.

12.4 Annual progress report

The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 End of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last Visit.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within fifteen days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

12.6 Public disclosure, publication policy and implementation

Results will be published in high-impact journals and will also be presented at international scientific meetings. The results are directly applicable by the physicians dealing with PD, e.g., neurologists, geriatricians, general practitioners, and nursing home doctors.

Our international network will enable us to present the results during international meetings on Neurology and Movement Disorders; e.g., International Congress of the Movement Disorders Society and the Congress on Parkinson's Disease and Related Disorders.

The project group includes a considerable number of the Dutch Movement Disorders experts. Also, already 63 neurology clinics have indicated that they will participate in the project (see appendix). The number of Dutch neurologists participating in the study will make it easy to disseminate the trial results. After completion of the trial, we will approach (the other) opinion leaders in the Netherlands, including medical heads of the Departments of Neurology and the “Nederlandse Vereniging voor Neurologie.” These persons will be informed about the trial results and our intention to add the results to the guidelines for treatment of PD.
Because the administration of levodopa is simple, safe, and inexpensive, we assume that implementation of the intervention will not be hindered by serious barriers — for example in terms of logistic or personnel constraints, or financial budget limitations — and can easily be incorporated into standard care.

The first author of all main publications concerning this trial is C.V.M. Verschuur, the Ph.D.-student that executes the study at the Academic Medical Center. The last author of all main publications concerning this trial will be R.M.A. de Bie, principal investigator of this study. The order of the other authors will be determined by the Steering Committee and R.M.A. de Bie.
Individual Investigators will be entitled to prepare ancillary papers on special topics. Approval by the Steering Committee is required before these papers can be submitted, unless these papers concern only patients of the individual Investigator and are not submitted on behalf of the LEAP-study group. Ancillary publications may not appear prior to the publication of the main results paper.

12.7 Agreements with Main Study Centers

Each Main Study Center aims to include 90 patients. For the first to 15th patient, the Main Study Center will receive a total of EUR 13.500,- in advance. For every subsequential patient that is included in the study, the Main Study Center will receive EUR 900,- for the total follow up after the patient has been included in the study. Each Main Study Center is responsible for the exact logistics of all Visits concerning the patients they included in the study.

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14. APPENDICES