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Levodopa in early Parkinsons disease

Submission date	Recruitment status	[_] Prospectively registered
02/08/2011	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
25/08/2011	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
18/10/2022	Nervous System Diseases	

Plain English summary of protocol

Background and study aims
The current widely-used treatment of Parkinsons disease (PD) consists of dopamine replacement with levodopa or dopamine agonists. There is considerable debate about when and how to start treatment with drugs. Although current guidelines indicate that treating the symptoms of PD should be started when normal movement becomes difficult, most neurologists still delay starting treatment of these symptoms. This results in an acceptance of disability early in the disease. The results of recent studies suggest that early treatment with levodopa might have a delayed positive effect on PD symptoms. The aim of this study is to investigate whether early treatment with levodopa has a delayed positive effect on PD symptoms and functional health, improves the ability to (maintain) work; and reduces the use of (informal) care, caregiver burden, and costs.

Who can participate?
Patients with newly diagnosed PD who dont need symptomatic treatment as judged by the treating neurologist

What does the study involve?
For 40 weeks, patients receive either levodopa/carbidopa or a dummy (placebo) three times a day; for the next 40 weeks, all patients receive levodopa/carbidopa three times a day. There are 8 assessments, all of which are performed by trained research nurses. The study measures disability, side effects, quality of life, ability to (maintain) work, the use of (informal) care, caregiver burden, and costs.

What are the possible benefits and risks of participating?
If the study shows a cost effective delayed positive effect of levodopa in newly diagnosed PD patients, treatment of symptoms should start as early as possible, i.e. immediately when the diagnosis is made. Subsequently, PD patients functional health and quality of life may improve substantially. This could prolong the normal level of social functioning and participation in the workforce. Levodopa has been the most commonly used medication for Parkinson's disease for over 40 years, with mostly minor side-effects. You can ask your neurologist for more information.

Where is the study run from?
Academic Medical Center (Netherlands)

When is the study starting and how long is it expected to run for?
August 2011 to November 2017

Who is funding the study?
Netherlands Organisation for Health Research and Development (ZonMw, Netherlands), the Stichting ParkinsonFonds (patient organisation, Netherlands) and Parkinsonismen Vereniging (patient organisation, Netherlands)

Who is the main contact?
Dr Rob de Bie
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Study website
http://leapamc.nl/

Contact information

Type(s)
Scientific

Contact name
Dr Rob de Bie

Contact details
Academisch Medisch Centrum
Postbus 22660
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1100DD

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
ZonMw 171102018 (Protocol) / 2011_057 (Medical Ethical Committee)

Study information

Scientific Title
Levodopa in EArly Parkinsons disease: a prospective, randomized, double-blind, placebo-controlled, delayed start trial

Acronym
LEAP

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

Ethics approval required
Old ethics approval format

Ethics approval(s)
Medical Ethical Committee of the Academic Medical Center in Amsterdam, 19/04/2011, ref: AMC: 2011_057

Study design
Prospective randomized double blind placebo-controlled delayed start multi-center clinical trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Parkinson's disease

Interventions
Patients will be randomised to 40 weeks treatment with levodopa / carbidopa 100 / 25 mg three times a day (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).

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Levodopa

Primary outcome measure

The difference in the mean total Unified Parkinson's Disease Rating Scale (UPDRS) scores between the early and delayed groups at 80 weeks

Secondary outcome measures

Current secondary outcome measures as of 01/04/2016:
1. 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:
1.1. Progression in Phase 1: Superiority of the UPDRS slope during phase 1 of the early group as compared to the delayed group
1.2. Progression in Phase 2: Non-inferiority of the UPDRS slope in phase 2 of the early group as compared to the delayed group
2. Disability measured with the AMC Linear Disability Scale (ALDS); 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
3. Between-group difference in mean total UPDRS scores at 80 weeks and the progression of UPDRS scores during phases 1 and 2 in patients who followed the study 'per protocol'
4. Between-group difference in mean total UPDRS scores at 80 weeks and the progression of UPDRS scores during phases 1 and 2 in patients with UPDRS scores in the highest quartile of scores at baseline who followed the study 'per protocol'
5. Number of patients that need additional medication for PD
6. Cognitive impairment, measured with the MMSE
7. Depression, measured with the BDI-II
8. Perceived quality of life measured with the PDQ-39
9. Quality Adjusted Life Years (QALY), after applying existing scoring algorithm to derive health utilities from observed European Quality of Life-5 Dimensions (EQ-5D) data
10. Working status and absence from paid work measured with a standardized questionnaire
11. Caregiver burden with a standardized questionnaire
12. Resource utilisation outside of the participating hospitals measured with a standardized questionnaire (for 10, 11 and 12 we used an adjusted version of the Short Form – Health and Labour Questionnaire and iMTA Valuation of Informal Care Questionnaire targeted at the study population)
13. Cost per unit decrease of the UPDRS and cost per QALY
14. Number of patients withdrawn from the study or lost to follow up
15. Dyskinesias, measured with items 32 to 35 of the UPDRS part IV
16. Levodopa-induced motor response fluctuations throughout the course of the study measured with items 36 to 39 of the UPDRS part IV and three standardized questions concerning wearing-off phenomena
17. (Serious) adverse events defined as the frequency, severity, nature, and duration of any adverse event throughout the course of the study

Previous secondary outcome measures:
1. 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
1.1. Progression in Phase 1: superiority of the UPDRS slope during phase 1 of the early group as compared to the delayed group
1.2. Progression in Phase 2: non-inferiority of the UPDRS slope in phase 2 of the early group as compared to the delayed group
2. Disability measured with the Academic Medical Center Linear Disability Score (ALDS). 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
3. Number of patients that need additional medication for PD
4. Number of patients that proceed early to phase 2
5. Number of patients withdrawn from the study or lost to follow up
6. Levodopa-induced motor response fluctuation; the frequency, severity, nature and duration of any levodopa-induced motor response fluctuation throughout the course of the study
7. (Serious) adverse events; the frequency, severity, nature and duration of any adverse event throughout the course of the study
8. Perceived quality of life measured with the PDQ-39
9. Cognitive impairment, measured with the MMSE
10. Depression, measured with the BDI-II
11. The utility measure in the cost-utility analysis measured with the EQ-5D
12. Working status and absence from paid work measured with a standardized questionnaire
13. Caregiver burden
14. Resource utilization outside of the participating hospitals through a standardized questionnaire

Overall study start date
01/08/2011

Completion date
29/11/2017

Eligibility

Key inclusion criteria
1. Iidiopathic Parkinson's disease (PD) with bradykinesia and at least two of the following signs:
1.1. Resting tremor
1.2. Rigidity
1.3. Asymmetry
2. Newly diagnosed PD within the past two years
3. Age 30 years and over
4. A life expectancy of more than two years
5. No limitations in functional health for which the patient needs PD-medication

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
446

Total final enrolment
445

Key exclusion criteria
1. Tremor as most prominent symptom, such as:
1.1. A severe resting tremor that is present (almost) continuously
1.2. Tremor of medium to large amplitude which results in functional disability (such as interfering with feeding)
2. Previous treatment with PD-medication, e.g., levodopa, dopamine agonist (DA), monoamine oxidase (MAO)-B-inhibitor, catechol-Omethyl transferase-inhibitor (COMT-inhibitor), or amantadine
3. Cognitive impairments, i.e., Mini Mental State Examination (MMSE) of 23 points or lower;
4. More than 28 points on the Beck Depression Scale II (BDI-II)
5. Diagnosis of depression by a psychiatrist in the last year
6. History of psychosis
7. History of glaucoma
8. The presence of signs indicating atypical or secondary parkinsonism such as:
8.1. The use of drugs that may cause parkinsonism (e.g., metoclopramide, cinarizine, anti-psychotics, natrium-valproate, lithium, amiodarone)
8.2. Metabolic disorders (e.g., Wilsons disease)
8.3. Encephalitis
8.4. Vascular parkinsonism
8.5. Repeated head-trauma
9. Alcohol abuse
10. Legally incompetent adults
11. Inability to provide written informed consent

Date of first enrolment
17/08/2011

Date of final enrolment
17/05/2016

Locations

Countries of recruitment
Netherlands

Study participating centre
Academisch Medisch Centrum
Amsterdam
Netherlands
1100DD

Sponsor information

Organisation
Academic Medical Center (AMC) (Netherlands)

Sponsor details
Department of Neurology
Postbus 22660
Amsterdam
Netherlands
1100DD

Sponsor type
Hospital/treatment centre

Website
http://www.amc.nl/

ROR
https://ror.org/03t4gr691

Funder(s)

Funder type
Government

Funder Name
Netherlands Organisation for Health Research and Development (ZonMw) (Netherlands) (ref: 171102018)

Alternative Name(s)
Netherlands Organisation for Health Research and Development

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
Netherlands

Funder Name
Stichting ParkinsonFonds (patient organisation, Netherlands)

Funder Name
Parkinsonismen Vereniging (patient organisation, Netherlands)

Results and Publications

Publication and dissemination plan
As the last measurements for the last patient will be performed at the end of 2017, the trialists expect to publish the results in the first half of 2018. If possible, they will present the results at the yearly Movement Disorder Society Congress. Further details will be confirmed at a later date.

Intention to publish date
01/07/2018

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Prof. Dr. R.M.A. de Bie (r.m.debie@amc.uva.nl). The output will be in SPSS. Consent of participants was obtained to perform analyses on the data. All data is anonymized.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	19/11/2015		Yes	No
Results article	results	24/01/2019		Yes	No
Results article		17/10/2022	18/10/2022	Yes	No