cholinesterase inhibitors to slow progression of visual hallucinations in Parkinson's disease

RESEARCHPROTOCOL

CHolinEsterase inhibitors to slow progression of Visual hALlucinations in Parkinson's disease: a multi-center placebo-controlled trial (CHEVAL)

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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 (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AD	**Alzheimer's Disease**
AE	**Adverse Event**
ALDS	**AMC Linear Disability Score**
AR	**Adverse Reaction**
BID	**"Bis in die" Latin for twice daily**
BPRS	**Brief psychiatric rating scale**
CA	**Competent Authority**
ChEI	**Cholinesterase inhibitors**
ChIP	**Cholinesterase inhibitor prognosticator**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EQ-5D	**EuroQol-5D**
ESS	**Epworth Sleepiness Scale**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
LEDD	**Levodopa Equivalent Daily Dose**
MAO	**Monoamine oxidase**
MDS	**Movement disorder society**
MMSE	**Mini mental state examination**
MoCA	**Montreal Cognitive Assessment**

METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
PD	**(Idiopathic) Parkinson's disease**
PD-CRS	**Parkinson's Disease – Cognitive Rating Scale**
PDD	**Parkinson's disease dementia**
PDP	**Parkinson's disease associated pyschosis**
RCT	**Randomized controlled trial**
(S)AE	**(Serious) Adverse Event**
SAPS	**Schedule for Assessment of Positive Symptoms**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
UPDRS	**Unified Parkinson's Disease Rating Scale**
VH	**Visual hallucinations**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**
ZCBI	**Zarit caregiver burden interview**

SUMMARY

Rationale:
Visual hallucinations (VH) are the most common non-motor symptoms in Parkinson's disease (PD). As an independent predictor for cognitive decline and nursing home placement they form an important disability milestone in the course of PD. According to current clinical guidelines minor VH do not require treatment per se. But as minor VH precede the stage of major VH without insight and PD associated psychosis (PDP) they offer an opportunity for early intervention. Neuroleptic drugs delay the transition into PDP but are unsuitable for early treatment of VH due to their side effects. We hypothesize that cholinesterase inhibitors (ChEI) are a well-tolerated alternative for the early treatment of minor VH to delay the progression to PDP.

Objective:
Investigate whether early treatment with ChEI delays the progression of minor VH to major VH without insight or PDP. In addition, we will measure motor control, psychotic symptoms, cognitive impairment, mood disorders, daytime sleepiness, adverse events and compliance, disability, caregiver burden and care use. We assess the cost-effectiveness of early chronic treatment of VH with ChEI.

Study design:
A randomized, double blind, placebo-controlled, multi-center trial with an economic evaluation.

Study population:
168 patients with PD and VH after fulfilling the in-and exclusion criteria.

Intervention:
Rivastigmine capsule 6 mg BID or placebo BID for 24 months.

Main study parameters/endpoints:
The primary outcome measure is the median time until PD patients with minor VH progress to major VH without insight. The clinical endpoint is defined as the start with antipsychotic treatment. Secondary outcome measures are changes in motor control, psychotic symptoms, cognitive impairment, mood disorders, daytime sleepiness, cholinergic deficiency, the number of adverse events, compliance, disability and caregiver burden. All relevant costs will be measured and valued.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

The burden of participation consists of a total of 5 clinical visits (every 6 months), 5 telephone interviews on adverse events during the escalation phase and 9 questionnaires on health related costs (every 3 months). There is a risk for adverse reactions with rivastigmine treatment; the most common are nausea and vomiting.

TABLE 1.	**Overview of assessments at baseline (t=0) and follow up**												
Time in months (visit nr)	**0 (1)**	**0,25**	**0,75**	**1,5**	**2,25**	**3**	**6 (2)**	**9**	**12 (3)**	**15**	**18 (4)**	**21**	**24 (5)**
Assessment													
Demography	X												
Venepuncture	X												
UPDRS	X						X		X		X		X
SAPS	X						X		X		X		X
MMSE	X						X		X		X		X
MoCa	X						X		X		X		X
PD-CRS	X						X		X		X		X
HADS	X						X		X		X		X
ESS	X						X		X		X		X
ChIP	X						X		X		X		X
Adverse event		X	X	X	X	X	X		X		X		X
Medication	X						X		X		X		X
ALDS	X						X		X		X		X
ZCBI	X						X		X		X		X
EQ-5D	X						X		X		X		X
Costs						X	X	X	X	X	X	X	X

KEYWORDS

Parkinson's disease; visual hallucinations; rivastigmine; cholinesterase inhibitor; randomized controlled trial; cost-effectiveness analysis

1. INTRODUCTION AND RATIONALE

In the Netherlands 50,000 people have PD. It is the second most common neurodegenerative disorder after dementia and affects 1.6% of the population above the age of 65 years. [1] PD is characterized by motor symptoms and a variety of non-motor symptoms. Autonomic, psychiatric, sensory, and sleep disorders accompany or precede motor symptoms. Non-motor symptoms can exacerbate with the anti-parkinsonian treatment. They form a dose-limiting factor for adequate motor control. [2] In a considerable proportion of patients, non-motor symptoms are the major determinant of disability. This emphasizes their detrimental role for the quality of life of PD patients and the necessity to find better treatment options. [3]

Visual hallucinations (VH) are the most common non-motor symptoms in PD. Cross-sectional studies have shown a prevalence of VH of approximately 50% in PD patients. [4] According to longitudinal studies the lifetime prevalence is up to 74% after 20 years of disease. [5] VH are considered the first sign of an advanced disease stage. Its presence is an independent predictor for developing cognitive deterioration and dementia. [6,7] At first, most PD patients (approximately 75%) are not frightened by the VH and recognize their false nature. [7] VH are considered benign as long as the content is not disturbing and the hallucinations do not lead to behavioral disturbances. When patients can no longer be convinced the images are not real, VH are considered 'malignant' and become part of PD associated psychosis (PDP). PDP is almost inevitable as 81% of patients with minor VH progress to major VH without insight within three years. [8] In this advanced disease stage, the VH may even further compromise physical safety. For example, a patient may fall when chasing an imaginary dog. Clearly, the loss of insight constitutes a major source of distress and anxiety to patients and imposes a heavy demand on the caregivers. It often leads to nursing home placement. [9] Therefore, the presence or absence of insight into VH constitutes an important dichotomy in the clinical spectrum.

The current national Parkinson's disease guideline indicates that minor VH require no specific treatment. [10] Patients may cope with simple strategies (e.g. look in another direction, turn on the light, discuss non-reality with their caregiver). [7] When VH change or become more severe the possibility of a delirium needs to be ruled out. The second step is reduction of dopaminergic medication (e.g. dopamine agonists, MAO reuptake inhibitors, levodopa) at the probable cost of adequate motor control. Clozapine treatment is the preferred choice when VH progress or other options fail. [10] This in spite of side effects like sedation and orthostatic hypotension. These are particularly inopportune for a PD patient

with gait difficulties, sleep disturbances, or autonomic failure. Moreover, clozapine is potentially hazardous because of the small risk of developing granulocytopenia or agranulocytosis. Finally, the use of clozapine in elderly patients with dementia is associated with higher mortality. [11-12] If clozapine treatment is started when VH are still minor, the median time until loss of insight can be delayed from 12 to 39 months. [13] Thus, clozapine can alter the progressive course of VH in PD, but is rather unsuitable for long-standing treatment due to the risk for serious side effects.

Cholinesterase inhibitors (ChEI) are recommended in PD dementia (PDD) because of their beneficial effects on cognition and behavioral symptoms. ChEI were tested in several small, open-label and randomized controlled trials (RCT), mostly in mild to moderate demented PD patients. [14-21] In a large RCT ChEI showed a greater therapeutic benefit in PD patients with VH. Psychotic symptoms - studied as a secondary outcome measure - were likely to improve along with the cognitive disturbances. [20] Data on the effects of early treatment of minor VH in non-demented PD patients are lacking. The predominant side effects of ChEI treatment are cholinergic in nature; the most frequent are nausea and vomiting. Less frequently an increase in motor symptoms occurs, especially tremor (see chapter 'interventions'). [14-21]

Studies on patient characteristics predicting beneficial response to ChEI treatment are scarce in PDD and in Alzheimer's disease (AD). One prospective cohort study assessed neuropsychological and clinical patient characteristics predicting response to cholinesterase inhibitor treatment on the domains of cognition and activities of daily living.[22] In this cohort, beneficial treatment response was associated with the presence of attentional deficits at baseline, measured by simple choice reaction time. Moreover, at baseline, responders to cholinesterase inhibitor treatment scored higher on a cluster of neuropsychiatric symptoms including apathy, anxiety, hallucinations and restlessness. The presence of attentional deficits in concurrence with these neuropsychiatric symptoms could be described as a cholinergic deficiency syndrome.[23] Quantification of these characteristics may potentially yield a clinical marker serving as a rationale to start cholinesterase inhibitor therapy in individual dementia patients. For this purpose an easy use instrument has been developed: the cholinesterase inhibitor prognosticator (ChIP). In a pending multi-centre validation study (ChIP-study) its diagnostic merits in identifying dementia patients with a beneficial cholinesterase inhibitor treatment response is being determined.

Several genes have been studied as possible risk factors for visual hallucinations in PD. No association had been found so far with different dopamine transporter gene polymorphisms.

Also, there was no association with cholecystokinin (CCK) promoter polymorphisms, angiotensin converting enzyme (ACE) II genotype, serotonin receptor or transporter genes, apolipoprotein E (APOE e4 or e2), microtubule associated protein tau (MAPT), a-synuclein promoter (SNCA-REP1) and catechol-o-mehyltransferase (COMT). [51] Nonetheless, gene polymorphisms for specific receptor or transporters might still explain differences in response to ChEI treatment.

In summary, VH are the most common non-motor symptoms in PD. As an independent predictor for cognitive decline and nursing home placement they form an important disability milestone in the course of PD. Minor VH do not require treatment per se according to current clinical guidelines. But as minor VH precede the stage of PDP, they offer an opportunity for early intervention. Neuroleptic drugs delay the transition into PDP but are unsuitable due to their side effects. We hypothesize that ChEI are a well-tolerated alternative for the early treatment of minor VH to delay the progression to PDP.

2. OBJECTIVES

Primary Objective:

To investigate whether early chronic ChEI treatment of VH in patients with PD delays the progression of minor VH (with retained insight) to major VH (without insight) or PDP.

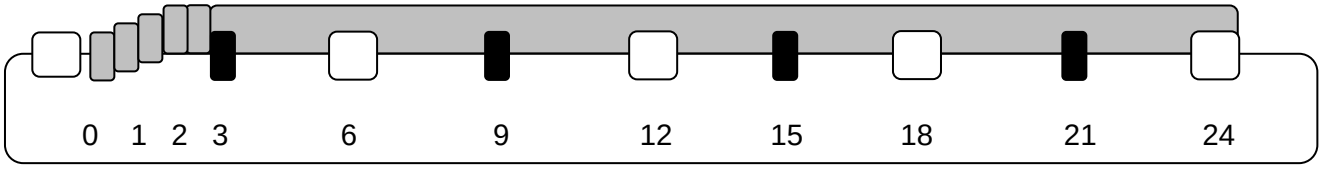
Secondary Objective(s):

Secondary outcomes are changes in motor control, severity of psychotic symptoms, cognitive impairment, mood disturbance, daytime sleepiness, adverse events, compliance and disability. We evaluate the use of the cholinesterase inhibitor prognosticator (ChIP) and DNA analysis in serum as a possible predictor for response to ChEI treatment. Besides clinical parameters, we will assess caregiver burden, care use, and costs. In addition, we will investigate the cost-effectiveness of early treatment with ChEI.

3. STUDY DESIGN

The study is a randomized, double-blind, placebo-controlled, multicenter trial with an economic evaluation alongside. Patients are randomized to treatment with rivastigmine or placebo, twice daily for a period of 24 months.

Overview of assessments during 24 month follow-up



dose escalation

week 1 1,5 mg rivastigmine/placebo
week 2-3 1,5 mg BID rivastigmine/placebo
week 4-6 3,0 mg BID rivastigmine/placebo
week 7-9 4,5 mg BID rivastigmine/placebo
week 10-12 6,0 mg BID rivastigmine/placebo

telephone interview
after week 1, 3, 6, 9 and 12

costs assessment

every 3 months

- direct and indirect costs

questionnaire

clinical assessment

every 6 months

- motor control:	UPDRS 3 - MDS; Levodopa Equivalent Daily Dose
- psychotic symptoms:	UPDRS 1 - MDS;
	Schedule for Assessment of Positive Symptoms;
- cognitive function:	Mini Mental State Examination;
	Montreal Cognitive Assessment
	PD-Cognitive Rating Scale;
- mood disorders:	Hospital Anxiety and Depression Scale
- daytime sleepiness:	Epworth Sleepiness Scale;
- cholinergic deficit:	Cholinersterase Inhibitor Prognosticator (baseline);
- treatment:	adverse events, compliance;
- disability:	AMC Linear Disability Score;
- caregiver burden:	Zarit Caregiver Burden Inventory;
- care use and costs	EuroQol-5D.

4. STUDY POPULATION

4.1 Population (base)

PD patients will be enrolled after fulfilling the in- and exclusion criteria and after having given written informed consent. Patients will be recruited from academic and community hospitals in the Netherlands. We approached a large number of hospitals to participate in our trial. To date, 30 neurology clinics have signed the “intent for participation” statement (Part “K” of the investigator’s file).

4.2 Inclusion criteria

The inclusion criteria are:

1. idiopathic PD with bradykinesia and at least two of the following signs; resting tremor, rigidity, and asymmetry (in accordance with clinical diagnostic criteria of the UK PD Society Brain Bank); [24]
2. the presence of minor VH for at least 4 weeks, defined by a score of 1 or 2 on the hallucinations item of the Unified Parkinson’s Disease rating Scale (UPDRS)1-MDS; [25]
3. age 40 years and over.

4.3 Exclusion criteria

The exclusion criteria are:

1. PDP, defined as the need for antipsychotic drug treatment in the opinion of the treating neurologist;
2. PDD, defined by a score < 26 on the Mini Mental State Examination (MMSE) [26];
3. current delirium (caused by infection or metabolic disturbance);
4. current treatment with drugs that have important central anticholinergic effects:

class	generic	brand
antiparkinsonians	amantadine biperiden trihexyfenidyl	Symmetrel Akineton Artane
antiarrhytmics	disopyramide	Ritmoforine
antidepressants	amitriptyline imipramine	Tryptizol

antiemetics	cyclizine	
antihistamines	clemastin dexchlorpheniramine meclozine promethazine	Tavegyl Polaramine Suprimal
spasmolytics	oxybutynine tolterodine	Dridase Detrusitol

5. current or recent (<6 months) treatment with ChEI, such as rivastigmine (Exelon) or galantamine (Reminyl);
6. VH in response (< 1 month) to increase of dopamingergic treatment;
7. history of psychosis, (known) sick sinus syndrome or other arrhythmia
8. current severe ophtalmologic disease defined as a visual acuity score of < 0.5 based on Snellen eye test

9.permanent stay in a nursing home;

10. no informed consent.

4.4 Sample size calculation

The sample size calculation is based on the results of two observational studies by Goetz, et al. In the first study (n=48; 3-year follow-up) the median time of conversion to psychosis was 16 months without treatment for hallucinations. [8] In the second study (n=64; median follow-up 27 months) the median time of conversion to psychosis was 39 months in patients treated with neuroleptics. [13]

Based on the results of these studies and presuming an exponential disease course, we estimate that within a 24 months observation period 65% of the patients in the placebo group reach the primary endpoint in terms of loss of insight or PDP compared to 35% in the treatment group. Conservatively but still highly relevant, we assume that 40% of actively treated patients will reach the endpoint within 24 months of observation.

When the sample size in each group is 63, a 0.05 level two-sided log-rank test for equality of survival curves will have 80% power to detect the difference between the control group proportion at 24 months of 0.35 (proportion of patients without psychosis) and the intervention group proportion at 24 months of 0.60 (proportion of patients without psychosis), with a constant hazard ratio of 2,055. Anticipating a dropout rate of 25%, we need a sample of 84 patients per treatment group (168 patients in total). [18,19,21]

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

PD patients will be randomly assigned to placebo or active treatment with rivastigmine during a period of 24 months. The route of administration is a capsule for oral use. The dose is 6 mg twice daily (BID). All patients start their treatment with a dose escalation phase of 12 weeks. In the first week patients use the lowest dose capsule containing 1.5 mg rivastigmine once a day (or matching placebo). If this is well tolerated the dose is raised for the next two weeks to 1.5 mg rivastigmine BID (or matching placebo). Every three weeks the dose is increased to 3.0, 4.5 and 6.0 mg rivastigmine BID (or matching placebo). Without intolerable side effects, patients continue on the standard maintenance dose of 6.0 mg rivastigmine BID (or matching placebo). Patients are monitored after 1,3,6,9 and 12 weeks from the start of treatment. If side effects persist patient should lower the dose. The patient will be instructed to keep the highest tolerated dose until the end of the study. The minimum permitted dose is set at 3.0 mg BID (or matching placebo). This enables patients to complete the 24 months of treatment.

5.2 Use of co-intervention (if applicable)

Patients will not receive any other kind of antipsychotic treatment such as clozapine, quetiapine or olanzapine. The local neurologist should continue his standard of care including necessary changes in (dopaminergic) medication.

5.3 Escape medication (if applicable)

Nausea, vomiting, loss of appetite, and weight reduction are very common side effects of rivastigmine treatment. To reduce the severity of these gastro-intestinal symptoms domperidone, an anti-emetic, can be prescribed [27]. In both the rivastigmine and the placebo group, patients suffering nausea are instructed to take domperidone tablet 10 mg TID. This add-on treatment should be restricted to the dose escalation phase.

Table 1. Treatment schedule

Phase	Week number	Rivastigmine dose
Dose escalation	Week 1	1,5 mg
	Week 2-3	1,5 mg BID
	Week 6	3,0 mg BID
	Week 7-9	4,5 mg BID
	Weeks 10-12	6,0 mg BID
Maintenance dose	Week 13-104	6,0 mg BID

* the central pharmacy will prescribe the medication.

6. INVESTIGATIONAL MEDICINAL PRODUCT

Cholinesterase inhibitors (ChEI) are recommended for use in PD dementia (PDD) because of their beneficial effects on cognition and behavioural symptoms. ChEI were tested in several small, open-label and randomized controlled trials (RCT), mostly in mild to moderate demented PD patients. [14-21]

6.1 Name and description of investigational medicinal product(s)

See Summary of Product Characteristics (SPC) for Rivastigmine CF 1,5 / 3,0 / 4,5 / 6,0 mg capsules. The capsule will be over capsulated by the central pharmacy according to standard procedures. Matching placebo capsules matching rivastigmine 1,5 mg and rivastigmine 6,0 mg will be manufactured.

6.2 Summary of findings from non-clinical studies

See the Summary of Product Characteristics (SPC) for Rivastigmine CF 1,5 / 3,0 / 4,5 / 6,0 mg capsules.

6.3 Summary of findings from clinical studies

See the Summary of Product Characteristics (SPC) for Rivastigmine CF 1,5 / 3,0 / 4,5 / 6,0 mg capsules..

6.4 Summary of known and potential risks and benefits

See the Summary of Product Characteristics (SPC) for Rivastigmine CF 1,5 / 3,0 / 4,5 / 6,0 mg capsules..

6.5 Description and justification of route of administration and dosage

Based on the available trials that have been conducted with ChEI in PD, there are no important differences in effect among specific ChEI brands with regard to cognition. Although less well studied, this applies to psychotic symptoms too. [18-21]

The effect of early treatment with rivastigmine on the progression of VH might go unnoticed to the individual PD patient. Because of this, when taking the proposed follow-up of 24 months is taken into account, our study design is susceptible for a high dropout rate because of side effects. The side effects of all available ChEI (donepezil, galantamine and rivastigmine) are comparable. Donepezil has probably the most favorable side-effect profile, but is not registered in The Netherlands. RCT's with galantamine in PD are lacking. Therefore, we prefer to use rivastigmine because of its highest scientific evidence: in almost all other trials conducted in PD(D) rivastigmine was used.

To prevent patients form early withdrawal due to gastro-intestinal side effects we propose a very slow dose escalation schedule. To reduce the severity of these gastro-intestinal symptoms domperidone, an anti-emetic, can be prescribed when necessary.

6.6 Dosages, dosage modifications and method of administration

We aim at a maintenance dose of 3,0 or 6,0 mg rivastigmine BID (or matching placebo). This is also the recommended maintenance scheme based on dose finding studies by the manufacturer. Our protocol is in accordance with the advised maintenance dose by the 'College voor zorgverzekeringen' (www.farmacotherapeutischkopmas.nl). However, none of the conducted trials in PD compared the effect of treatment with 1,.5 , 3,0 or 6,0 mg rivastigmine BID head-to-head. [14] The recommendations for rivastigmine use in PDD are based on data from a large multi-center trial. [19] The PD guideline does not dictate the rivastigmine dose when prescribed to PDD patients. [10] When gastro-intestinal symptoms are experienced in spite of the use of domperidone, patients are permitted to lower the maintenance dose. The minimum permitted dose is set at 3,0 mg rivastigmine BID. Probably this enables patients to complete the 24 months of treatment.

6.7 Preparation and labelling of Investigational Medicinal Product

Rivastigmine CF will be released by Centrafarm (Etten-Leur, Netherlands). The matching placebo will be manufactured by Basic Pharma (Geleen, Netherlands). Over capsulation and distributing of all the study medication, both rivasigmine and placebo, will be handled by ApotheekZorg,(Sittard, Netherlands) in close collaboration with the Basic Pharma Group (Geleen, Netherlands). The Investigator's brochure and IMPD of rivastigmine capsules 1,5 en 3,0 mg , is in part "D" of the investigator's file. Labelling will be performed according to the Good Manufacturing Practice (GMP) guidelines. For the description of the labelling-procedures, see part "D3" of the investigator's file.

6.8 Drug accountability

After randomisation, an e-mail is automatically generated and sent to ApotheekZorg. 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.

ApotheekZorg will allocate the randomized patient to a medication number that corresponds with the treatment group (rivastigmine or placebo) 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 ApotheekZorg until the time of unblinding. Code-breaking sheets for emergency use will be kept in a safe.

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint

The primary outcome measure is the time until PD patients with minor VH progress to major VH without insight. The clinical endpoint is defined as the start with antipsychotic treatment. This decision is left to the discretion of the treating neurologist. In this manner the design represents clinical practice. (The severity of VH is measured as a secondary outcome with the UPDRS 1 – MDS, to confirm insight is lost.)

7.1.2 Secondary study parameters/endpoints (if applicable)

Secondary outcomes measures are changes in the following assessments after 6,12,18 and 24 months:

I. Motor control measured with the UPDRS – MDS part 3 [25] and Levodopa Equivalent Daily Dose;
II. Psychotic symptoms using the UPDRS – MDS part 1 (hallucinations item) and the Schedule for Assessment of Positive Symptoms (SAPS) [25,28];
Besides changes in the severity of psychotic symptoms, the proportion of patients that progresses to a score ≥ 3 (i.e. loss of insight) in the two treatment groups (rivastigmine and placebo) is measured after 24 months.
III. Cognitive function based on the Mini Mental State Examination (MMSE) [26], Montreal Cognitive Assessment (MOCA) [29] and Parkinson's Disease-Cognitive Rating Scale (PD-CRS) [31];
IV. Mood disturbance according to the Hospital Anxiety and Depression Scale (HADS) [32]
V. Daytime sleepiness on the Epworth Sleepiness Scale (ESS) [33];
VI. Cholinergic deficiency, as a possible predictor for response to treatment, measured with the Cholinersterase Inhibitor Prognosticator (ChIP)
VII. Number and type of adverse events;
VIII. Compliance to treatment measured by the number of remaining capsules after every 6 months of follow-up;
IX. Disability based on the AMC Linear Disability Score (ALDS) [34];
X. Caregiver burden according to the Zarit Caregiver Burden Inventory (ZCBI) [35];
XI. Care use measured with the EuroQol-5D (EQ-5D) [36].

7.1.3 Other study parameters

Other study parameters include:

- patient characteristics (age, sex, smoking, medical history and current use of medication)
- disease specific characteristics (age at disease onset, disease duration, Hoehn and Yahr stage)
- exploratory DNA analysis for candidate genes involved in development of psychotic symptoms in PD or response to ChEI treatment

7.2 Randomisation, 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 VU University Medical Center. Eligible patients will be randomized by a computer in a 1:1 ratio to the rivastigmine group or the placebo group in a double-blind design. Untill the computerized randomization is fully operational, patients will be randomized by the research nurse or, in her absence, by T.J.M. van Mierlo or E.M.J. Foncke.

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 (<10 years, ≥10 years) using variable permuted blocks. Code-breaking sheets for emergency use will be kept in a 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. The randomization code can be broken in case of an emergency.

7.3 Study procedures

The treating neurologist will check the inclusion and -exclusion criteria. He asks the patient for permission to send contact information to the research nurse. If the patient is eligible and agrees, the neurologist will complete the patient registration form with name, gender, date of birth, telephone number and in- and exclusion criteria. After registration, a research nurse will contact the patient by phone within 10 working days. She will introduce the study to the patient, inform the patient on the gross outline of the trial and discuss the possible benefits and disadvantages. She will answer any additional question about the study. If the patient agrees an

appointment will be made (visit 1). All study visits will take place at home or in the outpatient clinic. Preferably this is in (or near) the same clinic where patients are treated by their neurologist. The study medication is prescribed by the neurologist in one of the four main study centers.

During Visit 1 Informed Consent will be obtained. The baseline characteristics will be recorded, as well as medication history, year and type of first PD symptoms (e.g. tremor, bradykinesia) and year of PD diagnosis. Current medication is noted and the Levodopa Equivalent Daily Dose (LEDD) will be calculated. Visual acuity is tested with a digital version of the Snellen chart (iPad). Three 7 mL EDTA blood samples for DNA analysis will be drawn and stored for future genetic research; including possible genetic modifiers of response to medication.
During Visit 1 patients will undergo several assessments by the research nurse:
- motor control: UPDRS 3 - MDS [25];
- psychotic symptoms: UPDRS 1 - MDS and SAPS [25,28];
- cognitive function: MMSE; MOCA [29}; PD-CRS [31];
- mood disturbance: HADS [32]
- daytime sleepiness: ESS [33];
- cholinergic deficit: ChIP;
- disability: ALDS [34];
- caregiver burden: Zarit Caregiver Burden Inventory (ZCBI) [35];
- care use: EuroQol-5D (EQ-5D) [36].

At the end of the visit the research nurse will randomize the patient by a central web-based computer program.

Medication is sent by mail through a central pharmacy during the complete study period. The research nurse inquires the patient about the medication received, medication intake and side effects by telephone after 1,3,6,9 and 12 weeks of treatment.

Four specified assessment visits will take place after Visit 1: at 6 months, 12 months, 18 months and 24 months (respectively Visits 2, 3, 4 and 5; see table 1). The assessments of Visit 1 are repeated by the research nurse and completed with a monitor for side effects, any change in (non-parkinsonian) medication and calculation of the LEDD. Patients are asked to bring the remaining number of capsules. These will be counted as a measure of compliance.

The endpoint (starting treatment with neuroleptics) or any other important event (in the opinion of the treating neurologist) is reported to the neurologist in one of the four main study centers, who has been appointed as local research coordinator. The treating neurologist fills out the trial termination form. This form includes the date and the primary outcome measure, the UPDRS-1 MDS score (3 or 4 on the hallucinations item, indicating that insight is lost). If the clinical endpoint is reached, the experimental treatment with rivastigmine or placebo is discontinued. As soon as possible, but not before the subjects condition allows participation and not later than 2 weeks from the end of treatment, the research nurse plans the next clinical visit. During this clinical visit the research nurse will follow the same protocol as with regular visits 2-5. The local research coordinator is acknowledged.

When the endpoint is reached and after the clinical visit, costs will continued to be measured every 3 months until 24 months from the start of treatment. If possible, even when treatment is discontinued, patients are visited after 24 months for the final clinical assessment (visit 5).

The consequences of an important event are discussed by the local research coordinator. The local research coordinator decides a patients needs to withdraw from the study and whether a final clinical visit must be completed. The research coordinator of the head study center is acknowledged.

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. Specific criteria for withdrawal are not predefined.

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. Subjects can also be withdrawn in case of protocol violations.

The datasets from withdrawn patients will be kept in the study database to facilitate analysis according to the intention-to-treat principle.

7.5 Replacement of individual subjects after withdrawal

Subjects will not be replaced. Drop out has been accounted for in our power calculation. Moreover the analysis will be done according to the intention-to-treat principle.

7.6 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.

TABLE 1.	**Overview of assessments at baseline (t=0) and follow up**												
Time in months (visit nr)	**0 (1)**	**0,25**	**0,75**	**1,5**	**2,25**	**3**	**6 (2)**	**9**	**12 (3)**	**15**	**18 (4)**	**21**	**24 (5)**
Assessment													
Demography	X												
Venepuncture	X												
UPDRS	X						X		X		X		X
SAPS	X						X		X		X		X
MMSE	X						X		X		X		X
MoCa	X						X		X		X		X
PD-CRS	X						X		X		X		X
HADS	X						X		X		X		X
ESS	X						X		X		X		X
ChIP	X						X		X		X		X
Adverse event		X	X	X	X	X	X		X		X		X
Medication	X						X		X		X		X
ALDS	X						X		X		X		X
ZCBI	X						X		X		X		X
EQ-5D	X						X		X		X		X
Costs						X	X	X	X	X	X	X	X

8. SPECIFIC METHODS

8.1 Assessment of motor control

8.1.1 Unified Parkinson's Disease Rating Scale – MDS part 3;

The UPDRS is a scale that was developed as an effort to incorporate elements from existing scales to provide a comprehensive but efficient and flexible means to monitor PD-related disability and impairment. The scale itself has four components, largely derived from preexisting scales that were reviewed and modified by a consortium of movement disorders specialists (Part I, Mentation, Behaviour and Mood; Part II, Activities of Daily Living; Part III, Motor; Part IV, Complications). Part III is a clinician-scored motor evaluation and has 14-items ranging from 0 (normal) to 4 (severely impaired) on subjects as speech, tremor, rigidity, bradykinesia, posture and gait. The sum of all scores represents the extent of motor control with higher scores reflecting less motor control [25].

8.2 Assessment of psychotic symptoms

8.2.1 UPDRS – MDS part 1

See chapter 7.1.1.

8.2.2 Schedule for Assessment of Positive Symptoms (SAPS);

The SAPS was developed to assess and provide qualitative information about specific features of hallucinations delusions, behavioural changes associated with psychosis, and thought disorder. The scale is designed to include single items as well as global ratings for each symptom cluster. The individual hallucinations items are rated on a continuum based on their frequency (occasional to daily, with the latter being most severe). However, the global hallucinations item scoring is based on both the frequency and the extent to which the hallucinations are disruptive. Studies using the SAPS in clinical trials of PD psychosis (especially the subsection on delusions and hallucinations) show that it is sensitive to change in response to effective treatment. The SAPS is easy to administer with a structured interview and clear anchors provided as part of the scale. It assesses the range of various subtypes of hallucinations and delusions, and this may provide a tool for cataloging the range of hallucinatory and delusional phenomena in PD. Like other scales, the SAPS was developed for use in patients with schizophrenia, not PD, so items do not rate the more common types of hallucinations or delusions in PD or capture the range of severity of those symptoms and vice versa (covering many symptoms that

are uncommon in PD). The scale specifically excludes illusions. It does not provide a systematic way of capturing the presence or character of all psychotic phenomena, including other minor forms. The hallucinations items are weighted toward auditory hallucinations. The presence of insight is not taken into account with scoring. The scale was not intended for use in patients with dementia or cognitive impairment that limits awareness that symptoms are present. [26, 37]

8.3 Assessment of cognitive function

8.3.1 Mini mental state examination (MMSE)

The MMSE or Folstein test is a brief 30-point questionnaire test that is used to screen for cognitive impairment. It is commonly used to screen for dementia and can also used to estimate the severity of cognitive impairment at a given point in time and to follow the course of cognitive changes in an individual over time. Although not developed specifically for PD patients, it is used consistently in PD studies and has the most empiric evidence among the rating scales considered. A unique advantage of the MMSE relative to the other scales is that it can measure cognitive change over time in PD, especially in patients with dementia (about 2–2.5 points per annum) and is sensitive to treatment effects in clinical trials. Despite its strengths, the MMSE does not measure the cognitive functions of reasoning, planning, and set shifting (e.g., executive functions), which are commonly impaired in PD patients early in the course of the disease. [26, 38]

8.3.2 Montreal Cognitive Assessment (MOCA)

The MoCA was originally developed to screen for mild cognitive impairment (MCI) in the general population. It is a 30-point test that can be administered in about 10 minutes, but unlike the MMSE, the MoCA also covers a range of executive functions. In PD studies, the MoCA has proven particularly sensitive to the mild cognitive changes seen in PD. The MoCA has demonstrated good test-retest, inter-rater reliability, and convergent validity. The main strengths of the MoCA are its rapid and easy administration, assessment of the broad range of cognitive domains, and its sensitivity to milder cognitive deficits and executive dysfunction in patients with PD. Cutoff values for dementia and MCI are also not firmly established. [29,30,38]

8.3.3 Parkinson's Disease-Cognitive Rating Scale (PD-CRS)

Neuropsychological batteries designed for PD are focused on fronto-subcortical deficits but are not sensitive for cortical dysfunction. The Parkinson's Disease-Cognitive Rating Scale (PD-CRS) was designed to cover the full spectrum of cognitive defects associated with PD. The PD-CRS includes 10 ''subcortical-type'' items (attention, working memory, Stroop test, phonemic, semantic, alternating, and action verbal fluencies, immediate and delayed verbal memory, clock drawing), and two ''cortical-type'' items (naming, copy of a clock). The PD-CRS appeared to be a reliable and valid PD specific battery that accurately diagnosed PDD and detected subtle fronto-subcortical deficits. Performance on the PD-CRS showed that PDD is characterized by the addition of cortical dysfunction upon a predominant and progressive fronto-subcortical impairment. [31]

8.4 Assessment of mood disorders

8.4.1 Hospital Anxiety and Depression Scale (HADS)

The HADS is a short self-rated scale of 14 items yielding sub scores for depression and anxiety. Anxiety symptoms are rated separately from the depression symptoms but, due to high comorbidity between anxiety and depression, some researchers have used the total HADS as a measure of global mood disorder. Sensitivity and specificity for DSM criteria for major depressive disorder and other depression scales were reported as good. Sensitivity to change has been shown to be good, both for studies evaluating pharmacotherapy and psychotherapy for depression. [32, 39]

8.5 Assessment of cholinergic deficit

8.5.1 Cholinersterase Inhibitor Prognosticator (ChIP)

This instrument, designed as an application for iPad, consists of 5-minute simple choice reaction time in combination with a 4-item neuropsychiatric questionnaire. A combination of both these features is supposed to provide an objective measure of cholinergic deficiency.

The first part is a visual vigilance test based on the Continuous Performance Test (CPT).[40] During the test patients are seated behind a desk with the iPad located close in front of them. Stimuli consist of a one digit number (0-9) presented in the

middle of the screen. For each trial the application randomly selects a specific number as the target stimulus. Patients are instructed to keep their dominant trigger finger close to the screen and press a touch-screen button, constantly located at the bottom of the screen, as soon as possible whenever the target appears. In case another stimulus appears the patient is instructed to do nothing. Each stimulus is presented until the patient presses the button with a maximum of 3 seconds. Stimuli are serially presented in a random fashion with a 1, 2, 3, 4, or 5 second inter-stimuli-interval blank, which randomly varies in blocks of 5. After an 8 stimuli practise trial, the test starts and a total of 50 stimuli are presented with a 50% target rate. Full-trial duration is approximately 5 minutes. During the trial, reaction time and accuracy of response are registered. The second part of the application is a questionnaire based on a subset of four NPI-items previously suggested to reflect cholinergic deficiency , (hallucinations, anxiety, apathy and aberrant motor behaviour). [21,22, 40]

8.6 Assessment of daytime sleepiness:

8.6.1 Epworth Sleepiness Scale (ESS)

The ESS is a self-administered instrument for measuring daytime sleepiness, first published in 1991. Subjects need to rate the likelihood they will doze off in eight daily situations from 0 (would never doze) to 3 (high chance dozing). The final score is the summation of the eight items, with a maximum total score of 24. The severity is a continuum form normal to pathological sleepiness. In patients with dementia the ESS needs to be administered by a caregiver. The ESS is influenced by psychological factors including anxiety and depression. [33]

8.7 Assessment of disability

8.7.1 AMC Linear Disability Score (ALDS)

The Academic Medical Center Linear Disability Score (ALDS) item bank was developed to quantify functional status in terms of the ability to perform activities of daily life. The ALDS item bank covers a large number of activities, which are suitable for assessing respondents with a very wide range of functional status and many types of chronic conditions. Each item in the ALDS item bank describes an activity of daily life. Examples include: 'Walking for more than 15 minutes'; 'showering'; and 'washing up'. The items were obtained from a systematic review of

generic and disease specific instruments designed to measure functional health status. The ALDS has been proven a flexible and feasible instrument to assess the level of disability in patients with newly diagnosed Parkinson disease. [34]

8.8 Assessment of caregiver burden

8.8.1 Zarit Caregiver Burden Inventory (ZCBI)

The ZCBI is used to ascertain the distress experienced by caregivers of elderly or disabled persons. It is formed by 22 items about the impact of the patient's disabilities on caregiver's physical and emotional health, as well as its repercussions on social and financial aspects. For each item, caregivers have to indicate how often they have felt the suggested feeling or perception, from never (score 0) to nearly always (score 4). The ZCBI is scored by summing the responses of the individual items (range: 0–88). A higher score indicates higher perceived CB. The ZCBI is a valid measure for measurement of caregiver burden in a PD setting. [35, 42]

8.9 Assessment of care use

8.9.1 EuroQol-5D (EQ-5D)

The EQ-5D comprises five questions on mobility, self care, pain, usual activities, and psychological status with three possible answers for each item (1=no problem, 2=moderate problem, 3=severe problem; see appendix). A summary index with a maximum score of 1 can be derived from these five dimensions by conversion with a table of scores. The maximum score of 1 indicates the best health state, by contrast with the scores of individual questions, where higher scores indicate more severe or frequent problems. In addition, there is a visual analogue scale (VAS) to indicate the general health status with 100 indicating the best health status. The EQ-5D is a feasible and valid instrument to measure QoL in Parkinson's disease and reflects the severity and complications of the disease [36,43]

9. SAFETY REPORTING

9.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

9.2 Adverse and serious adverse events

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product. All adverse events during the first 12 weeks of treatment (dose escalation phase) reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

All SAEs will be reported through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse reactions.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

9.2.1 Suspected unexpected serious adverse reactions (SUSAR)

Adverse reactions are all untoward and unintended responses to an 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 (e.g. Investigator's Brochure for an unapproved IMP or Summary of Product Characteristics (SPC) for an authorised medicinal product).

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.
The expedited reporting of SUSARs through the web portal *ToetsingOnline* is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

9.2.2 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, Medicine Evaluation Board and competent authorities of the concerned Member States.

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 reactions, ordered by organ system,
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.3 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.

9.4 Data Safety Monitoring Board (DSMB)

An independent Data and Safety Monitoring Board (DSMB) - consisting of two clinicians and one statistician - will monitor the safety of the trial and the overall conduct of the study. The DSMB will perform one interim safety analysis after 84 patients have been randomized and completed the 24-months follow-up evaluation (interim safety analyses will not be based on pre-specified stopping boundaries). The DSMB will also be asked to check the planned sample size assumptions. The DSMB can recommend the research group to early terminate the study when there is clear evidence of harm or when the calculated sample size turns out to be too small to provide adequate statistical power for identifying the primary endpoint.

The advice(s) of the DSMB will be notified upon receipt by the sponsor to the METC that approved the protocol. With this notification a statement will be included indicating whether the advice will be followed. See DSMB charter for further details.

10. STATISTICAL ANALYSIS

10.1 Clinical evaluation

Analyses will be based on the intention-to-treat principle. Baseline characteristics and outcome parameters will be summarized using descriptive statistics.

The main analysis of this trial consists of a single comparison between the treatment groups of the primary outcome within a 24 months observation period with the log-rank test. Time-to-event analysis will be performed using Kaplan-Meier survival curves. Additionally, the primary outcome will be analyzed using multivariate Cox regression, adjusting for clinically relevant baseline imbalances and the stratifying variables.

With regard to the secondary outcomes between-group differences will be analysed using the X^2 test, Fisher exact test, unpaired t-test or Mann-Whitney U test, when appropriate. The repeated data structure of the secondary outcomes will be additionally analysed with (linear) mixed models. P-values <0.05 are considered statistically significant; statistical uncertainty will be quantified via 95% confidence intervals.

10.2 Interim analysis

The DSMB will perform one interim safety analysis after 84 patients have been randomized and completed the 24-months follow-up evaluation (interim safety analyses will not be based on pre-specified stopping boundaries). See also chapter 8.4.

10.3 Economic evaluation

10.3.1 General considerations

The aim of the economic evaluation is to evaluate cost-effectiveness and cost-utility of ChEI compared with placebo in PD patients with VH. The economic evaluation will be performed from a societal perspective. Both a cost-effectiveness and cost-utility analysis will be performed. The time horizon of the economic evaluation is 24 months, so discounting will be used. Sensitivity analyses will be performed to assess the robustness of the results using different assumptions regarding costs and effects.

10.3.2 Cost-analysis

All relevant costs will be measured using internet questionnaires, that are completed by the committed, specialized PD nurse or a caregiver. There will be an assessment at baseline and after 3, 6, 9, 12, 15, 18, 21 and 24 months of follow-up. [44] Direct costs include costs of medication (ChEI), other medication for PD, medical devices, GP care, costs of visits to other primary care providers, costs of ambulatory and inpatient hospital care, costs of home care and costs of nursing home care. Costs for the informal caregiver will also be included and measured through interviews by a research nurse. Indirect costs include absenteeism from paid and unpaid work. The friction cost approach will be used in the primary analysis to estimate indirect costs. [45] For the valuation of health care utilization standard prices published in the Dutch costing guidelines will be used. [46] Medication use will be valued using prices of the Royal Dutch Society for Pharmacy.

10.3.3 Patient outcome analysis

Societal costs will be related to the following effect measures in the economic evaluation:

1. VH with loss of insight or PDP;
2. quality-adjusted life-years (QALYs) based on the Dutch tariff for the EQ5D-5L. [44, 47]

The analysis will be done according to the intention-to-treat principle. Missing cost and effect data will be imputed using multiple imputation according to the MICE algorithm developed by Van Buuren. [48] Incremental cost-effectiveness ratios (ICERs) will be calculated by dividing the difference in mean total costs between the treatment groups by the difference in mean effects.

Bias-corrected and accelerated bootstrapping with 5000 replications will be used to estimate 95% confidence intervals around cost differences and the uncertainty surrounding the ICERs. Rubin's rules will be used to pool the results from the different multiply imputed datasets. Uncertainty surrounding the ICERs will be graphically presented on cost-effectiveness planes.

Cost-effectiveness acceptability curves will also be estimated using the net benefit framework. [49] Cost-effectiveness acceptability curves show the probability that

collaborative care is cost-effective in comparison with usual care for a range of different ceiling ratios thereby showing decision uncertainty. [50]

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The CHEVAL-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 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 to ensure 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 ask the patient permission to be contacted by a research nurse. The neurologist will provide the patient with written information about the study and with the Informed Consent Form (see part “E” of the investigator’s file).The research nurse in the VUmc will register the patient in the Local Logistics Database (LLD), after which the the local research nurse will be informed automatically. Within ten days, the local research nurse will contact the patient by phone to answer any questions about the study. This nurse, will be specially trained for the task to inform the patient. 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. This appointment can be made at the patient's home or 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 or at home. Before the first measurement the nurse will ask the patient to sign the informed consent and check in- and exclusion criteria again.

11.3 Benefits and risks assessment, group relatedness

ChEI are a well-known and usually well-tolerated class of drugs. For implementation purposes it is a great advantage that they are already widely available and easy to prescribe. Many neurologists are experienced in ChEI treatment for patients with Alzheimers disease. ChEI are fairly inexpensive, so financial budget limitations will not be a barrier to incorporate ChEI into daily practice.

If the study demonstrates that ChEI are able to delay the progression to more severe VH without insight, PD patients will benefit in several ways. In contrast with the current treatment for VH, dopamine replacement therapy can be maintained with an unaltered level of motor control. Furthermore, the presence of VH correlates with the incidence of major depression and anxiety. [7] A successful intervention for VH will consequently cut down the prevalence of the associated mood disorders. It would mean a better quality of life for elderly patients with a chronic disease and a reduction of the burden on their caregivers.

Less VH could mean less emergency admissions to hospitals and nursing homes. In addition, PD patients would be able to remain in their own homes, in the proximity of their families. Resources for intramural care are used more properly, while the total amount of months in an institution is reduced.

The predominant side effects of ChEI treatment are cholinergic in nature; the most frequent are nausea and vomiting. Less frequently an increase in motor symptoms occurs, especially tremor. [14-17]

The DNA analysis can possibly show abnormalities that are not related to PD, but are highly associated with another disease. If there's a possible health risk for the patient and the patient would benefit of any kind of preventive action or early treatment, he should be informed about these findings. This consideration is largely dependent on the kind of mutation that has been found or the severity of the health risk. After the projectleader is

informed a meeting for the patient with his treating neurologist or family physician (if the patient gives permission) is arranged to discuss the results of the DNA-analysis and it's consequences.

In case of possible health related risks for any other family member of the patient based on the DNA analysis, the patient is informed first. The family members will be informed by letter and will be able to contact a specialist for more information when this is desired.

11.4 Compensation for injury

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

The sponsor (also) has an 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 and documents

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 (part “E” of the investigator’s file).

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 com¬pleted. 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 at the time of inclusion. The local investigator will ensure that the 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 research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

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 sponsor.

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 15 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 and publication policy

Our project group consists of a considerable number of the Dutch Movement Disorders experts including the chair of the Werkgroep Bewegingsstoornissen Nederlandse Vereniging voor Neurologie (NVN) and the chair of the Centrale Werkgroep Multidisciplinaire Richtlijn Parkinson. Through these important opinion leaders in the Netherlands our results will be added to new treatment guidelines and guideline updates. Over the past years the movement disorder neurologists in the Netherlands have built a strong network for clinical research. This research collaboration is experienced in conducting large multi-center trials (several supported by ZonMw funds). Thirty neurology clinics throughout the country intend to participate in the project (see appendix and the chapter 'feasibility of rectruitment'). Their willingness shows the broad national support and acknowledgement for the present study.

The results will be published in high-impact journals and will 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.

With the help of our international network (advisory board) we will be able to present our results during the International Congress of the Movement Disorders Society and the World Congress on Parkinson's Disease and Related Disorders.

The first author of all main publications concerning this trial is T.J.M. van Mierlo, the Ph.D.-student that executes the study at the VU University Medical Center. The last author of all main publications concerning this trial will be E.M.J. Foncke, principal investigator of this study. The order of the other authors will be determined by the Steering Committee and E.M.J. Foncke.

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 CHEVAL-study group. Ancillary publications may not appear prior to the publication of the main results paper.

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