Conservative iron chelation as a disease-modifying strategy in Parkinson's disease

FAIR-PARK-II

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Signature page

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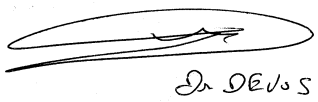

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3	European Clinical Research Infrastructure Network	ECRIN	France
4	INSERM - Transfert SA	IT	France
5	Apo-Pharma inc. corp	APOPHARMA	Canada
6	Instituto de Medicina Molecular	IMM	Portugal
7	Fundació privada Clínic per a la Recerca Biomèdica	FCRB	Spain
8	University of Newcastle upon Tyne	UNEW	United Kingdom
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10	Medizinische Universitat Innsbruck	MUI	Austria
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12	Stichting Katholieke Universiteit	RUNMC	The Netherlands
13	Philipps Universitat Marburg	PUM	Germany
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I.SYNOPSIS

PROMOTOR	CHRU de Lille Direction de la Recherche et de l'Innovation 2 avenue Oscar Lambret 59037 LILLE Cedex FRANCE
TITLE	Project acronym: FAIR-PARK-II Project full title: "Conservative iron chelation as a disease-modifying strategy in Parkinson's disease. It's a European multicentre, parallel-group, placebo-controlled, randomized clinical trial of deferiprone (DFP)"
COORDONNATOR	Professeur Devos D. Département de Pharmacologie Médicale Université de Lille, Faculté de Médecine, 1 Place de Verdun, F-59045 LILLE Cedex, & Clinique Neurologique, Hôpital R Salengro & Fédération de la Recherche Clinique, CHRU F-59037 LILLE cedex
NUMBER OF CENTRES	24 centers The recruitment strategy will be based on the participation of 24 expert centres involved in the European MDS network. Experience indicates that we shall be able to identify 7 de novo PD patients per centre per year (i.e. total of 14 patients per centre for the two-year study). We shall also secure fast, appropriate recruitment by using the Fox Trial Finder (https://foxtrialfinder.michaeljfox.org). The Fox Trial Finder will not only list our on-going PD clinical trial on its website but will also match registrants to our trial (i.e. best-suited to their specific traits). The Fox Trial Finder also has a secure, anonymous messaging system, making it much easier to find PD patients and involve them in our RCT. A specific website of the clinical trial will be set up to help the recruitment. The website will be connected with the website of the European Parkinson's disease Association (EPDA). Indeed, EPDA is actively involved in the dissemination of the project to the PD community. The Cure Parkinson Trust has also accepted to relay the informations to help the recruitment.
STUDY DESIGN	A multicentre, parallel-group, randomized, placebo-controlled trial of DFP 15 mg/kg BID. A 9-month treatment period (period 1) will be followed by a 1-month post-treatment monitoring period (period 2), in order to assess the disease-modifying effect in the absence of a symptomatic effect (i.e. an effect of inhibition of catechol-O-methyl transferase (COMT) activity (ICOMT) on dopamine metabolism) of DFP (versus placebo). Considering the short half-life of DFP, one month will be enough to assess the level of handicap of patients in the absence of ICOMT due to DFP treatment.
INDICATION	De Novo Parkinson's disease

BACKGROUNDS & OBJECTIVES	• Background and overall aim The problem: Parkinson's disease (PD) is a common, chronic, fast-progressing, non-communicable disease. As the second most frequent neurodegenerative disorder worldwide, PD affects millions of people - about 1% of the over-60s and up to 4% of people in the oldest age groups. It is estimated that the prevalence will at least double by 2030. None of the currently available drugs can slow down the dramatic progression of the motor handicap (e.g. falls) and non-motor handicap (dementia), which generally lead to institutionalization and death. At present, only symptomatic treatments are available (i.e., drugs that partially and transiently reduce the patient's level of handicap). None of the treatments has demonstrated the ability to decrease the long-term progression of handicap. Today, most patients with PD irremediably progress to a severe state of dependence. In Europe, the cost of PD was estimated to be at least €13.9 billion in 2010. The huge and increasing socio-economic impact of PD and the immense emotional burden placed on patients and their caregivers represent a great challenge to society. There is an urgent need for a "game-changer" strategy, with the development of disease-modifier treatments with neuroprotective and/or neurorestoration effects that can help to avoid this dramatic situation in PD and, more generally, in other neurodegenerative diseases with common physiopathological mechanisms. For many years, the excess oxidative stress related to mitochondriopathy has been considered as one of the main mechanisms involved in cell death (Schapira and Patel, 2014). Oxidative stress is exacerbated by free iron. Chelation of this free iron is known to dramatically increase cell survival. Indeed, iron deposition and oxidation are two major pathways involved in the physiopathology of PD and have been extensively studied (for a review, see Cabantchik et al. 2013). There is a large body of evidence that shows that iron chelation-based antioxidants greatly enhance cell survival in PD cell models and that iron chelators have therapeutic potential in mouse models of PD. However, we reasoned that to develop this therapeutic approach in humans, chelation strategies that target local and regional iron overload (i.e. siderosis) in the brain will necessarily need to avoid systemic iron depletion via the redistribution of iron to endogenous acceptors (i.e. in order to prevent harmful systemic metal loss): this is the new concept of "conservative iron chelation". We recently demonstrated (for the first time) the feasibility, efficacy and acceptability of the conservative iron chelation approach in pilot translational studies in PD with a prototype drug: deferiprone (1,2-dimethyl-3-hydroxypyridin-4-one, DFP) (in the FAIR-PARK-I project led by the applicant and funded by French Ministry of Health). The only available blood-brain-barrier-permeable iron chelator DFP is approved for treating systemic iron overload in transfused patients with thalassemia. DFP has been on the EU market since 1999, with a favourable risk/benefit balance at dose of 75 to 100 mg/kg/day. We shall adopt a repositioning strategy by using DFP at a lower dose of 30 mg/kg/day in this new indication for local iron overload in PD. DFP will be the first-in-class drug for this novel therapeutic strategy. On the basis of our preclinical and clinical

	data from FAIR-PARK-I, the present FAIR-PARK-II project should constitute a model for future cytoprotection strategies in neurodegenerative diseases; if DFP treatment is associated with significant slower disease progression, it would be the first non-dopaminergic drug to have a proven disease-modifying effect in PD. Conservative iron chelation was assessed in cell-based models, corroborated in an animal model of regional siderosis and then translated into a clinical setting (Devos et al., 2014). These preclinical, translational and pilot clinical studies (Devos et al., 2014; details of our results are specified elsewhere in this application): have demonstrated that iron chelation with DFP: (i) induced greater neuroprotection in cell models (dopaminergic neurons: LHUMES model, patients' lymphocytes) than deferoxamine (used as a reference iron chelator) through a powerful antioxidant effect. (ii) reduced regional siderosis of the brain and the motor handicap in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) neurotoxin mouse model. (iii) reduced regional siderosis of the brain in PD patients (iv) reduced motor handicap of PD patients (possibly through central and peripheral inhibition of catechol-O-methyl transferase (ICOMT) in a double-blind, placebo-controlled study in 40 patients. (v) slowed the progression of motor handicap in a pilot study in early-stage PD patients (thus suggesting a disease-modifying effect) in a double-blind, placebo-controlled study in 40 patients with a delayed start paradigm. (vi) had a good safety profile, although weekly blood counts are required during the first six months to detect the (reversible) neutropenia that typically occurs in 2-3% of treated patients. Thus, DFP appears to have disease-modifying potential and also inhibits dopamine metabolism through ICOMT (Waldmeier et al. 1993; Devos et al., 2014; Dexter et al., 2014). The latter associates a more direct symptomatic benefit for the patients, together with the expectation of slower disease progression. The ICOMT activity could be also of high value because there is a lack of well-tolerated drugs with central ICOMT. Entacapone has only peripheral ICOMT activity (and thus a lower efficacy). Although tolcapone has both central and peripheral ICOMT activity, its prescription is restricted indicated by a high risk of hepatitis. Interestingly, these clinical results were recently confirmed by another independent pilot study on 18 PD patients, which showed a reduction in brain iron overload and a better clinical effect for DFP at 30 mg/kg/day than for placebo and DFP at 20 mg/kg/day (Dexter et al., 2014). Thus, the two pilot studies have been used to calculate the required sample size to lead our project based upon a large randomized clinical trial to demonstrate this new therapeutic concept

	Moreover, by taking advantage of collaborations and involvement in other European studies, we shall assess DFP's impact and the prognostic value of biomarkers obtained from large-scale, on-going studies. This will increase the scientific impact and dissemination of our study (i.e. publications) and limit the risk of failure and negative results. Finally, the health economics and societal impacts will be monitored because it is increasingly acknowledged that conclusions based on conventional clinical trials may not be useful for making decisions on management in a "real-life" clinical setting. If DFP is associated with significant slowing of disease progression in FAIR-PARK-II, it would be the first non-dopaminergic drug to have a proven disease-modifying effect. As such, DFP would also have a huge socio-economic impact. In order to move towards an assessment of DFP's potential real-world benefits data, we shall concomitantly analyse the drug's impact on health economics aspects and the PD patients' and caregivers' quality of life via questionnaires and the continuous quantitative monitoring of PD-associated handicaps in the home environment (i.e., bradykinesia, gait and balance, tremor, sleep) using the SENSE PARK device (developed in the frame of FP7). At present, no neuroprotective drugs are available. If our academic proof-of-concept study demonstrates a disease modifying effect, this new therapeutic strategy could be offered to the population of patients with PD as a whole. This would represent a considerable market and would have a huge socio-economic impact. Objectives The trial's overall objective can be summarized as follows: to demonstrate for the first time in a large phase II, multicentre, parallel-group, placebo-controlled, randomized clinical trial (RCT) that conservative iron chelation, with the prototype drug, DFP, will slow down the progression of handicap in PD patients and will not be associated with a negative clinically benefit/risk ratio. A putative slow-down in the progression of handicap will be monitored in a multicentre, placebo-controlled RCT with 372 patients with de novo PD (the best population for assess a disease-modifying effect without the bias caused by the effects of dopaminergic treatment). They will be assigned to receive either DFP (15 mg/kg bis in die (BID)) or placebo. Based on the two pilot studies, the optimal dose of 30 mg/kg/day will be used. A 9-month treatment period (period 1) will be followed by a 1-month post-treatment monitoring period (period 2), in order to assess the disease-modifying effect in the absence of a symptomatic effect (i.e. an effect of ICOMT activity on dopamine metabolism) of DFP (versus placebo). Considering the short half-life of DFP, one month will be enough to assess the level of handicap of patients in the absence of ICOMT due to DFP treatment. The project will run for 72 months and we shall address: (i) the risk/benefit balance of this new disease-modifying treatment strategy for PD.

	(ii) surrogate and theranostic biomarkers of efficacy and safety. (iii) health economics and societal impacts. For the risk/benefit balance, the primary efficacy criterion will be the total score on the Movement Disorders Society- Unified Parkinson's Disease Rating Scale (MDS-UPDRS), which encompasses motor handicaps and non-motor handicaps (i.e. cognition and behaviour) and activities of daily living (see 1.3). Experience from the large ADAGIO and ELLDOPA studies indicates that we shall be able to maintain de novo PD patients in the absence of symptomatic treatment for 36 weeks with a low drop-out rate - a sufficiently long time period over which to observe a difference vs. the placebo group). The total MDS-UPDRS score is the usual primary efficacy criterion in PD trials. It includes all the motor and non-motor aspects of the disease and the activity of daily living (part II), which is less sensitive to the placebo effect. The Movement Disorders Society recommends this criterion. The secondary criteria will include the separate analysis of the MDS-UPDRS subscale scores, quality of life, personal autonomy, safety criteria, and biomarkers of efficacy and safety. The surrogate and theranostic biomarkers will include: • Magnetic resonance imaging (MRI), i.e. indirect measurements of iron with an R2* sequence • Transcranial ultrasound (i.e. indirect measurements of iron via the hyperechogenicity of substantia nigra). • Dopamine transporter SPECT imaging (123I-FP-CIT, DATscan®) • Biochemical biomarkers (in blood and cerebrospinal fluid (CSF)). • Pharmacogenetic markers (i.e. ceruloplasmin genotypes for the disease-modifying effect of iron chelation and COMT genotypes for the symptomatic action of DFP). Objective 1: To successfully manage the demonstration of the Investigating DFP efficacy as a treatment for PD in a large placebo-controlled study and thus demonstrate (for the first time in a neurodegenerative disease) the concept of conservative iron chelation as a disease modifier treatment. We aim to demonstrate a lower progression of motor and non-motor handicap at week 36 in PD receiving DFP as compared with placebo. Objective 2: To demonstrate the feasibility of a multi-site European clinical trial of a potential PD treatment with a demonstrated safety profile, with a specific monitoring. Objective 3: To fund the larger scale investigation of DFP in PD patients, which the existing preclinical and clinical data strongly mandate and to promote a European clinical trial network of PD clinicians and researchers. Objective 4: To investigate clinical, radiological, biological and genetic biomarkers of PD progression in response to DFP.

	Objective 5: To bring the first data of DFP's potential real-world benefits based upon the drug's impact on health economics aspects and the continuous monitoring of motor and non-motor handicap at home. Objective 6: To expedite the availability of disease-modifying treatments to PD patients. Based upon our demonstration of efficacy and safety of conservative iron chelation with the only available and prototype drug, DFP, we aim to promote and support the clinical development of iron chelators as a new treatment modality in PD. The following clinical development with large phase II studies and registration of DFP, the first in class, by ApoPharma could be done within 7 years. We also aim to promote the clinical development (from phase I) of future other iron chelators (i.e. hydroxypyridinones) for PD and other neurodegenerative diseases (i.e. Alzheimer, ALS, multisystem atrophy, etc.). Objective 7: To describe the effect of DFP on the disease progression, taking into account the dropout rate with a combined criterion of disease progression measured by the total score of the MDS-UPDRS and the dropout because of disease worsening.
PRIMARY & SECONDARY CRITERIA	• The primary efficacy criterion: the change in the total MDS-UPDRS score between baseline and 36 weeks (i.e. the end of the placebo-controlled phase for analysis of both disease-modifying and symptomatic effects). Experience from the large ADAGIO and ELLDOPA studies indicates that we shall be able to maintain de novo PD patients in the absence of symptomatic treatment for 36 weeks with a low drop-out rate - a sufficiently long time period over which to observe a difference vs. the placebo group).The total MDS-UPDRS score is the usual primary efficacy criterion in PD trials. It includes all the motor and non-motor aspects of the disease and the activity of daily living (part II), which is less sensitive to the placebo effect. • The secondary criteria will include: (i) The disease-modifying effect: will be measured as the changes in the overall MDS-UPDRS score between baseline and week 40 (i.e. the end of the one-month post-treatment monitoring period), to analyse the disease-modifying effect without bias from the symptomatic effect of ongoing DFP treatment) on the study population as a whole (n= 372). (ii) The global effect on motor and non-motor symptoms: will be analysed as the change in the different subscales of the MDS-UPDRS (part I: cognition and behaviour; part II: activities of daily living; part III: motor handicap; part IV: fluctuations) and MDS-UPDRS part II+III, the Stand Walk Sit test, overall cognitive status (score in the Montreal Cognitive Assessment) between baseline and week 36; and between baseline and week 40 for the study population as a whole (n= 372). (iii) Effects on quality of life and autonomy will be analyzed as the change in the Parkinson's Disease Quality of Life (PDQ-39, via a 39-item self-questionnaire) and the Clinical Global Impression scored by the examiner and the patient between baseline and

	week 36, and between baseline and week 40 for the study population as a whole (n= 372). (iv) A health economics assessment will be performed via a specific questionnaire and EQ-5D questionnaire (It provides a simple descriptive profile and a single index value for health status) between baseline and week 36, on the study population as a whole (n= 372). • Descriptive analysis: (v) A combined criterion of disease progression measured by the decline of the total score of the MDS-UPDRS between baseline and 36 weeks and the occurrence of a drop out related to disease worsening (CAFD). This endpoint is analogous to the CAFS proposed by Berry JD and al. (Berry et al., 2013[1]) and details about its computation can be found in this paper. Briefly, the CAFD ranks subject outcomes on the basis of time to drop out (related to disease) or change in MDS-UPDRS scores from baseline to 36 weeks. Patients who drop out are ranked on the basis of time to drop out, with earlier time ranked the worst. Patients who are always followed are ranked higher than were those who came out the study, based on the change from baseline in MDS-UPDRS total score, with largest negative changes ranked worst. Drop out related to disease worsening will be identified as following: when the patient report a worsening of the specific signs of PD: i.e. akinesia, rigidity, tremor, gait or a global disease worsening as a reason for drop out. The reason of drop out and the AE are coded according to the MedDRA dictionary. The adverse event not specifically related with disease progression will not be taken into account (e.g. isolated pain, isolated fatigue, headache, nausea, dizziness etc. (vi) Safety criteria will include • A weekly complete blood count (CBC, including a white blood cell (WBC) count and a differential, absolute neutrophil count (ANC) and platelet count) will be performed weekly (± 3 days) from the start of treatment onwards for 24 weeks and then monthly until week 36. For the patients' comfort, the test can be performed in a medical laboratory close to their home. The results will be immediately faxed to the study centre. A standard operating procedure (SOP) in each centre will ensure prompt review of the

[1] Berry JD, Miller R, Moore DH, Cudkowicz ME, van den Berg LH, Kerr DA, Dong Y, Ingersoll EW, Archibald D.

The Combined Assessment of Function and Survival (CAFS): a new endpoint for ALS clinical trials. Amyotroph Lateral Scler Frontotemporal Degener. 2013;14:162-8.

	results. An additional WBC count will be required in the event of fever. If the ANC falls below a value of 1.5 x 10^9/L (neutropenia) and/or 0.5 x 10^9/L (agranulocytosis), the investigator will immediately contact the patient and take appropriate measures. Therapeutic education and SOP in case of fever, neutropenia or agranulocytosis will be also provided to all the patients • An iron status check: haemoglobin, serum iron, ferritinemia, transferrin, total binding capacity, transferrin saturation coefficient, 24-hour urine iron. • Clinical chemistry tests: fasting glucose, urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT). Contraceptive counselling will also be provided for all sexually active males and females). • General health status and a full physical examination, including vital signs, bodyweight, electrocardiogram and blood pressure. • Adverse events, concomitant medication(s) and observance: participants will be questioned about the occurrence of AEs, the use of any medications and the compliance with the study therapy, at each scheduled or unscheduled visit. • β HCG (for women of childbearing potential) will be performed every month and the result will be immediately faxed by the patient's local medical lab Exploratory endpoints: A biomarker analysis to assess the biomarkers' potential surrogate value For reasons of cost and of harmonisation of the sequences and the procedures, the following exams will be performed only in “expert” centers”. Hence, the biomarkers are not optional for patients in the selected centers (all patients in an expert center will have all the examinations). These biomarkers will be analysed on a subpopulation of patients. • MRI: the relaxation time of the substantia nigra, the caudate nucleus, the putamen pallidum and the dentate nucleus will be assessed with an R2* MRI sequence between baseline and week 36 on a subgroup of the population (n=150). This will enable us to indirectly measure DFP's action on the ferric iron content of these structures (i.e. measurements of ferritin, hemosiderin and neuromelanin). This will evidence the drug's action in the brain in general and in the target structures in particular, whereas healthy structures should not be modified. Deferiprone chelates free, ferrous, labile iron, which is not directly measurable in vivo. Accordingly, ferric iron levels subsequently decrease; this modification becomes visible after 3 to 6 months. • Dopamine transporter (DaT) scan: we shall perform 123I-FP-CIT study (123I- Ioflupane labeled N-(3-fluoropropyl)-2beta-carbomethoxy-3beta-(4-iodophenyl) nortropane (FP- CIT) between baseline and week 40 on the same subgroup of the MRI population (n=150) and compare it with other biomarkers. The

	DaT expression will provide a direct measurement of the status of the presynaptic dopaminergic nigrostriatal neurons (i.e. a smaller reduction in the DFP group than in the control group). This would demonstrate neuroprotection. • Transcranial ultrasound: the substantia nigra's echogenicity is known to be correlated with tissue iron content. Quantitative measurement of the area of echogenicity will be performed between baseline and week 36 on a subgroup of patients (50<n<100, depending on technical aspects). This will provide an indirect measurement of the iron content and should evidence the drug's action on the target area for neuroprotection. • Data from the continuous assessment of PD-relevant domains with an unobtrusive, continuous; quantitative measurement tool (SENSE-PARK, FP7) will collect data during 2 weeks after randomization visit, 2 weeks before week 36 and 2 weeks before week 40 on a subgroup of patients (n=60). • A specific biochemistry screen, with a view to understanding the mechanisms that might (i) underlie an improvement in brain function and clinical function and (ii) identity surrogate biomarkers. The biochemical screen (performed at the randomization visit andat week 36 consists of a panel of blood tests (150<n<338 according to the level of difficulty of the preparation and collection: 150 for difficult preparations and 338 for DNA collection). • Surrogate marker: Iron metabolism: ferritin (a low level of ferritin might be associated with a higher degree of benefit for DFP treatment (Dexter et al., article submitted). • Surrogate marker: Ceruloplasmin levels, ceruloplasmin ferroxidase activity, and the ceruloplasmin genotype (the D544E polymorphism, AT) will be assessed, in order to study to the drug's putative disease-modifying effect as a function of the genotype. The AT genotype might be associated with a greater effect of DFP on clinical symptoms and a greater reduction in the R2* value (relative to the AA group) (Grolez et al., submitted). • Surrogate marker: the COMT Val158Met polymorphism will be assessed, in order to study the drug's symptomatic effect as a function of the genotype (i.e. DFP's ICOMT effect). • Heavy metal assays: blood iron zinc, copper, magnesium, chrome, manganese, nickel, lead and cadmium levels, 24-hour urine copper and zinc excretion. • Oxidative stress (total antioxidant status, lipid peroxidation (malonaldehydes (MDA)), protein carbonyls, 8-OHdG glutathione, super oxide dismutase (SOD)). Protein carbonyls will be assayed after centrifugal filtration-concentration (with a kit from Immunodiagnostik AG, Bensheim, Germany). Both MDA concentrations and glutathione status (i.e. glutathione disulphide and reduced glutathione) will be determined in tissue homogenates by using HPLC with fluorescence detection. Concentrations of the DNA adduct 8-OHdG will be studied in tissue homogenates using commercially available enzyme immunoassays (Highly Sensitive 8-OHdG Check, from Gentaur

	France SARL, Paris, France). Enzymatic activities of SOD and glutathione peroxidase in whole blood and the antioxidant capacity of plasma (using Trolox as a standard (Sigma)) will be performed as published elsewhere (23). • Vitamins B1, B6, B12, E, A, and C, folates. • Inflammatory factors: tumour necrosis factor alpha and interleukin-6 • Optional studies: (optional for the patients because the examination is more invasive) 1. Additional blood analysis (extra volume of 40 ml) a. Mitochondrial function, with functional assays on lymphocytes: mitochondrial membrane potential and reactive oxygen species production (flow cytometry) b. Neural, endothelial and platelet microparticles 2. CSF analysis (lumbar puncture): dopamine, metabolites, ferritin, and oxidative stress markers • A prolactin dosage on samples collected for centralized analysis at visits V0 and V3 by comparing the treated and untreated group will be performed at the end of the study.
INCLUSION CRITERIA	1. Adult patients 2. Parkinson's disease diagnosed according The Movement Disorder Society Clinical Diagnotic Criteria for Parkinson's Disease (PD). 3. Treatment-naïve, i.e. the best population for assessing a disease-modifying effect without the interaction of dopaminergic treatment (no dopaminergic agonists, L-dopa, anticholinergics, monoamine oxidase B inhibitors (e.g. rasagiline) or deep brain stimulation). 4. Patients covered by a Health Insurance System in countries where required by law 5. Written informed consent dated and signed prior to the beginning of any procedures related to the clinical trial
EXCLUSION CRITERIA	1. Disease duration greater than 18 months. 2. Patients with high frequency of comorbidity or vital risks that may reasonably impair life expectancy 3. Subject with handicap required dopaminergic treatment at the inclusion and therefore likely not to bear 9 months without symptomatic treatment 4. Hoehn and Yahr stage 3 or more. 5. Significant cognitive impairment (a Mini Mental State Examination score <24 or an equivalent impairment on a similar scale) or dementia diagnosed in accordance with the Movement Disorders Society criteria (Emre et al., 2007). 6. Atypical or secondary parkinsonism (supranuclear palsy, multisystem atrophy, etc.) or significant cortical or subcortical atrophy (i.e. atypical for PD). 7. Progressing axis I psychiatric disorders (psychosis, hallucinations, substance addiction, bipolar disorder, or severe depression), in accordance with the Diagnostic and Statistical Manual of Mental Disorders.

	8. Subjects undergoing brain stimulation. 9. Due to the high risk of agranulocytosis caused by the IMP and the unknown mechanism by which this agranulocytosis is induced, it is not allowed to combine Deferiprone with other medicinal products causing agranulocytosis (as described in the IB). Such medicinal products are the already mentioned clozapine and also some NSAIDs (e.g. Phenylbutazone or Metamizole), antithyroid agents, sulfonamide antibiotics or metothrexate. 10. A history of relapsing neurotropenia 11. Hypersensitivity to deferiprone. 12. Patients with agranulocytosis or with a history of agranulocytosis. 13. Patients taking a treatment at risk of agranulocytosis (clozapine, Closaril®/Leponex®). 14. Patients with anaemia (regardless of the latter's aetiology) or a history of another haematological disease. Haemochromatosis is not an exclusion criterion. 15. Pregnant or breastfeeding women or women of childbearing potential not taking highly effective contraception. 16. Kidney or liver failure. 17. Other serious diseases. 18. Inability to provide informed consent. 19. Participation in another clinical trial with investigational medicinal product within 3 months prior to inclusion in the study 20. Patient who has suffered mild or moderate depressive episode and isn't in remission and on a stable medication for at least 8 weeks 21. Patient > 130 kg Exclusion criteria for the biomarker study and the ancillary study (i) MRI: • Subjects for whom MRI is contraindicated (metal objects in the body, severe claustrophobia, pacemaker, incompatible surgical material). • Very severe rest tremor, which could induce MRI artefacts. (ii) Lumbar puncture: • Blood coagulation disorders, antiplatelet drugs or anticoagulants. • Intracranial hypertension. (iii) Contraindications to nitrous oxide: • Ventilation with FiO2 >50%, emphysema or pneumothorax • Altered states of consciousness, non-cooperative patient (need to stop the nitrous oxide)
SUBJECTS NUMBER	372

SAMPLE SIZE	The main objective of the FAIR-PARK II trial is to demonstrate an effect of DFP on the course of PD (including both disease-modifying and symptomatic effects). The primary endpoint is the change in the total MDS-UPDRS score between baseline and 36 weeks (i.e. before the one-month washout period). Assuming a conservative correlation coefficient of 0.5 between the total MDS-UPDRS scores at baseline and at 36 weeks, the standard deviation of the change in the total MDS-UPDRS score (a 260-point scale, with 84 items) is equal to the standard deviation of the total MDS-UPDRS score (at either baseline or at 36 weeks). On the basis of two earlier large, randomized controlled trials (ADAGIO, Olanow et al., 2009 and ELLDOPA, Fahn et al., 2004), we have assumed that the standard deviation of the total MDS-UPDRS score is 9.0. In the ADAGIO trial, the difference in the 36-week change in the total UPDRS score (a 176-point scale, with 55 items) between the rasagiline group and the placebo group was 3 points (Olanow et al., 2009). In our pilot study, the difference in the 36-week change in the motor UPDRS score (a 108 points subscales with 27 items) between the DFP and placebo groups was also 3 points (Devos et al., 2014). On the basis of these two studies, we expect to demonstrate a minimum DFP vs. placebo difference in the primary endpoint of 3 points (corresponding to an effect size of 0.33) on the total MDS-UPDRS score. To detect this difference in a two-sided t test *with an alpha risk of 5% and* a power of 80%, we calculate that a total of 286 subjects (i.e. 143 subjects in each arm) will be required. Taking account of an anticipated dropout rate of 15% (similar to that in the ADAGIO trial), a total of 338 subjects (i.e. 169 subjects in each arm) should be included. But 3 years after the beginning of the inclusion of patients in the study and despite to a strict adherence of the investigators to the protocol, a strong monitoring and data quality check, we observed a 23% drop out rate. To take into account this slightly higher dropout rate and maintain the statistical power of the study, we plan to include a total of 372 patients (186 per arm). Although the primary statistical analysis of primary endpoint will be adjusted for baseline values, the sample size calculation does not take account of this adjustment, in order to maximize the power for the main secondary endpoint: the change in the total MDS-UPDRS score between baseline and 40 weeks (i.e. after the one-month washout period that assesses only the disease-modifying effect, in the absence of the symptomatic effect). With a total of 372 included subjects and a conservative correlation coefficient of 0.5, we should be able to detect a minimum effect size of 0.28 with a power of 80%. In the ADAGIO trial, the disease-modifying effect corresponded to a difference of 1.8 points between the rasagiline and placebo groups (corresponding to an effect size of 0.20). According to Cohen (Cohen, J. (1988), Statistical Power Analysis for the Behavioral Sciences, 2nd Edition. Hillsdale: Lawrence Erlbaum), this effect size is considered to be small. We provided different power calculation scenarios by varying the effect size for planning purposes; these are not intended to replace the exact power calculation. Figure 1 shows power calculations that do not take account of the correlation coefficient

	between baseline and final measures, whereas Figure 2 shows power calculations that assume a correlation coefficient between baseline and final measures of 0.5. All sample size/power calculations were performed with the PASS software (version 12, NCSS LLC, Kaysville, UT, USA).
MEDICATION	Pharmacotherapeutic group: iron chelator. The active substance is 3-hydroxy-1,2-dimethylpyridine-4-one (DFP, FERRIPROX®), a bidentate ligand that binds to iron in a 3:1 molar ratio. DFP decreases excessive iron and ferritin levels. Its low molecular weight and liposolubility enable it to cross the blood-brain barrier. Clinical haematology studies have demonstrated that DFP is effective in promoting iron excretion and that a dose of 25 mg/kg three times per day can prevent the progression of iron accumulation (as assessed by serum ferritin levels) in patients with transfusion-dependent thalassemia. However, chelation therapy may not necessarily protect against iron-induced organ damage. DFP (provided by ApoPharma) is unique among available iron chelators in that it readily penetrates the CNS and has been shown to function as an iron redeployment agent. The drug has been approved for many years in the indication of haemosiderosis in thalassemia major patients undergoing chronic blood transfusion. We intend to reposition DFP, with a disease-modifying effect in PD. Patients will receive placebo or 30 mg/kg per day DFP divided into two doses (at 08.00 and 20.00). An initial DFP dose escalation will be applied every third day during a period of 15 days We shall check on tolerability (assessed by interviews and examinations) and compliance (assessed by interviews and tablets counts) every 3 months. Interviews of patients and caregivers will be performed by the investigators. In the event of poor tolerance, we shall delay the titration phase by 1 week. The dose can be temporarily reduced to 20 mg/kg per day (suspicious of adverse event or variation of blood ANC toward neutropenia). However, we shall ask to the centers to maintain the patients at the dose of 30 mg/kg per day.
STUDY PROCEDURS AND TIMELINES	• Study procedures and timelines - A screening visit (Sc) - V0, V36 (9 months), V40 (10 months): Three comprehensive examinations (i.e. rating of the total MDS-UPDRS and all secondary criteria) at the randomization visit (V0, at D7-15 ± 1 week after Sc), week 36 and week 40. - V12 (3 months), V24 (6 months): Rating of the total MDS-UPDRS and a check on all the safety criteria during a brief consultation: at week 12 and week 24. A weekly CBC (with the WBC) for the first 24 weeks and then monthly until week 36. The results will be immediately faxed by the patient's local medical lab or the study center's central lab. DFP or placebo will be taken from the day following randomization until the morning dose on the day of the visit at week 36.

	• Patients will be invited to participate in an ancillary study involving CSF analysis at the randomization visit and at week 36, in order to perform a full set of CSF biochemistry assays and with a view to determining the biological benefits of DFP treatment at the central nervous system level and to identifying biological markers. Patients will be invited to participate in an ancillary study for additional blood analysis (extra volume of 40 ml) a. Mitochondrial function, with functional assays on lymphocytes: mitochondrial membrane potential and reactive oxygen species production (flow cytometry) b. Neural, endothelial and platelet microparticles Overall study duration: 54 months. Planned inclusion period: 47 months. Study duration for individual patients: 10.5 months (two weeks between screening and randomization, nine months of double-blind treatment and then a one-month wash-out period). For budgetary reasons, the additional 34 patients will only perform the main study.
EXPECTED RESULTS	We expect to observe a significantly lower mean total MDS-UPDRS score at weeks 36 and 40 in the DFP group (relative to the placebo group). This will enable us to demonstrate the efficiency of iron chelation as the first non-dopaminergic disease-modifying strategy in PD. This will be the first in class treatment to slow down the disease progression. The results will be obtained during the four year of the project, and the main paper will be published before the end of the fifth year. We do not expect to observe anaemia (or other iron metabolism disorders) with 30 mg/kg/day; anaemia was not a problem in the two independent pilot studies of smaller numbers of patients. We expect to see a good safety profile, with a low drop-out rate due to adverse events in all European centres and a low rate of neutropenia/agranulocytosis (with no harmful consequences), thanks to close monitoring with weekly blood counts. DFP has been on the EU market since 1999, with a favourable risk/benefit balance at 100 mg/kg/day (< 3% of neutropenia). This will enable us to demonstrate the safety of the new therapeutic concept of conservative iron chelation in PD. We aim to demonstrate a positive impact on the quality of life by the PDQ39 questionnaire. To date, there is no theranostic biomarker. We intend to demonstrate the theranostic value of the clinical, radiological, biological and genetic biomarkers for the response to DFP - notably the ferric iron overload measured by ultrasound and MRI, the level of degeneration measured by DaT imaging, the COMT genotype for symptomatic improvements at week 36 and the ceruloplasmin genotype for the disease modifier effect the blood and CSF levels of ferritin measured at week 36. The results will

	be obtained at the end of fifth year of the project and separated publications will be made at the end of the sixth year. To date, there is no surrogate biomarker. We expect to demonstrate the surrogate value of clinical, radiological, biological and/or genetic biomarkers for monitoring PD progression by analysing the large population of de novo patients in the placebo group for 40 weeks and comparing them with the advanced PD population in the PREDISTIM PHRC-2012 multicentre study (led by the applicant), the BADGE-PD-PHRC 2010 and DIGPD-PHRC 2008 (two PD cohorts led by JC. Corvol), the population of patients with Alzheimer's disease (AD) in the FP7 NILVAD study, led by Professor Lawlor) and the population of patients with amyotrophic lateral sclerosis (ALS) in the JPND SOPHIA study (led by Professor Van den Berg). Results will be obtained at end of the fifth year of the project and publications will be made at the end of the sixth year. We intend to demonstrate that DFP has favourable impact on health economics aspects, as measured by a specific questionnaire. We also expect to see a concomitant, positive impact on the activities of daily living by performing the continuous assessment of the PD-relevant domains with an unobtrusive, quantitative, continuous measurement tool (SENSE-PARK, FP7). We expect to set up an efficient European clinical trial network in PD, in order to promote the forthcoming European studies. This will be reinforced through many teleconferences and meetings with the study group, the efficient completion of the study within 6 years, the many papers generated by the study group and the activities led by different work package leaders and investigators. The collaboration with the three FP7 studies (NILVAD, SOPHIA and SENSE-PARK) will also reinforce the European PD network. We expect to widely disseminate the demonstration of this new therapeutic concept, in order to promote and support the clinical development of DFP and future other iron chelators (i.e. hydroxypyridinones) for PD and other neurodegenerative diseases (i.e. Alzheimer, ALS, multisystem atrophy, etc.).
RISK / BENEFIT BALANCE EXPECTED	Expected benefits: We expect to observe a significantly lower handicap in the DFP group and thus a lower disease progression. It appears to have no loss of opportunity for the patients under placebo since there is still no validated neuroprotective treatment. Rasagiline has shown a weak disease modifying effect, for which a pure symptomatic effect remains subject of debate. Moreover, it has been specified in the exclusion criteria that "Subjects with a handicap likely to require symptomatic dopaminergic treatment in the coming nine months" in order to avoid patients having a handicap requiring symptomatic effect. Possible risks: - Risk of neutropenia (< 3%)

	- No anemia expected - Adverse effect of DFP (see products characteristics).
PERIOD OF PROHIBITION AGAINST PARTICIPATION TO ANOTHER INTERVENTIONAL STUDY EXCLUSION PERIOD	YES – DURATION: 10.5 months (Duration of participation of the patient to the study) YES – DURATION: 48h after the end of the study. In case of early termination until Week 36, an exclusion period of one month should be respected.
DATA AND SAFETY MONITORING BOARD (DSMB)	In case of serious adverse event, the investigator of the centre will have to declare it within 24 hours to the Sponsor. The Sponsor will inform the coordinator investigator and the DSMB. The DSMB will examine AE reports on a regular basis.
STATISTICAL METHODS	The main statistical analyses (of primary and secondary clinical efficacy and safety outcomes) will be performed by the University of Lille's Biostatistics Department, under the supervision of Professor A. Duhamel. The data will be analyzed using SAS software (SAS Institute Inc., Cary, NC, USA) and all statistical tests will be two-tailed with an alpha risk of 0.05. The main analysis for primary and secondary efficacy clinical outcomes will be performed on an intention-to-treat basis. A secondary per-protocol analysis will also be performed. A detailed statistical analysis plan will be written and finalized prior to the first inclusion of patient for the primary and secondary clinical efficacy/safety outcomes. For other outcomes and ancillary studies, statistical analysis plans will be provided to the Executive Board and the SAB prior to any data analysis. The primary endpoint (the change in the total MDS-UPDRS score between baseline and 36 weeks) in the DFP and placebo groups will be compared in an analysis of covariance (after adjustment for the baseline total MDS-UPDRS score). Missing data (due to withdrawal or others reasons) for primary endpoint will be handle by multiple imputation using chained equations (m=10 imputations using primary endpoint and patient's characteristics at inclusion) (according to Rubin's guidelines). As exploratory analysis, a linear mixed model for repeated measures will be also used to estimate and compare the slopes (i.e. the change in MDS-UPDRS points per week) in the DFP and placebo groups from baseline though to 36 weeks. We shall use a mixed model with random coefficients (the intercept and time effect), as described by Molenberghs (Linear mixed model for longitudinal data, Springer 2000). The secondary efficacy outcomes (i) to (iv) will be analyzed using the same methods as for the primary endpoint. For the combined criterion of disease progression (CAFD), descriptive statistics (absolute and relative frequencies) will be used. The safety analysis will be completed in all patients, who will be randomly assigned to a study group. The usual descriptive parameters (including the calculation of confidence intervals) will be provided for all safety criteria. Intergroup differences in quantitative parameters will be compared in a Student's t test for normally distributed variables and a Mann-Whitney U test if not

	(except if logarithmic transformation can be applied). The assumption of normality will be checked graphically and by using a Shapiro-Wilk test. Intergroup differences in qualitative parameters will be compared using a Chi-square test or Fisher's exact test. This trial will be registered with ClinicalTrials.gov and its reporting will follow the CONSORT guidelines.
RULES OF TRANSPARENCY	a. Commitment to register the trial in a public register (Clinicaltrials.gov) before inclusion of the first participant b. Commitment to post trial results in a public register (Clinicaltrials.gov) one year after the trial is completed, i.e. last follow up of the last patient for the primary outcome. c. Commitment to publish results irrespective of findings. d. Commitment to make raw anonymised data sets available to the scientific community upon request. The data will be also shared after the trial through ZENODO. e. Declaration of no conflicts of interest. Commitment to fairly describe the contribution of all partners in the publications
STUDY DURATION	6 years

I. BACKGROUND AND STUDY RATIONALE

The problem: Parkinson's disease (PD) is a common, chronic, fast-progressing, non-communicable disease. As the second most frequent neurodegenerative disorder worldwide, PD affects millions of people - about 1% of the over-60s and up to 4% of people in the oldest age groups. It is estimated that the prevalence will at least double by 2030. **None of the currently available drugs can slow down the dramatic progression of the motor handicap (e.g. falls) and non-motor handicap (dementia), which generally lead to institutionalization and death**. At present, only symptomatic treatments are available (i.e., drugs that partially and transiently reduce the patient's level of handicap). None of the treatments has demonstrated the ability to decrease the long-term progression of handicap. **Today, most patients with PD irremediably progress to a severe state of dependence.** In Europe, the cost of PD was estimated to be at least €13.9 billion in 2010. The huge and increasing socio-economic impact of PD and the immense emotional burden placed on patients and their caregivers represent a great challenge to society.

There is an urgent need for a "game-changer" strategy, with the development of disease-modifier treatments with neuroprotective and/or neurorestoration effects that can help to avoid this dramatic situation in PD and, more generally, in other neurodegenerative diseases with common physiopathological mechanisms.

For many years, the excess oxidative stress related to mitochondriopathy has been considered as one of the main mechanisms involved in cell death (Schapira and Patel, 2014). Oxidative stress is exacerbated by free iron. Chelation of this free iron is known to dramatically increase cell survival. Indeed, iron deposition and oxidation are two major pathways involved in the physiopathology of PD and have been extensively studied (***for a review, see Cabantchik et al. 2013***). There is a large body of research evidence to show that iron chelation-based antioxidants greatly enhance cell survival in PD cell models and that iron chelators have therapeutic potential in mouse models of PD.

However, we reasoned that to develop this therapeutic approach in humans, chelation strategies that target local and regional iron overload (i.e. siderosis) in the brain will necessarily need to avoid systemic iron depletion via the redistribution of iron to endogenous acceptors (i.e. in order to prevent harmful systemic metal loss): this is the new concept of "conservative iron chelation". **We recently demonstrated (for the first time) the feasibility, efficacy and acceptability of the conservative iron chelation approach in pilot translational studies in PD with a prototype drug: deferiprone (1,2-dimethyl-3-hydroxypyridin-4-one, DFP) (in the FAIR-PARK-I project led by the applicant and funded by French Ministry of Health).** The only available blood-brain-barrier-permeable iron chelator DFP is approved for treating systemic iron overload in transfused patients with thalassemia. DFP has been on the EU market since 1999, with a favourable risk/benefit balance at 100 mg/kg/day. **We shall adopt a repositioning strategy by using DFP at a lower dose of 30 mg/kg/day in this new indication for local iron overload in PD. DFP will be the first-in-class drug for this novel therapeutic strategy.**

On the basis of our preclinical and clinical data from FAIR-PARK-I, **the present FAIR-PARK-II project should constitute a model for future cytoprotection strategies in neurodegenerative diseases; if DFP treatment is associated with significant slower disease progression, it would be the first non-dopaminergic drug to have a proven disease-modifying effect in PD.**

"Cell-based models :

Deferiprone's (DFP) chelating ability in intact human dopaminergic neurons, a Lund human mesencephalic (LUHMES) cell line, was studied under oxidative stress conditions that simulated various aspects of the PD brain. Treatment of cells with 1-methyl-4-phenyl-pyridinium (MPP +, which affects mitochondrial complex I activity), menadione (which induces aberrant mitochondrial redox cycling), or N-ethylmaleimide (NEM, which depresses the cell's antioxidant capacity by blocking GSH) resulted in adenosine triphosphate (ATP) depletion and an ensuing drop in cell viability. Treatment with DFP conferred cytoprotection from various oxidative insults, which, in part, is associated (directly or indirectly) with chelation of labile iron, as demonstrated in a variety of model systems. In the present study, fairpark-I,, the DFP protective features observed in cells subjected to different oxidative insults were largely abrogated by precomplexation with exogenous Fe(III). DFP's ability to increase the survival of pro-oxidantchallenged

cells was also demonstrated in human lymphocytes, which are reportedly modified in PD patients receiving dopaminergic/L-dopa treatment. The application of DFP to human lymphocytes challenged with pro-oxidants resulted in higher survival and lower ROS formation. We attribute this partial protective effect of DFP to its ability to reduce the levels of labile cell iron (Devos et al., 2014).

In vivo studies with animal models of Parkinson's disease

The effect of DFP treatment on brain parameters with relevance to PD was initially studied in the acute 1-methyl-4-phenyl-1,2,3,6-tetrapyridine (MPTP) mouse. This model recapitulates several features of the human disease 7 days after intoxication. Oral administration of the membrane-permeant, bidentate chelator DFP at 150 mg/kg bid and 100 mg/kg bid partially relieved the oxidative damage generated within the SN by MPTP treatment, as reflected by the increase in the number of dopaminergic [i.e., tyrosine hydroxylase (TH)-positive] cells. Per os treatment with DFP afforded twice as much protection (i.e., 60%) as the intraperitoneally administered hexadentate deferoxamine (DFO) (which binds Fe(III) with a 1:1 stoichiometry) did (i.e., 30%). DFP's ability to reach the SN was deduced from the observed reduction in iron accumulation in MPTP-intoxicated mice, as measured in situ by MRI or in isolated tissue by atomic absorption spectrometry. Importantly, the pharmacological effects of oral DFP administration were reflected as an improvement in the animals' motor function, the number of rearing, and the maximum speed. Similar to what has been previously observed in the MPTP mice model with clioquinol, we found that the DFP pretreatment did not significantly affect the MPTP to MPP + conversion, as reflected in the respective MPP + striatal levels (ng/mg protein) of control (saline) versus DFP-pretreated mice: 0.4 – 0.2 and 0.3 – 0.1 ($n = 12$, $p > 0.05$). DFP also led to increased levels of reduced glutathione (GSH) relative to the oxidized glutathione (GSSG) and to reduced oxidation products of lipid (i.e., malondialdehyde- MDA formation) and of DNA (i.e., 8-oxodeoxyguanosine formation). As with other cases of toxicity resulting from iron accumulation in cell organelles, we found that DFP demonstrably neutralized mitochondria labile iron pools (measured in organelles isolated from mice brains and calcein labeled with the aid of calcein-AM). We also looked at whether DFP's ability to chelate labile cell iron (and thereby reduce ROS formation and ensuing oxidative stress) was associated with a reduction in dopamine depletion in dopaminergic neurons affected by the MPTP treatment. Indeed,MPTP treatment caused a major decrease in striatal [18F]-DOPA distribution and dopamine level. DFP partly rescued this dopamine depletion and significantly modified dopamine's metabolic conversions (as reflected by the levels of DOPA metabolites). (Devos et al., 2014).

Conservative iron chelation was assessed in cell-based models, corroborated in an animal model of regional siderosis and then translated into a clinical setting (Devos et al., 2014). These preclinical, translational and pilot clinical studies (Devos et al., 2014; *details of our results are specified elsewhere in this application*): have demonstrated **that iron chelation with DFP:**

(i) induced greater neuroprotection in cell models (dopaminergic neurons: LHUMES model, patients' lymphocytes) than deferoxamine (used as a reference iron chelator) through a powerful antioxidant effect.

(ii) reduced regional siderosis of the brain and the motor handicap in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) neurotoxin mouse model.

(iii) reduced regional siderosis of the brain in PD patients

(iv) reduced motor handicap of PD patients (possibly through central and peripheral inhibition of catechol-O-methyl transferase (ICOMT) in a double-blind, placebo-controlled study in 40 patients.

(v) slowed the progression of motor handicap in a pilot study in early-stage PD patients (thus suggesting a disease-modifying effect) in a double-blind, placebo-controlled study in 40 patients with a delayed start paradigm.

(vi) had a good safety profile, although weekly blood counts are required during the first six months to detect the (reversible) neutropenia that typically occurs in 1-3% of treated patients.

Thus, DFP appears to have disease-modifying potential and also inhibits dopamine metabolism through ICOMT (Waldmeier et al. 1993; Devos et al., 2014; Dexter et al., 2014). The latter associates a more direct symptomatic benefit for the patients, together with the expectation of slower disease progression. The ICOMT activity could be also of high value because there is a lack of well-tolerated drugs with central

ICOMT. Entacapone has only peripheral ICOMT activity (and thus a lower efficacy). Although tolcapone has both central and peripheral ICOMT activity, its prescription is indicated by a high risk of hepatitis.

Interestingly, these clinical results were recently confirmed by another independent pilot study on 18 PD patients, which showed a reduction in brain iron overload and a better clinical effect for DFP at 30 mg/kg/day than for placebo and DFP at 20 mg/kg/day (Dexter et al., 2014). Thus, the two pilot studies have been used to calculate the required sample size to lead our project based upon a large randomised clinical trial to demonstrate this new therapeutic concept .

Moreover, by taking advantage of collaborations and involvement in other European studies, we shall assess DFP's impact and the prognostic value of biomarkers obtained from large-scale, on-going studies. This will increase the scientific impact and dissemination of our study (i.e. publications) and limit the risk of failure and negative results.

Finally, the health economics and societal impacts will be monitored because it is increasingly acknowledged that conclusions based on conventional clinical trials may not be useful for making decisions on management in a "real-life" clinical setting. If DFP is associated with significant slowing of disease progression in FAIR-PARK-II, it would be the first non-dopaminergic drug to have a proven disease-modifying effect. As such, DFP would also have a huge socio-economic impact. In order to move towards an assessment of DFP's potential real-world benefits data, we shall concomitantly analyse the drug's impact on health economics aspects and the PD patients' and caregivers' quality of life via questionnaires and the continuous quantitative monitoring of PD-associated handicaps in the home environment (i.e., bradykinesia, gait and balance, tremor, sleep) using the SENSE PARK device (developed in the frame of FP7).

At present, no neuroprotective drugs are available. If our academic proof-of-concept study demonstrates a disease modifying effect, this new therapeutic strategy could be offered to the population of patients with PD as a whole. This would represent a considerable market and would have a huge socio-economic impact.

The trial's overall objective can be summarized as follows: to demonstrate for the first time in a large phase II, multicentre, parallel-group, placebo-controlled, randomized clinical trial (RCT) **that conservative iron chelation, with the prototype drug, DFP, will slow down the progression of handicap in PD patients** and will not be associated with clinically significant adverse haematological events or other systemic effects. A putative slow-down in the progression of handicap will be monitored in a multicentre, placebo-controlled RCT with 372 patients with *de novo* PD (the best population for assess a disease-modifying effect without the bias caused by the effects of dopaminergic treatment). They will be assigned to receive either DFP (15 mg/kg *bis in die* (BID)) or placebo. Based on the two pilot studies, the optimal dose of 30 mg/kg/day will be used. A 9-month treatment period (period 1) will be followed by a 1-month post-treatment monitoring period (period 2), in order to assess the disease-modifying effect in the absence of a symptomatic effect (i.e. an effect of ICOMT activity on dopamine metabolism) of DFP (versus placebo). Considering the short half-life of DFP, one month will be enough to assess the level of handicap of patients in the absence of ICOMT due to DFP treatment.

The project will run for 72 months and we shall address:

(i) the risk/benefit balance of this new disease-modifying treatment strategy for PD.

(ii) surrogate and theranostic biomarkers of efficacy and safety.

(iii) health economics and societal impacts.

For the risk/benefit balance, the primary efficacy criterion will be the total score on the Movement Disorders Society- Unified Parkinson's Disease Rating Scale (MDS-UPDRS), which encompasses motor handicaps and non-motor handicaps (i.e. cognition and behaviour) and activities of daily living (see 1.3). Experience from the large ADAGIO and ELLDOPA studies indicates that we shall be able to maintain *de novo* PD patients in the absence of symptomatic treatment for 36 weeks with a low drop-out rate - a sufficiently long time period over which to observe a difference vs. the placebo group). The total MDS-UPDRS score is the usual primary efficacy criterion in PD trials. It includes all the motor and non-motor aspects of the disease

and the activity of daily living (part II), which is less sensitive to the placebo effect. The Movement Disorders Society recommends this criterion.

The secondary criteria will include the separate analysis of the MDS-UPDRS subscale scores, the Stand Walk Sit test, quality of life, personal autonomy, safety criteria, and biomarkers of efficacy and safety.

The surrogate and theranostic biomarkers will include:

- Magnetic resonance imaging (MRI), i.e. indirect measurements of iron with an R2* sequence
- Transcranial ultrasound (i.e. indirect measurements of iron via the hyperechogenicity of substantia nigra).
- Dopamine transporter SPECT imaging (^{123}I-FP-CIT, DATscan®)
- Biochemical biomarkers (in blood and cerebrospinal fluid (CSF)).
- Pharmacogenetic markers (i.e. ceruloplasmin genotypes for the disease-modifying effect of iron chelation and COMT genotypes for the symptomatic action of DFP).

Expected results

We expect to observe a significantly lower mean total MDS-UPDRS score at weeks 36 and 40 in the DFP group (relative to the placebo group). This will enable us to demonstrate the efficiency of iron chelation as the first non-dopaminergic disease-modifying strategy in PD. This will be the first in class treatment to slow down the disease progression. The results will be obtained during the five year of the project, and the main paper will be published before the end of the sixth year

We do not expect to observe anaemia (or other iron metabolism disorders) with 30 mg/kg/day; anaemia was not a problem in the two independent pilot studies of smaller numbers of patients. We expect to see a good safety profile, with a low drop-out rate due to adverse events in all European centres and a low rate of neutropenia/agranulocytosis (with no harmful consequences), thanks to close monitoring with weekly blood counts. DFP has been on the EU market since 1999, with a favourable risk/benefit balance at 100 mg/kg/day (< 3% of agranulocytosis). This will enable us to demonstrate the safety of the new therapeutic concept of conservative iron chelation in PD. The results will be obtained at the fifth year of the project and the final report on outcomes before the end of the sixth year.

We aim to demonstrate a positive impact on the quality of life by the PDQ39 questionnaire.

To date, there is no theranostic biomarker. We intend to demonstrate the theranostic value of the clinical, radiological, biological and genetic biomarkers for the response to DFP - notably the ferric iron overload measured by ultrasound and MRI, the level of degeneration measured by DaT imaging, the COMT genotype for symptomatic improvements and the ceruloplasmin genotype for the disease modifier effect and the blood and CSF levels of ferritin measured at week 36. The results will be obtained at the end of fifth year of the project and separated publications will be made at the end of the sixth year.

To date, there is no surrogate biomarker. We expect to demonstrate the surrogate value of clinical, radiological, biological and/or genetic biomarkers for monitoring PD progression by analysing the large population of *de novo* patients in the placebo group for 40 weeks and comparing them with the advanced PD population in the PREDISTIM PHRC-2012 multicentre study (led by the applicant), the BADGE-PD-PHRC 2010 and DIGPD-PHRC 2008 (two PD cohorts led by JC. Corvol), the population of patients with Alzheimer's disease (AD) in the FP7 NILVAD study, led by Professor Lawlor) and the population of patients with amyotrophic lateral sclerosis (ALS) in the JPND SOPHIA study (led by Professor Van den Berg). Results will be obtained at end of the fifth year of the project and publications will be made at the end of the sixth year.

We intend to demonstrate that DFP has favourable impact on health economics aspects, as measured by a specific questionnaire.

We also expect to see a concomitant, positive impact on the activities of daily living by performing the continuous assessment of the PD-relevant domains with an unobtrusive, quantitative, continuous measurement tool (SENSE-PARK, FP7).

We expect to set up an efficient European clinical trial network in PD, in order to promote the forthcoming European studies. This will be reinforced through many teleconferences and meetings with the study group, the efficient completion of the study within 6 years, the many papers generated by the study group and the activities led by different work package leaders and investigators. The collaboration with the three FP7 studies (NILVAD, SOPHIA and SENSE-PARK) will also reinforce the European PD network.

We expect to widely disseminate the demonstration of this new therapeutic concept, in order to promote and support the clinical development of DFP and future other iron chelators (i.e. hydroxypyridinones) for PD and other neurodegenerative diseases (i.e. Alzheimer, ALS, multisystem atrophy, etc.).

II. OBJECTIVES

3.1 Main objective

The main objective of the FAIR-PARK II trial is to demonstrate an effect of DFP on the course of PD (including both disease-modifying and symptomatic effects).

The primary efficacy criterion: the change in the total MDS-UPDRS score between baseline and 36 weeks (i.e. the end of the placebo-controlled phase for analysis of both disease-modifying and symptomatic effects). Experience from the large ADAGIO and ELLDOPA studies indicates that we shall be able to maintain de novo PD patients in the absence of symptomatic treatment for 36 weeks with a low drop-out rate - a sufficiently long time period over which to observe a difference vs. the placebo group). The total MDS-UPDRS score is the usual primary efficacy criterion in PD trials. It includes all the motor and non-motor aspects of the disease and the activity of daily living (part II), which is less sensitive to the placebo effect.

3.2 Secondary objectives

The secondary criteria will include:

(i) The disease-modifying effect: will be measured as the changes in the overall MDS-UPDRS score between baseline and week 40 (i.e. the end of the one-month post-treatment monitoring period), to analyse the disease-modifying effect without bias from the symptomatic effect of ongoing DFP treatment) on the study population as a whole (n= 372).

(ii) The global effect on motor and non-motor symptoms: will be analysed as the change in the different subscales of the MDS-UPDRS (part I: cognition and behaviour; part II: activities of daily living; part III: motor handicap; part IV: fluctuations) and MDS-UPDRS part II+III, the Stand Walk Sit test, overall cognitive status (score in the Montreal Cognitive Assessment) between baseline and week 36; and between baseline and week 40 for the study population as a whole (n= 372).

(iii) Effects on quality of life and autonomy will be analyzed as the change in the Parkinson's Disease Quality of Life (PDQ-39, via a 39-item self-questionnaire) and the Clinical Global Impression scored by the examiner and the patient between baseline and week 36, and between baseline and week 40 for the study population as a whole (n= 372).

(iv) A health economics assessment will be performed via a specific questionnaire and EQ-5D questionnaire (It provides a simple descriptive profile and a single index value for health status) between baseline and week 36 on the study population as a whole (n= 372).

Descriptive analysis

(v) A combined criterion of disease progression measured by the decline of the total score of the MDS-UPDRS between baseline and 36 weeks and the occurrence of a drop out related to disease worsening (CAFD).

This endpoint is analogous to the CAFS proposed by Berry JD and al. (Berry et al., 2013) and details about its computation can be found in this paper.

Briefly, the CAFD ranks subject outcomes on the basis of time to drop out (related to disease) or change in MDS-UPDRS scores from baseline to 36 weeks. Patients who drop out are ranked on the basis of time to drop out, with earlier time ranked the worst. Patients who are always followed are ranked higher than were those who came out the study, based on the change from baseline in MDS-UPDRS total score, with largest negative changes ranked worst.

Drop out related to disease worsening will be identified as following: when the patient report a worsening of the specific signs of PD: i.e. akinesia, rigidity, tremor, gait or a global disease worsening as a reason for drop out. The reason of drop out and the AE are coded according to the MedDRA dictionary. The adverse event not specifically related with disease progression will not be taken into account (e.g. isolated pain, isolated fatigue, headache, nausea, dizziness etc..(vi) Safety criteria will include

- A weekly complete blood count (with differential leucocytes count and absolute neutrophils count) will be performed weekly (± 3 days) from the start of treatment onwards for 24 weeks and then monthly until week 36. For the patients' comfort, the test can be performed in a medical laboratory close to their home. The results will be immediately faxed to the study centre. A standard operating procedure (SOP) in each centre will ensure prompt review of the results. An additional WBC count will be required in the event of fever. If the ANC falls below a value of 1.5 x 10^9/L (neutropenia) and/or 0.5 x 10^9/L (agranulocytosis), the investigator will immediately contact the patient and take appropriate measures. Therapeutic education and SOP in case of fever, neutropenia or agranulocytosis will be also provided to all the patients
- An iron status check: haemoglobin, serum iron, ferritinemia, transferrin, total binding capacity, transferrin saturation coefficient, 24-hour urine iron.
- Clinical chemistry tests: fasting glucose, urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT). Contraceptive counselling will also be provided for all sexually active males and females).
- General health status and a full physical examination, including vital signs, bodyweight, electrocardiogram and blood pressure.
- Adverse events, concomitant medication(s) and observance: participants will be questioned about the occurrence of AEs, the use of any medications and the compliance with the study therapy, at each scheduled or unscheduled visit.
- β HCG (for women of childbearing potential) will be performed every month and the result will be immediately faxed by the patient's local medical lab

Exploratory endpoints:

A biomarker analysis to assess the biomarkers' potential surrogate value

For reasons of cost and of harmonisation of the sequences and the procedures, the following exams will be performed only in "expert" centers". Hence, the biomarkers are not optional for patients in the selected centers (all patients in an expert center will have all the examinations). These biomarkers will be analysed on a subpopulation of patients.

- MRI: the relaxation time of the substantia nigra, the caudate nucleus, the putamen pallidum and the dentate nucleus will be assessed with an R2* MRI sequence between baseline and week 36 on a subgroup of the population (n=150). This will enable us to indirectly measure DFP's action on the ferric iron content of these structures (i.e. measurements of ferritin, hemosiderin and neuromelanin). This will evidence the drug's action in the brain in general and in the target structures in particular, whereas healthy structures should not be modified. Deferiprone chelates free, ferrous, labile iron, which is not directly measurable in vivo. Accordingly, ferric iron levels subsequently decrease; this modification becomes visible after 3 to 6 months.
- Dopamine transporter (DaT) scan: we shall perform 123I-FP-CIT study (123I- Ioflupane labeled N-(3-fluoropropyl)-2beta-carbomethoxy-3beta-(4-iodophenyl) nortropane (FP- CIT) between baseline and week 40 on the same subgroup of the MRI population (n=150) and compare it with other biomarkers. The DaT expression will provide a direct measurement of the status of the presynaptic dopaminergic nigrostriatal neurons (i.e. a smaller reduction in the DFP group than in the control group). This would demonstrate neuroprotection.
- Transcranial ultrasound: the substantia nigra's echogenicity is known to be correlated with tissue iron content. Quantitative measurement of the area of echogenicity will be performed between baseline

and week 36 on a subgroup of patients (50<n<100, depending on technical aspects). This will provide an indirect measurement of the iron content and should evidence the drug's action on the target area for neuroprotection.

- Data from the continuous assessment of PD-relevant domains with an unobtrusive, continuous; quantitative measurement tool (SENSE-PARK, FP7) will collect data during: 2 weeks after randomization visit, and 2 weeks before week 36 and 2 weeks before week 40 on a subgroup of patients (n=60).

- A specific biochemistry screen, with a view to understanding the mechanisms that might (i) underlie an improvement in brain function and clinical function and (ii) identity surrogate biomarkers. The biochemical screen (performed at the randomization visit and at week 36) consists of a panel of blood tests (150<n<338 according to the level of difficulty of the preparation and collection: 150 for difficult preparations and 338 for DNA collection).

- Surrogate marker: Iron metabolism: ferritin (a low level of ferritin might be associated with a higher degree of benefit for DFP treatment (Dexter et al., article submitted).

- Surrogate marker: Ceruloplasmin levels, ceruloplasmin ferroxidase activity, and the ceruloplasmin genotype (the D544E polymorphism, AT) will be assessed, in order to study to the drug's putative disease-modifying effect as a function of the genotype. The AT genotype might be associated with a greater effect of DFP on clinical symptoms and a greater reduction in the R2* value (relative to the AA group) (Grolez et al., submitted).

- Surrogate marker: the COMT Val158Met polymorphism will be assessed, in order to study the drug's symptomatic effect as a function of the genotype (i.e. DFP's ICOMT effect).

- Heavy metal assays: blood iron zinc, copper, magnesium, chrome, manganese, nickel, lead and cadmium levels, 24-hour urine copper and zinc excretion.

- Oxidative stress (total antioxidant status, lipid peroxidation (malonaldehydes (MDA)), protein carbonyls, 8-OHdG glutathione, super oxide dismutase (SOD)). Protein carbonyls will be assayed after centrifugal filtration-concentration (with a kit from Immunodiagnostik AG, Bensheim, Germany). Both MDA concentrations and glutathione status (i.e. glutathione disulphide and reduced glutathione) will be determined in tissue homogenates by using HPLC with fluorescence detection. Concentrations of the DNA adduct 8-OHdG will be studied in tissue homogenates using commercially available enzyme immunoassays (Highly Sensitive 8-OHdG Check, from Gentaur France SARL, Paris, France). Enzymatic activities of SOD and glutathione peroxidase in whole blood and the antioxidant capacity of plasma (using Trolox as a standard (Sigma)) will be performed as published elsewhere (23).

- Vitamins B1, B6, B12, E, A, and C, folates.

- Inflammatory factors: tumour necrosis factor alpha and interleukin-6

III. STUDY DESIGN

4.1 Study design

- A multicentre, parallel-group, randomized, placebo-controlled trial of DFP 15 mg/kg BID. A 9-month treatment period (period 1) will be followed by a 1-month post-treatment monitoring period (period 2), in order to assess the disease-modifying effect in the absence of a symptomatic effect (i.e. an effect of inhibition of catechol-O-methyl (COMT) activity (ICOMT) on dopamine metabolism) of DFP (versus placebo). Considering the short half-life of DFP, one month will be enough to assess the level of handicap of patients in the absence of ICOMT due to DFP treatment.

4.2 Subjects/population(s)

4.2.1 Inclusion criteria:

1. Adult Patients
2. Parkinson's disease diagnosed according The Movement Disorder Society Clinical Criteria for Parkinson's Disease (PD)
3. Treatment-naïve, i.e. the best population for assessing a disease-modifying effect without the interaction of dopaminergic treatment (no dopaminergic agonists, L-dopa, anticholinergics, monoamine oxidase B inhibitors (e.g. rasagiline) or deep brain stimulation).
4. Patients covered by a Health Insurance System in countries where required by law
5. Written informed consent dated and signed prior to the beginning of any procedures related to the clinical trial

4.2.2 Exclusion criteria

1. Disease duration greater than 18 months.
2. Patients with high frequency of comorbidity or vital risks that may reasonably impair life expectancy
3. Subject with handicap required dopaminergic treatment at the inclusion and therefore likely not to bear 9 months without symptomatic treatment
4. Hoehn and Yahr stage 3 or more.
5. Significant cognitive impairment (a Mini Mental State Examination score <24 or an equivalent impairment on a similar scale) or dementia diagnosed in accordance with the Movement Disorders Society criteria (Emre et al., 2007).
6. Atypical or secondary parkinsonism (supranuclear palsy, multisystem atrophy, etc.) or significant cortical or subcortical atrophy (i.e. atypical for PD).
7. Progressing axis I psychiatric disorders (psychosis, hallucinations, substance addiction, bipolar disorder, or severe depression), in accordance with the Diagnostic and Statistical Manual of Mental Disorders.
8. Subjects undergoing brain stimulation.
9. Due to the high risk of agranulocytosis caused by the IMP and the unknown mechanism by which this agranulocytosis is induced, it is not allowed to combine Deferiprone with other medicinal products causing agranulocytosis (as described in the IB). Such medicinal products are the already mentioned clozapine and also some NSAIDs (e.g. Phenylbutazone or Metamizole), antithyroid agents, sulfonamide antibiotics or metothrexate.
10. A history of relapsing neutropenia
11. Hypersensitivity to deferiprone.
12. Patients with agranulocytosis or with a history of agranulocytosis.

13. Patients taking a treatment at risk of agranulocytosis (clozapine, Closaril®/Leponex®).
14. Patients with anaemia (regardless of the latter's aetiology) or a history of another haematological disease. Haemochromatosis is not an exclusion criterion.
15. Pregnant or breastfeeding women or women of childbearing potential not taking highly effective contraception.
16. Kidney or liver failure.
17. Other serious diseases.
18. Inability to provide informed consent.
19. Participation in another clinical trial with investigational medicinal product within 3 months prior to inclusion in the study
20. Patient who has suffered mild or moderate depressive episode and isn't in remission and on a stable medication for at least 8 weeks
21. Patient > 130kg

- ***Exclusion criteria for the biomarker study and the ancillary study***

  (i) MRI:

  • Subjects for whom MRI is contraindicated (metal objects in the body, severe claustrophobia, pacemaker, incompatible surgical material).

  • Very severe rest tremor, which could induce MRI artefacts.

  (ii) Lumbar puncture:

  • Blood coagulation disorders, antiplatelet drugs or anticoagulants.

  • Intracranial hypertension.

  (iii) ***Contraindications to nitrous oxide***:

  • Ventilation with FiO2 >50%, emphysema or pneumothorax

  • Altered states of consciousness, non-cooperative patient (need to stop the nitrous oxide)

IV. PRACTICAL CONDUCT OF THE STUDY LOGISTICS

5.1 Recruitment procedures

The recruitment strategy will be based on the participation of 24 expert centres involved in the European MDS network. Experience indicates that we shall be able to identify 7 de novo PD patients per centre per year (i.e. total of 14 patients per centre for the two-year study).

We shall also secure fast, appropriate recruitment by using the Fox Trial Finder (https://foxtrialfinder.michaeljfox.org). The Fox Trial Finder will not only list our on-going PD clinical trial on its website but will also match registrants to our trial (i.e. best-suited to their specific traits). The Fox Trial Finder also has a secure, anonymous messaging system, making it much easier to find PD patients and involve them in our RCT. A specific website of the clinical trial will be set up to inform the patients and the caregivers. The website will be connected with the website of the European Parkinson's disease Association (EPDA). Indeed, EPDA is actively involved in the dissemination of the project to the PD community. The Cure Parkinson Trust has also accepted to relay the informations. This initiative will be also tested at the European level for the countries, which are interested and have several centres**.**

5.2 Patient information and the provision of written, informed consent

The subjects will receive comprehensive verbal and written information on the trial: the nature of the trial; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without affecting the quality of their future care and with no obligation to give the reason for withdrawal. The participant will be allowed as much time as required to consider the information and will have the opportunity to question the investigator or another independent person before deciding whether or not to participate in the trial. Each participant must personally sign and date the latest approved version of the informed consent form before any trial-specific procedures are performed. A copy of the completed ICF must be provided to the subject. Before its use, the ICF must meet local regulations and be approved by the EC.

Concerning the study data, by signing the ICF, the patient will accept that the study data may be examined by the Sponsor, the CAs, ECs, a mandated auditor and/or the study monitor in compliance with the statement of confidentiality.

5.3 Visit description

All the biological and imaging examinations are blindly performed and secondary blindly and centrally analysed after the completion of the study.

• Optional studies: (optional for the patients because the examination is more invasive)

1. ***Additional blood analysis (extra volume of 40 ml)***

a. Mitochondrial function, with functional assays on lymphocytes: mitochondrial membrane potential and reactive oxygen species production (flow cytometry).

b. Neural, endothelial and platelet microparticles.

- 2. ***CSF analysis (lumbar puncture)***: dopamine, metabolites, ferritin, and oxidative stress markers

Only some centers will participate at these following ancillary studies:

1. ***MRI***: MRI sequence between baseline and week 36 on a subgroup of the population (n=150).
2. ***Dopamine transporter (DaT) scan*** between baseline and week 40 on the same subgroup of the MRI population (**n=150**) and compare it with other biomarkers.
3. ***Transcranial ultrasound***: the substantia nigra's echogenicity is known to be correlated with tissue iron content. Quantitative measurement of the area of echogenicity will be performed between baseline and week 36 on a subgroup of patients (**50<n<100, depending on the skills ability of the expert centers**).
4. ***Data from the continuous assessment of PD-relevant domains with an unobtrusive, continuous***; quantitative measurement tool (SENSE-PARK, FP7) will collect data during 2 weeks after randomization visit, 2 weeks before week 36 and 2 weeks before week 40 on a subgroup of patients (**n=60**).

In this sub study, participants have to use a wearable system validated in a previous EU project (SENSE-PARK) during 3 two-week blocks. Sensor system and software will be provided for all participants, who can keep their system until study end.

On site, staff members should calculate for every study participant included in the substudy:

- at inclusion:
  - training of study participants for how to use the system: 90 minutes
- during the study
  - serving as contact person for questions which may arise during usage of the system, and providing feedback to sponsor in case of difficulties that cannot be solved locally
- at the end of study
  - shipment of devices back

5. **A specific biochemistry screen**, with a view to understanding the mechanisms that might (i) underlie an improvement in brain function and clinical function and (ii) identity surrogate biomarkers. The biochemical screen performed at the randomization visit and at week 36 consists of a panel of blood tests (**150<n<338 according to the level of difficulty: 150 for difficult preparations and 338 for genetic analysis**).

Screening visit:

The screening will include the following:

- Medical History and Clinical Examination
- Mini Mental State Examination
- Demography and disease history
- Concomitant Medications - Medications taken during the past 3 months
- Weight, height, Electrocardiogram
- Columbia Suicide Severity Rating Scale
- Checklist of inclusion and exclusion criteria
- Laboratory test:
    - Blood count, haemoglobin, haematocrit,
    - Hepatic (ASAT, ALAT, alkaline phosphatase, bilirubin, gamma GT),
    - Hepatic tests (B and C)
    - Kidney tests (ionogramm and urea creatinine)
    - Iron status (ferritin, serum iron, transferrin, transferrin saturation coefficien, Serum Total Iron-Binding Capacity)
    - Other metals (copper, zinc)
    - β HCG (for non-menauposal women)
    - Hormonal status (FSH-LH) for women
    - Fasting glucose
- Patients have to bring back the 24h urine sample for the randomization visit

Randomization visit:

Two weeks (+/- 1 week) between screening and randomization.

The clinical assessment has to be made always at the same time of the day (e.g. 10 am) in the exact same conditions of assessment and always by the same investigator with the control of the previous MDS-UPDRS scores.

The randomization visit will include the following:

- Clinical Examination
- Weight, Electrocardiogram,
- Eligibility Screening, Checklist of inclusion and exclusion criteria
- Randomization by IWRS system
- Minimal Specific biochemistry with 24 hour urine iron(samples for central analysis)
- Total MDS- UPDRS
- MOCA
- Stand Walk Sit test
- PDQ-39: quality of life
- Health economics questionnaire
- EQ-5D
- Adverse event and serious adverse event
- Optional studies and ancillary studies
    - Specific biochemistry *(150<n<338) (samples for central analysis)
    - Additional blood analyses (lymphocytes and microparticles) (samples for central analysis)
    - Lumbar puncture (samples for central analysis) and coagulation assessment
    - Transcranial ultrasound
    - SENSEPARK
    - DatScan
    - MRI
- β HCG (for women of childbearing potential)

A weekly CBC (with the WBC) for the first 24 weeks and then monthly until week 36. The results will be immediately faxed by the patient's local medical lab or the study centre's central lab.
β HCG (for women of childbearing potential) will be performed every month and the result will be immediately faxed by the patient's local medical lab

Visit 1: Week 12:

12 weeks (+/- one week) between randomization visit and V1

The clinical assessment has to be made always at the same time of the day (e.g. 10 am) in the exact same conditions of assessment and always by the same investigator with the control of the previous MDS-UPDRS scores.

The visit 1 will include the following:

- Clinical Examination
- Weight, Electrocardiogram,
- Concomitant treatment
- Clinical and Patient Global Impression
- Total MDS- UPDRS
- Columbia Suicide Severity Rating Scale
- Laboratory test
    - Blood count, haemoglobin, haematocrit,
    - Hepatic (ASAT, ALAT, alkaline phosphatase, bilirubin, gamma GT),
    - Kidney tests (ionogramm and urea, creatinine)
    - β HCG (for non-menauposal women)
    - fasting glucose
- Adverse event and serious adverse event
- Treatment compliance
- CBC (with the WBC)

Visit 2: Week 24:

12 weeks (+/- one week) between V1 and V2.

The clinical assessment has to be made always at the same time of the day (e.g. 10 am) in the exact same conditions of assessment and always by the same investigator with the control of the previous MDS-UPDRS scores.

The visit 2 will include the following:

- Clinical Examination
- Weight, Electrocardiogram
- Concomitant treatment
- Total MDS- UPDRS
- Columbia Suicide Severity Rating Scale
- Laboratory test
    - Blood count, haemoglobin, haematocrit,
    - Hepatic (ASAT, ALAT, alkaline phosphatase, bilirubin, gamma GT),
    - Kidney tests (ionogramm and urea creatinine)
    - β HCG (for non-menauposal women)
    - fasting glucose
- Adverse event and serious adverse event

- Treatment compliance
- CBC (with the WBC)

Patients have to bring back the 24 hours urine sample for the vist of week 36.

Visit 3: Week 36:

12 weeks (+/- one week) between V2 and V3.

The clinical assessment has to be made always at the same time of the day (e.g. 10 am) in the exact same conditions of assessment and always by the same investigator with the control of the previous MDS-UPDRS scores.

DFP or placebo will be taken from the day following randomization until the morning dose on the day of the visit at week 36.
The visit 3 will include the following:

- Clinical Examination
- Weight, Electrocardiogram
- Concomitant treatment
- Minimal Specific biochemistry (samples for central analysis)
- Laboratory test
    - Iron status (ferritin, serum iron, transferrin, transferrin saturation coefficient, 24-hour urine iron, Serum Total Iron-Binding Capacity)
    - Other metals (copper, zinc)
    - β HCG (for women of childbearing potential)
- Treatment compliance
- Total MDS- UPDRS
- Columbia Suicide Severity Rating Scale
- MOCA
- Stand Walk Sit test
- PDQ-39: quality of life
- Clinical and Patient Global Impression
- Health economics questionnaire
- EQ-5D
- Adverse event and serious adverse event
- Optional studies and ancillary studies
    - Specific biochemistry *(150<n<338) (samples for central analysis)
    - Additional blood analyses (lymphocytes and microparticles) (samples for central analysis)
    - Lumbar puncture (samples for central analysis) and coagulation assessment
    - Transcranial ultrasound
    - SENSEPARK
    - MRI

Visit 4: Week 40:

4 weeks (+/- one week) between V3 and V4

The clinical assessment has to be made always at the same time of the day (e.g. 10 am) in the exact same conditions of assessment and always by the same investigator with the control of the previous MDS-UPDRS scores.

The visit 4 will include the following:

- Clinical Examination
- Weight, Electrocardiogram
- Total MDS- UPDRS
- MOCA
- Stand Walk Sit test
- PDQ-39: quality of life
- Clinical and Patient Global Impression
- event and serious adverse event
- Ancillary studies
    - SENSEPARK
    - DatScan
- β HCG (for women of childbearing potential)

A phone call for safety will be performed every month by the medical team

Supplementary visit for safety concern but the patient is not withdrawn from the study:

The visit will include the following:

- Clinical Examination
- Weight, Electrocardiogram
- Concomitant treatment
- Laboratory test
    - Blood count, haemoglobin, haematocrit,
    - Hepatic (ASAT, ALAT, alkalin phosphatase, bilirubin, gamma GT),
    - Kidney tests (ionogramm and urea creatinine)
    - β HCG (for non-menauposal women)
    - Iron status (ferritin, serum iron, transferrin, transferrin saturation coefficient, Serum Total Iron-Binding Capacity)
    - Other metals (copper, zinc)
    - Fasting glucose
- Treatment compliance
- Adverse event and serious adverse event
- Treatment compliance
- Columbia Suicide Severity Rating Scale
- MDS-UPDRS

If the patient stops the study: the visit 3 (week 36) has to be done within 6 days after the last dose of IMP.

5.4 Flow Chart

MAIN STUDY	Sc Screening	V0 Randomization	V1 W12	V2 W24	V3 W36	V4 W40
Provision of study information and written, informed consent	+					
Inclusion and exclusion criteria	+	+				
Mini Mental State Examination	+					

Demography, disease history	+					
Height	+					
Weight, ECG, blood pressure	+	+	+	+	+	+
Clinical examination	+	+	+	+	+	+
Complete blood count (with differential leucocytes count and absolute neutrophils count) haemoglobin, haematocrit	+	Weekly for 6 months, then monthly				
Hepatic (ASAT, ALAT, alkaline phosphatase, bilirubin, gamma GT)	+		+	+		
Fasting glucose	+		+	+		
Kidney tests (ionogramm and urea creatinine)	+		+	+		
Iron status (ferritin, serum iron, transferrin, transferrin saturation coefficient, Serum Total Iron-Binding Capacity) (analysis on site at the screening and centrally for V3)	+				+	
Other metals (copper, zinc) (analysis on site at the screening and centrally for V3)	+				+	
Hepatitis B and C	+					
Hormonal status (FSH-LH) for women	+					
β HCG (for women of childbearing potential)	+	Every month until W40				
Minimal Specific biochemistry (samples of the basic set for central analysis and mandatory for all participating centers		+			+	
Total MDS-UPDRS (parts I, II, III and IV)		+	+	+	+	+
Columbia Suicide Severity Rating Scale	+		+	+	+	
MOCA		+			+	+
Stand Walk Sit test		+			+	+
Quality of life (PDQ-39)		+			+	+
Clinical and Patient Global Impression			+		+	+
Health economics questionnaire (for the patient and the caregiver if applicable)		+			+	+
EQ–5D (for the patient and the caregiver if applicable)		+			+	+

Adverse events questionnaire		+	+	+	+	+
Adverse event and serious adverse event	+	+	+	+	+	+
Concomitant treatment	+	+	+	+	+	+
Treatment compliance			+	+	+	
Phone call by medical team		Monthly				
(1) Optional study: additional blood analyses (lymphocytes and microparticles) (samples for central analysis)		+			+	
(1) Optional study: lumbar puncture (samples for central analysis) and coagulation assessment		+			+	
(1) Ancillary study: Transcranial ultrasound *(50<n<150)		+			+	
(1) Ancillary study: At-home device (SENSE PARK) *(n=60)		+			+	+
(1) Ancillary study: DaT Scan *(n=150)		+				+
(1) Ancillary study: MRI *(n=150)		+			+	
(1) Ancillary study: Specific biochemistry **(150<n<338) (samples from expert and recommended sets for central analysis)		+			+	
Prolactin dosage		+			+	

(1) The last 34 patients to be included will not perform either the optional or ancillary studies.
+ Assessment to be made always at the same time of the day in the exact same conditions and by the same investigator
* in subgroup of patients (from 650 to 150 patients)
**dependant on individual sites biochemistry samples as agreed by the Sonsor
1 Patients will be invited to participate in an ancillary study involving CSF analysis at the randomization visit and at week 36, in order to perform a full set of CSF biochemistry assays and with a view to determining the biological benefits of DFP treatment at the central nervous system level and to identifying biological markers.

5.5 Randomization and masking

Administration of DFP or placebo will be randomized and balanced by centre. The randomization and the treatment allocation are performed centrally by an Interactive Web Response System. The IWRS generates the patient randomization list according to which it allocates treatment arms to the patients.

Randomization was balanced by center. The 1:1 randomization sequence (based on a block size of four and the use of a computer random-number generator) was produced by the statistics department at Lille University Hospital (Lille, France). The randomization list must be sent to an independent service provider (Abplus, France), which assigns deferiprone or placebo to the patient. Assignment is masked from the patients, carers, study staff, investigators, and data analysts

A sealed copy of the randomization list will also be stored at the CHRUL's Fédération de la Recherche Clinique (FRC) department.

5.6 Duration

- Overall study duration: 54 months.
- Planned inclusion period: 47 months.
- Study duration for individual patients: 10.5 months (two weeks between screening and randomization, nine months of double-blind treatment and then a one-month wash-out period).

5.7 Image Processing

MRI Images will be acquired on the same MRI machine and with the same antenna for the duration of the study in each center.
Locally, the quality of image will be checked. The images will then be transferred to the CATI ("center of acquisition and automated image processing"). These images will be centralized and checked to ensure: 1) the quality of the images and the absence of artifacts; 2) the positioning of the head; 3) the consistency of image settings and parameters used. The centers will be contacted in case of poor-quality images, and a new MRI will be performed insofar as possible.
The images will be stored centrally in an anonymized DICOM formats.

In the same way, the CATI will be responsible for quality control of the DATSCAN data, transfer and storage.

5.8 Withdrawal of Participants from the trial

Each participant has the right to withdraw from the trial at any time. Furthermore, the investigator may discontinue a participant from the trial at any time if the said investigator considers it necessary for any reason, including:

- a significant protocol deviation.
- significant non-compliance with the treatment regimen (< 80%) or trial requirements.
- an AE that requires discontinuation of the IMP or results in inability to continue to comply with trial procedures.
- Conversely, if the AE were mild, the patient would be allowed to take transiently a reduced dose of deferiprone at 20 mg/kg/day. We recommend to keep trying to slowly re-increase the dose at 30 mg/kg/day at the next visit.
- withdrawal of consent.
- loss to follow-up.
- Elevation of ALT or AST ≥ 5 x ULN or ALT or AST ≥ 3 x ULN with simultaneous total bilirubin ≥ 2 x ULN.
- The need of antipsychotic during the study

If the participant is withdrawn because of an AE, the investigator will arrange for follow-up visits or telephone contact until the AE has resolved or stabilised. In all cases, the available data will be retained for the safety analysis.

The investigator can decide to stop the drug if necessary and the patient should bring back the reminding drugs

In all trial withdrawals due to AEs, the DSMB will be notified and consulted on potential causal links.
→ Investigators will be asked to care for the patients until the end of the study. However, if dopamine therapy is required because of unexpected worsening of PD, the patient will be withdrawn from the study.

The drop-out rates in the two arms will be compared in terms of safety and the requirement for dopatherapy.
→ At the end of the study, standard care will be provided

The trial could be stop by decision of the relevant competent authority, the sponsor, the coordinator investigator and the DSMB.

5.9 Period of prohibition against participation to another interventional study / Exclusion period

Period of prohibition against participation to another interventional study: 10.5 months
Exclusion period: 48h after the end of the study.
In case of early termination until Week 36, an exclusion period of one month should be respected.

5.10 The risk/benefit ratio

The patients will receive specialized care and monthly monitoring. They will receive either the IMP or placebo. *De novo* PD patients do not always receive dopaminergic treatment in the first months of disease progression. Symptomatic dopaminergic treatment is generally prescribed if the patients' symptoms impact on the daily living. Thus, the patients randomized into our RCT will not have experienced any impact (or at most a slight impact) of their symptoms on daily living; this will enable us to delay the administration of other symptomatic treatments by 10 months.
The main risk of DFP is agranulocytosis, which will be rapidly detected by close monitoring and which will lead to immediate withdrawal from the study (to avoid a clinical impact). Iron depletion is a slow, predictable phenomenon that has never been observed in PD patients treated with a dose of 30 mg/kg/day; it should not pose a serious problem. Neutropenia and agranulocytosis can be corrected rapidly (within a few days) once drug treatment has been discontinued. Furthermore, we are used to monitoring this haematological hazard in our centre, since clozapine is widely used to treat dopaminergic psychosis. This standard monitoring also requires CBC results to be faxed weekly by the patient's local clinical lab and checked regularly by us. These controlled risks must be balanced against the prospect of identifying the first ever disease-modifying drug in this field.

5.11 Recommendations for contraception measures

- Definition of women of childbearing potential:
  A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral ~~o~~ophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the trial, the FSH and the LH level will be performed for all women.
  The woman will be not considered of childbearing potential if she has no menses for 12 months without an alternative medical cause and a high follicle stimulating hormone

- Recommendations for sexually active male participants whose partners are women of childbearing potential and for women of childbearing potential who participate at the study:

  If women of childbearing potential who participate at the study have a negative pregnancy test result at screening, she must agree to use a highly effective method (see below) during the study and for 30 days following the last dose of study medication.

We recommend male condom and one of these methods:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation :
    - oral
    - intravaginal
    - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation
    - oral
    - injectable
    - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- Abstain from heterosexual intercourse reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual life style of the subject

- Recommendation on the duration for use of highly effective contraception :

We recommend of highly effective contraception during the treatment and until 90 days after the last dose of treatment (for sexually active male participants whose partners are women of childbearing potential) and until 30 days after the last dose of treatment (for women of childbearing potential participants)

5.12 Concomitant medication prohibited

Since DFP binds to metallic cations, the potential exists for interactions between DFP and trivalent cation-dependent medicinal products (such as aluminium-based antacids)
Previous or current treatment with bromocriptine (inhibition of the metabolism of deferiprone; 3-O-glucoronide conjugate)
Previous or current treatment with any antiparkinsonian drug
Current treatment with coenzyme Q10 or idebenone. (Patients who are on these medications but stop taking them at least 2 weeks prior to baseline may be enrolled.)
Current use of a Deep Brain Stimulation (DBS) system
Investigational product or any drugs that are known to cause neutropenia or agranulocytosis
The safety of concurrent use of deferiprone and vitamin C has not been formally studied. Based on adverse interaction that can occur between deferoxamine and vitamin C, caution should be exercised when co-administering deferiprone and vitamin C

V. TREATMENT

6.1 Medication

Pharmacotherapeutic group: iron chelator.
The active substance is 3-hydroxy-1,2-dimethylpyridine-4-one (DFP, FERRIPROX®), a bidentate ligand that binds to iron in a 3:1 molar ratio. DFP decreases excessive iron and ferritin levels. Its low molecular weight and liposolubility enable it to cross the blood-brain barrier. Clinical haematology studies have demonstrated that DFP is effective in promoting iron excretion and that a dose of 25 mg/kg three times per day can prevent the progression of iron accumulation (as assessed by serum ferritin levels) in patients with transfusion-dependent thalassemia. However, chelation therapy may not necessarily protect against iron-induced organ damage. DFP (provided by ApoPharma) is unique among available iron chelators in that it readily penetrates the CNS and has been shown to function as an iron redeployment agent. The drug has been approved for many years in the indication of haemosiderosis in thalassemia major patients undergoing chronic blood transfusion. **We intend to reposition DFP, with a disease-modifying effect in PD**.

DFP is rapidly absorbed from the upper part of the gastrointestinal tract. The serum concentration of DFP reportedly peaks 45 to 60 minutes after a single dose in fasted patients and as much as two hours in non-fasted patients. Following a dose of 30 mg/kg, the peak serum concentrations is lower in non-fasted patients (85 µmol/l) than in fasted patients (126 µmol/l), although there was no decrease in the amount of DFP absorbed when it was given with food. We shall thus recommend taking the treatment in the fasting state, 30 minutes before each meal. DFP is predominantly metabolized to a glucuronide conjugate. This metabolite lacks iron-binding capability, due to inactivation of DFP's 3-hydroxy group. Serum concentrations of the glucuronide peak 2 to 3 hours after administration of DFP.
In humans, DFP is eliminated mainly via the kidneys; 75% to 90% of the ingested dose is reported as being recovered in the urine in the first 24 hours, as free DFP, the glucuronide metabolite and the iron-DFP complex. Estimations of faecal elimination vary from one report to another. The elimination half-life is 2 to 3 hours in most patients. DFP has not shown any direct mutagenic properties; however, it has displayed clastogenic characteristics in *in vitro* assays and in *in vivo* tests in animals. There are no data on the use of DFP in patients with kidney or liver failure. Since DFP is eliminated mainly via the kidneys, there may be an increased risk of complications in patients with impaired renal function. Likewise, since DFP is metabolized in the liver, caution must be exercised in patients with hepatic dysfunction. Renal and hepatic function should be monitored in this patient population during DFP therapy. If there is a persistent increase in serum ALT levels, interruption of DFP therapy should be considered.
Interactions between DFP and other medicinal products have not been reported. Since DFP binds to metallic cations, the potential exists for interactions between DFP and trivalent cation-dependent medicinal products (such as aluminium-based antacids). Consequently, the concomitant ingestion aluminium-based antacids and DFP is not recommended. There are no special precautions for storage, other than storage below 30°C.
Patients will receive *placebo or 30 mg/kg per day DFP* with pills of 600 mg divided into two doses (at 08.00 and 20.00).

Table of the doses according to the weight of the patient

Weight (kg)	Theoretical dose	Real dose	Theoretical number of pills	Real number of pills	8am dose	8pm dose	Dose escalation every 3 days during 15 days
40	1200	1200	2	2	1	1	½ pill twice a day
45	1350	1500	2,3	2,5	1	1+1/2	½ pill twice a day
50	1500	1500	2,5	2,5	1	1+1/2	½ pill twice a day
55	1650	1800	2,8	3	1+1/2	1+1/2	½ pill twice a day
60	1800	1800	3	3	1+1/2	1+1/2	½ pill twice a day
65	1950	2100	3,3	3,5	1+1/2	2	½ pill twice a day
70	2100	2100	3,5	3,5	1+1/2	2	½ pill twice a day
75	2250	2400	3,8	4	2	2	½ pill twice a day
80	2400	2500	4	4	2	2	½ pill twice a day
85	2550	2700	4,3	4,5	2	2+1/2	½ pill twice a day
90	2700	2700	4,5	4,5	2	2+1/2	½ pill twice a day
95	2850	3000	4,8	5	2+1/2	2+1/2	½ pill twice a day
100	3000	3000	5	5	2+1/2	2+1/2	½ pill twice a day
105	3150	3300	5,3	5,5	2+1/2	3	1 pill twice a day
110	3300	3300	5,5	5,5	2+1/2	3	1 pill twice a day
115	3450	3600	5,8	6	3	3	1 pill twice a day
120	3600	3600	6	6	3	3	1 pill twice a day
125	3750	3900	6,3	6,5	3	3+1/2	1 pill twice a day
130	3900	3900	6,5	6,5	3	3+1/2	1 pill twice a day

An initial DFP dose escalation will be applied every third day during a period of 15 days. After 15 days the final dose of 30 mg/kg/day has to be reached. In case of adverse events, the dose would be reached within a maximum of 3 weeks.

We shall check on tolerability (assessed by interviews and examinations) and compliance (assessed by interviews and tablets counts) every 3 months. Interviews of patients and caregivers will be performed by the investigators.
In the event of poor tolerance, we shall delay the titration phase by 1 week. The dose can be temporarily reduced to 20 mg/kg per day, and we shall ask centres to achieve and maintain the highest possible tolerated dose (i.e. 30 mg/kg per day). However, in the pilot studies the general safety profile was good. No broken of the blind code is planned.
The DSMB will examine AE reports on a regular basis.

In other indications of DFP, monitoring of the plasma zinc concentration is recommended if a dose of 100 mg/kg/day is used, with zinc supplementation in the event of a deficiency (two Rubozinc® capsules a day or more, depending on the extent of the deficiency). No zinc depletion has been observed with a DFP dose of 30 mg/kg/day. The plasma zinc concentration will be checked at screening visit and at week 36.

6.2 Drug procurement, packaging and distribution

Deferiprone and deferiprone-matching placebo will be provided as white to off-white delayed-release,

capsule-shaped, scored tablets in bottles of 100 tablets each, high-density polyethylene (HDPE) bottles with child-resistant closure.

ApoPharma will be responsible to ensure that deferiprone and deferiprone-matching placebo tablets are manufactured in accordance with Good Manufacturing Practice (GMP) regulations and requirements and requirements. The bottles will be provided with labels whose content is in accordance with all applicable regulatory requirements.

Drug will be stored in a local depot in Europe and will be shipped from this depot to clinical sites with temperature monitoring device (TMD). Sites will receive an initial supply of both products to have it ready upon randomization of the first patients and will be replenished throughout the study as needed. The study medication at each site will be kept in a secure location under adequate storage conditions, as per label requirements, with access to authorized individuals only. The room must have a calibrated digital temperature-monitoring device, and the daily recording of the temperature of the storage facility must be recorded. The site must report temperature deviations immediately to the sponsor and ApoPharma, and quarantine the product until ApoPharma deems it acceptable for use.

It is the responsibility of the investigator to ensure that all study drug received at the study center is inventoried and accounted for throughout the study. Records of receipt, storage and administration of the study drug supplied must be maintained, and the drug accountability will be verified by the sponsor or sponsor's designee during on-site monitoring visits. At the conclusion of the study, a final inventory must be performed by the investigator or delegate. The sponsor will be responsible for determining the specific conditions for destruction of unused product.

6.3 Methods of monitoring treatment compliance

Treatment will be dispensed to patients by name and bottles will be returned during follow-up visits. Treatment dispensed will contain enough drugs for 14 weeks of treatment.

The treatment will be dispense at V0 (randomization visit), V1 (W12) and V2 (W24)

To facilitate compliance to treatment throughout the 36 weeks of the treatment the following approaches will be used:

- Subjects will receive a diary.
- Compliance to the drug schedule will be checked during each visit after 12 weeks of treatment.

All participants will be instructed to return any unused drugs to the investigator at each visit.

VI. STATISTICS

7.1 Sample size

The main objective of the FAIR-PARK II trial is to demonstrate an effect of DFP on the course of PD (including both disease-modifying and symptomatic effects). The primary endpoint is the change in the total MDS-UPDRS score between baseline and 36 weeks (i.e. before the one-month washout period). Assuming a conservative correlation coefficient of 0.5 between the total MDS-UPDRS scores at baseline and at 36 weeks, the standard deviation of the change in the total MDS-UPDRS score (a 260-point scale, with 84 items) is equal to the standard deviation of the total MDS-UPDRS score (at either baseline or at 36 weeks). On the basis of two earlier large, randomized controlled trials (ADAGIO, Olanow et al., 2009 and ELLDOPA, Fahn et al., 2004), we have assumed that the standard deviation of the total MDS-UPDRS score is 9.0. In the ADAGIO trial, the difference in the 36-week change in the total UPDRS score(a 176-point scale, with 55 items) between the rasagiline group and the placebo group was 3 points (Olanow et al., 2009). In our pilot study, the difference in the 36-week change in the motor UPDRS score (a 108 points subscales with 27 items) between the DFP and placebo groups was also 3 points (Devos et al., 2014). On the basis of these two studies, we expect to demonstrate a minimum DFP vs. placebo difference in the primary endpoint of 3 points (corresponding to an effect size of 0.33) on the total MDS-UPDRS score. To detect this difference in a two-sided t test *with an alpha risk of 5% and* a power of 80%, we calculate that a total of 286 subjects (i.e. 143 subjects in each arm) will be required. Taking account of an anticipated dropout rate of 15% (similar to that in the ADAGIO trial), a total of 338 subjects (i.e. 169 subjects in each arm) should be included. But 3 years after the beginning of the inclusion of patients in the study and despite to a strict adherence of the investigators to the protocol, a strong monitoring and data quality check, we observed a 23% drop out rate. To take into account this slightly higher drop out rate and maintain the statistical power of the study, we plan to include a total of 372 patients (186 per arm).

Although the primary statistical analysis of primary endpoint will be adjusted for baseline values, the sample size calculation does not take account of this adjustment, in order to maximize the power for the main secondary endpoint: the change in the total MDS-UPDRS score between baseline and 40 weeks (i.e. after the one-month washout period that assesses only the disease-modifying effect, in the absence of the symptomatic effect). With a total of 338 included subjects and a conservative correlation coefficient of 0.5, we should be able to detect a minimum effect size of 0.28 with a power of 80%. In the ADAGIO trial, the disease-modifying effect corresponded to a difference of 1.8 points between the rasagiline and placebo groups (corresponding to an effect size of 0.20). According to Cohen (Cohen, J. (1988), *Statistical Power Analysis for the Behavioral Sciences, 2nd Edition.* Hillsdale: Lawrence Erlbaum), this effect size is considered to be small.

We provided different power calculation scenarios by varying the effect size for planning purposes; these are not intended to replace the exact power calculation. Figure 1 shows power calculations that do not take account of the correlation coefficient between baseline and final measures, whereas Figure 2 shows power calculations that assume a correlation coefficient between baseline and final measures of 0.5.

All sample size/power calculations were performed with the PASS software (version 12, NCSS LLC, Kaysville, UT, USA).

***Figure 1. Power as a function of different effect sizes, using a two-sided t test with an** alpha **risk** of 5% **and** a dropout rate of 15%.*

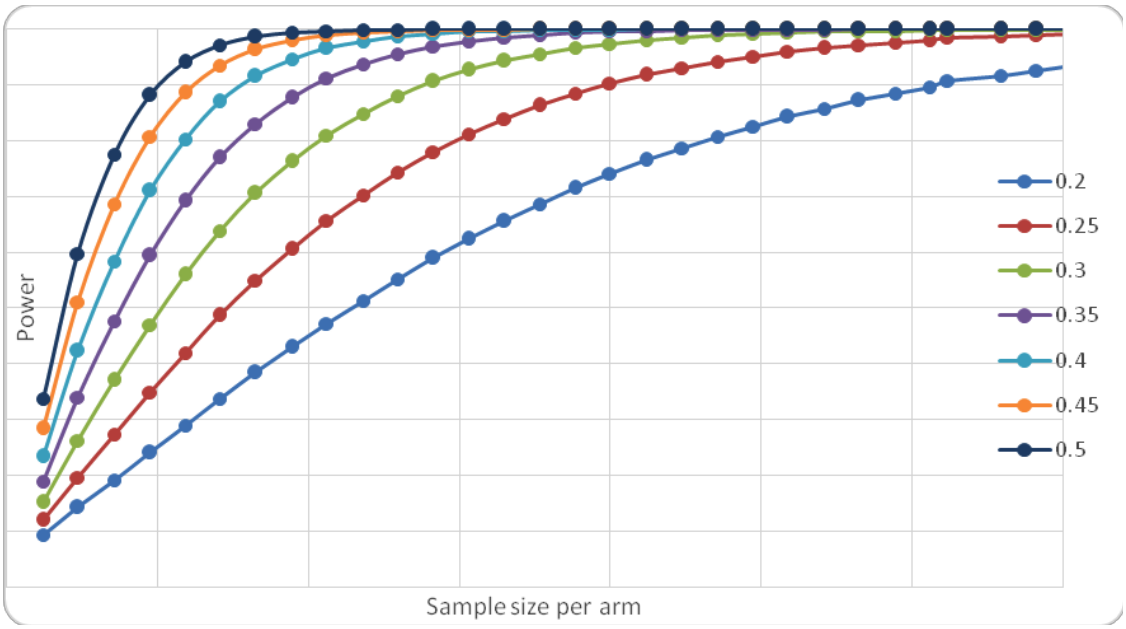
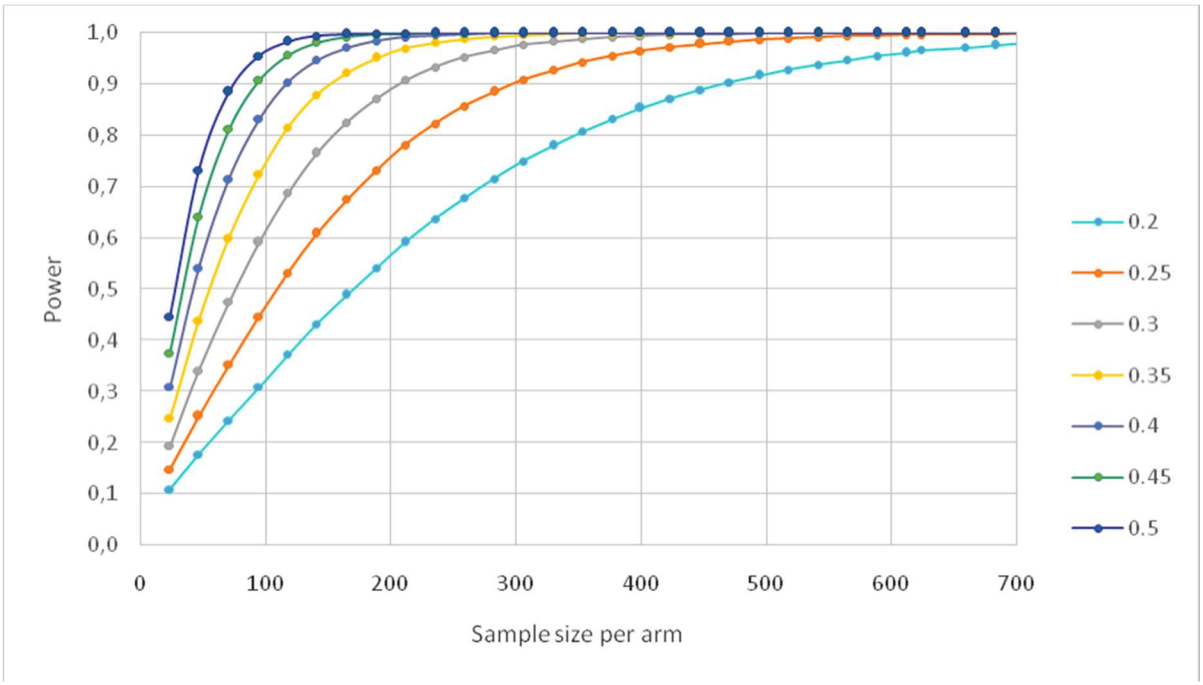


Figure 2. Power calculations as a function of different effect sizes, using a two-sided t test with an alpha risk** of 5%, a dropout rate of 15% and a **correlation coefficient between baseline and final measures of 0.5.



7.2 Statistical methods

The main statistical analyses (of primary and secondary clinical efficacy and safety outcomes) will be performed by the University of Lille's Biostatistics Department, under the supervision of Professor A. Duhamel. The data will be analyzed using SAS software (SAS Institute Inc., Cary, NC, USA) and all statistical tests will be two-tailed with an alpha risk of 0.05. The main analysis for primary and secondary efficacy clinical outcomes will be performed on an intention-to-treat basis. A secondary per-protocol analysis will also be performed. A detailed statistical analysis plan will be written and finalized prior to the first inclusion of patient for the primary and secondary clinical efficacy/safety outcomes. For other outcomes and ancillary studies, statistical analysis plans will be provided to the Executive Board and the SAB prior to any data analysis.

The primary endpoint (the change in the total MDS-UPDRS score between baseline and 36 weeks) in the DFP and placebo groups will be compared in an analysis of covariance (after adjustment for the baseline total MDS-UPDRS score). Missing data (due to withdrawal or others reasons) for primary endpoint were handled by multiple imputation using chained equations (m=10 imputations using primary endpoint and patient's characteristics at inclusion) (according to Rubin's guidelines). As exploratory analysis, a linear mixed model for repeated measures will be also used to estimate and compare the slopes (i.e. the change in MDS-UPDRS points per week) in the DFP and placebo groups from baseline though to 36 weeks. We shall use a mixed model with random coefficients (the intercept and time effect), as described by Molenberghs (Linear mixed model for longitudinal data, Springer 2000).

The secondary efficacy outcomes corresponding to "disease-modifying effect", "global effect on motor and non-motor symptoms", "quality of life" and "health economics assessment" will be analyzed using the same methods as for the primary endpoint. For the combined criterion of disease progression (CAFD), descriptive statistics (absolute and relative frequencies) will be used.

The safety analysis will be completed in all patients, who will be randomly assigned to a study group. The usual descriptive parameters (including the calculation of confidence intervals) will be provided for all safety criteria. Intergroup differences in quantitative parameters will be compared in a Student's *t* test for normally distributed variables and a Mann-Whitney U test if not (except if logarithmic transformation can be applied). The assumption of normality will be *checked* graphically and by using a Shapiro-Wild test. Intergroup differences in qualitative parameters will be compared using a Chi-square test or Fisher's exact test.

Missing data for the primary and all secondary outcomes (due to withdrawal or others reasons) were imputed under missing at random assumption (MAR), using regression switching approach (chained equation with m=50 imputations obtained using the MICE package from R statistical software version 3.03) (REF1). We will use predictive mean matching method for continuous variables (this procedure ensures that imputations are restricted to the observed values and is recommended by Van Buuren), logistic regression for binary variables, ordinal logistic regression for ordinal variables, or multinomial logistic model for qualitative variables. The imputed values will be checked by using the tools available in the MICE package. Imputation procedure were performed in each trial arm separately, by including the baseline variables as covariates. The separate estimates and standard errors from each of the imputed datasets will be combined using the Rubin's rules into an overall estimate with standard error, confidence intervals and p value (REF2 REF3). Complete-case analysis will be performed as a sensitivity analysis as recommend by Sterne et al. (REF4).

This trial will be registered with ClinicalTrials.gov and its reporting will follow the CONSORT guidelines

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REF1 : (Van Buuren S, Groothuis-Oudshoorn K. Mice: Multivariate Imputation by Chained Equations in R. Journal of Statistical Software 2011 : 45 (3) : .

REF2 : Rubin D.B. 1987. Multiple Imputation for Nonresponse in Surveys. New York: John Wiley and Sons, REF3 : Li, K.-H., Meng, X.-L., Raghunathan, T.E., and Rubin, D.B. 1991. Significance levels from repeated p-values with multiply-imputed data. Statistica Sinica, 1(1), 65-92).

REF4 Jonathan A C Sterne,1 Ian R White,2 John B Carlin,3 Michael Spratt,1 Patrick Royston,4 Michael G Kenward,5 Angela M Wood,6 James R Carpenter5Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 2009;338:b2393..

VII. BIOLOGY AND BIOLOGICAL COLLECTION

Independently from the safety blood analysis realised on site, a collection of biological samples will be realised during the study, at V0 and V3. The samples will be collected once the participant will sign the specific informed consent.

The samples will be used for peripheral measurement of biomarkers and also for genetic analysis, especially to determine specific polymorphisms associated with drug effect, dopamine and glutamine metabolisms.

Based upon the technical feasibility of each centre (i.e feasibility questionnaires), the collection will be divided into 3 parts:

The first one is “the basic biology” and is mandatory for every participating centre to achieve the objectives of the FPII study. This part corresponds to a volume of 10 millilitres of blood per sampling time.

The second part corresponds to the “recommended biology” which corresponds to a volume of 78 ml of blood.

The third part corresponds to the “expert biology” which corresponds to a volume of 20 ml of blood.

Based upon the will of the patient involved in the study, two additional samples could be proposed to the patient:

- Additional blood analysis (extra volume of 40 ml): only expert centres can propose to their patients this analysis

a. Mitochondrial function, with functional assays on lymphocytes: mitochondrial membrane potential and reactive oxygen species production (flow cytometry).

b. Neural, endothelial and platelet microparticles.

- CSF analysis (lumbar puncture): dopamine, metabolites, ferritin, and oxidative stress markers

The volume of CSF for each time point is 4 millilitres.

The samples will be collected and treated in each centres, excepted for DNA extraction (realized by Lille University Hospital BRC).

In order to harmonize sampling, specific kits will be furnished for each part of the biology (I,II,III and CSF) by the Lille University Hospital Biological Resources Centre (BRC). The BRC will also provide a specific manual for sample handling and storage.

Once treated, samples will be stored within 4 hours at -80°C, in secured freezers.

Samples will be stored on site until they will be transferred to the Lille University Hospital BRC by a dedicated carrier, under dry ice condition, according to local and European Regulations on the transportation of dangerous goods.

The Lille University Hospital Biobank (CRB/CIC1403) will manage biological samples for subsequent analysis, storage and management in terms of referencing, storage, and traceability of inputs, outputs and incidents. These aspects of Biobank activities are certified compliant to both ISO 9001v2008 and NF-S-96900 by AFNOR Certification (certificate number: resp: 2011/40514.1 and 2013/57247.1) . Storage and centralization of organic products are coordinated by the CRB/CIC1403 through biological samples management software that enables a rigorous traceability of each sample. This system uses specific tags barcode. This software called Databiotec® is located and managed by the CRB/CIC1403 Lille. Access is controlled by password. Each connection is saved, and access to the database is limited by a user

personal profile. All movements and events linked to the existence of a sample (inputs, outputs, reintegration, cold chain incidents) are recorded and searchable in the software. This management software and sample tracking to manage: - The code number of the subjects, - Labelling of samples - The contents of the tubes, - affiliation of tubes to a specific protocol - The dates of entry and exit of the bank, - The type of pathology, - Possible problems encountered. Each sample will be uniquely identified, and linked to a study and a subject. The sample is identified using barcodes. The method and sampling conditions, practitioners, clinical, complementary tests, contamination, quality, dangerousness, and sample location are stored. The sample storage temperature is monitored by continuous recording and the different containers are under centralized alarm. An emergency freezer is available to quickly overcome any failure. Storage facilities are secured (electronic access code, alarm, CCTV). The Biological Resource Center manages, on time today, biological samples from 80 studies, from monocentric one to European multicentric scaled studies. Each year, the Biological Resource Center generates between 100,000 and 120,000 biological samples referred to research.

During the study, new scientific data showed that the deferiprone would lead to an increase in prolactin without clinical consequences observed.

Dopamine is the main physiological inhibitor of prolactin. Patients with Parkinson's disease have a prolactin deficiency and hyperprolactinemia could therefore be expected. However, patients are treated by pulsatile (non-physiological) administrations of dopaminergic treatments, one might theoretically expect a normalization of prolactin. However, we lack data on prolactin levels in Parkinson's disease. There are reported cases of hyperprolactinemias in treated patients but no long-term cohort data.

A prolactin assay on samples collected for centralized analysis at visits V0 and V3 by comparing the treated and untreated group will be performed at the end of the study.

	Blood test analyzed at site medical lab	Blood test analyzed at the Lille University Hospital Biobank (CRB/CIC1403)
Blood count with absolute neutrophil count haemoglobin, haematocrit	+	
Hepatic (ASAT, ALAT, alkaline phosphatase, bilirubin, gamma GT)	+	
Kidney tests (ionogramm and urea creatinine)	+	
Iron status (ferritin, serum iron, transferrin, transferrin saturation coefficient, , Serum Total Iron-Binding Capacity)	+ (except for V3 which is analysed centrally)	+ (V3 samples)
Other metals (copper, zinc)	+ (except for V3 which is analysed centrally)	+ (V3 samples)
Hepatitis B and C	+	
Hormonal status (FSH-LH) for women	+	
β HCG (for women of childbearing potential)	+	
Minimal Specific biochemistry with 24-hour urine (samples for central analysis)		+
Optional study: additional blood analyses (lymphocytes and microparticles) (samples for central analysis)		+
Optional study: lumbar puncture (samples for central analysis)		+
Ancillary study: Specific biochemistry *(150<n<338) (samples for central analysis)		+
Prolactin at V0 and V3. (samples for central analysis)		+

VIII. SAFETY ASSESMENT AND MANGEMENT

9.1 Definition

- ***Definition of an AE***

Adverse events are considered to be all harmful and unexpected medical manifestations experienced by a person participating in biomedical research (regardless of the cause of the said manifestation) and which occur between inclusion (evidenced by the date of signature of the consent form) and end of the investigation set out in the protocol.

- ***Definition of a serious adverse event (SAE)***

Serious adverse event (article R.1123-39 of the Public Health Act and the ICH E2B guide)

Any undesirable event which:

- ✓ leads to death,
- ✓ endangers the life of the person taking part in the research study,
- ✓ necessitates admission to hospital, or prolongation of hospitalisation,
- ✓ causes serious or sustained incapacity or handicap,
- ✓ is expressed by a congenital anomaly or malformation,
- ✓ or any event considered to be medically serious,

and concerning the drug, whatever the dose administered.

- ***Causality***

The relationship of each AE to the IMP must be determined by a medically qualified individual according to the following definitions:

1. Yes: Reasonable Possibility
2. No: No Reasonable Possibility

9.2 Potential AE linked to the protocol

The occurrence of AEs will be determined by the subject's spontaneous reporting, the investigator's non-leading questions (e.g. "how are you feeling?") and by observations made during the subject's clinical evaluations. If abnormal, clinically significant results are observed during these evaluations, the investigator will monitor the concerned parameters repeatedly until they have returned to normal or stabilized and will then report these abnormalities as AEs.

- ***The known most serious potential AE is agranulocytosis***, which will be monitored for via performance of a weekly CBC. It can be complicated by a pulmonary or urinary infection or even septicaemia, which can be suspected in all cases of fever and will prompt a repeat CBC (in addition to the weekly CBC) and immediate withdrawal of the drug in cases of neutropenia or agranulocytosis. In clinical trials, agranulocytosis receded within a median of 11 days after the discontinuation of DFP. In the post-marketing setting, fatal cases were reported. The information available to ApoPharma indicates that adequate monitoring of the neutrophil count and/or an adequate management of patient was not performed in the majority of the fatal cases (e.g., monitoring of the neutrophil count was not performed or deferiprone was not discontinued at onset of signs of infection or the physician who attended the patient was not aware the patient was being treated with a medicine that could cause agranulocytosis, and consequently managed the infection inappropriately). We believe that with the close monitoring planned here (a weekly CBC), the risk of agranulocytosis is minimal as long as we discontinue the treatment in the event of neutropenia. An immunoallergic mechanism can be suspected, since there is no clear relationship with the dose (as would be expected for a toxic mechanism). Schematically, three profiles of neutropenia have been observed: (i) a sudden decrease in the ANC over a few hours/days, which frequently leads to agranulocytosis, (ii) a slow decrease in the ANC over several weeks, (iii) fluctuation of the ANC over several months. In all three cases, recovery occurs within a few days of withdrawal of DFP. Unpublished case reports have

shown that addition of folic acid can aid recovery from neutropenia in the two last cases, although this has not been definitively demonstrated. A weekly CBC is recommended during the first 6 months of treatment, followed by monthly testing for the remainder of the treatment period. It is essential to remind physicians and patients to perform an extra blood count in the event of fever and infection, in order to enable quick withdrawal of DFP and recovery from neutropenia.

- **The occurrence of slow, predictable serum iron depletion** has not been observed in the two previous pilot studies in PD, however, a slight decrease of hematocrit and hemoglobin have been observed in the studies with Friedreich ataxia and PKAN. It may then happen but are not considered as harmful (i.e. no symptoms of anemia and no restless legs syndrome). This will be closely monitored by weekly blood count.
  In case of exceptional decrease of haemoglobin, extra iron status analysis will be done with the safety biological analysis.
- ***Benign effects*** (fatigue, headache, nausea, muscle pain, diarrhoea, etc.) are more frequent at the start of treatment and are generally mild and transient.
  - Gastrointestinal effects are more frequent at the beginning of therapy. In most patients they resolve within a few weeks without the need to discontinue treatment. In some patients, it may be beneficial to reduce the dose of DFP and then scale it back up to the original dose.
  - Joint disorder events (ranging from mild pain in one or more joints to severe arthritis with effusion and significant disability) have also been reported in patients treated with DFP. Mild joint disorders are generally transient.
  - Increased levels of serum liver enzymes have been reported in patients taking DFP. In the majority of these patients, the increase is asymptomatic and transient and returns to baseline without discontinuation or dose reduction.

Adverse event	Incidence (per 100 patient-years)	Percentage of patients affected
Reddish/brown urine	29.2	53.8
Nausea	8.6	15.9
Abdominal pain	7.6	14.1
Vomiting	7.2	13.3
Arthralgia	5.1	9.4
Elevated liver enzymes	3.7	6.8
Neutropenia	2.5	5.9
Increased Appetite	2.9	5.4
Diarrhoea	1.4	2.0
Agranulocytosis	0.5	0.8

- Low plasma zinc levels have been associated with DFP treatment in a small proportion of patients. The levels normalize with oral zinc supplementation. This has not been observed at the low dose of 30 mg/kg/day.

- Neurological disorders have been observed in children to whom two and a half times the maximum recommended dose of 100 mg/kg/day were deliberately prescribed for several years. These neurological disorders progressively regressed following discontinuation of DFP. Neurological disorders have been observed in Friedreich's ataxia with a dose of 60 mg/kg/day but never with a dose of 30 mg/kg/day in patients with neurological disease and in the two pilot RCTs on PD patients.
- Electrocardiography and blood pressure: no reported anomalies.

- ***Management of cases of neutropenia***

Individuals taking deferiprone must be monitored for neutropenia, defined as a confirmed absolute neutrophil count (ANC) less than 1.5 x 10^9/L. - Variation of blood count including ANC are normal. There is no need to stop the drug if NC is not below 1.5 x 10^9/L (no toxicity for platelets, lymphocytes, eosinophils) Categories of neutropenia are as follows:

Category	Black Population	All Other Races
Mild	A confirmed ANC < 1.0 x 10^9/L but ≥ 0.65 x 10^9/L	A confirmed ANC < 1.5 x 10^9/L but ≥1.0 x 10^9/L
Moderate	A confirmed ANC < 0.65 x 10^9/L but ≥ 0.5 x 10^9/L	A confirmed ANC < 1.0 x 10^9/L but ≥ 0.5 x 10^9/L
Severe/agranulocytosis	A confirmed ANC < 0.5 x 10^9/L	

For a case of neutropenia to be confirmed, there must be 2 consecutive counts, a maximum of 3 days apart, that are both less than the specified value. If the 2 counts are not in the same severity category, a third count will be required to determine the severity. If a patient has just a single ANC value less than 1.5 x 10^9/L (< 1.0 x 10^9/L for a black patient), this is to be documented in the CRF as “decreased ANC”, but is not to be defined as neutropenia. The investigator is to use judgment as to whether the decrease is clinically significant.

In addition to having ANC monitored, patients will be advised to immediately report any symptoms indicative of infection such as fever (≥ 38.5°C), sore throat, and flu-like symptoms at any time during treatment or during the first week following treatment. They will be provided with an emergency services card with contact information, and advised to carry it with them at all times.

Depending of the severity of neutropenia, patients will either remain in or be withdrawn from the study. The management of different severities of neutropenia is described below.

Mild and moderate neutropenia:

A patient who develops either mild or moderate neutropenia is to interrupt treatment as soon as the neutropenia is confirmed, and ANC is to be monitored every 2 days until resolution.

The patient should re-initiate treatment once the event is resolved, defined as 2 consecutive ANC ≥ 1.5 x 10^9/L (ANC ≥ 1.0 x 10^9/L for a black patient).

If ANC is still < 1.5 x 10^9/L after 14 days, the investigator is to do the following:

- Withdraw patient from the study and monitor him/her until resolution of the event
- Advise patient regarding protective isolation
- Examine patient the same day (if possible), including drug history and physical examination
- Notify the SAE form

Severe neutropenia/agranulocytosis:

A patient in whom a single ANC measurement < 0.5 x 10^9/L is detected is to immediately stop treatment, without waiting for confirmation of the count, and a second measurement is to be done the following day. If the second ANC is still < 0.5 x 10^9/L, the patient is to be permanently withdrawn from the study, and ANC is to be monitored daily until resolution. The following procedures should be done by the investigator or the treating physician, as appropriate:

• Provide protective isolation; if clinically indicated, admit patient to hospital and obtain vital signs every 4 hours

• Examine the patient the same day, if possible, including drug history and physical examination

• With the patient's consent, collect a blood sample to attempt to identify genetic or other biomarkers related to agranulocytosis

• Notify ApoPharma Inc. using the SAE form.

The following additional measures describe a suggested medical management and monitoring:

• If possible, consider obtaining bone marrow aspirate for:
  o Histology
  o Progenitor culture
  o Frozen storage (1 mL sample)

• If possible, consider obtaining bone marrow biopsy (minimum length 3 mm)

• Perform septic work-up including chest X-ray, blood, urine, and throat cultures

• Obtain q4h temperatures from patient (monitored by family at home if patient is not in the hospital)

• If warranted, administer granulocyte stimulating factors, such as G-CSF 10 µg/kg, on an in-patient basis if possible, beginning the same day that the ANC is confirmed as < 0.5 x 10^9/L; administer daily until ANC is > 1.5 x 10^9/L on 2 consecutive days

• If ANC < 0.5 x 10^9/L for 7 days, repeat bone marrow biopsy and aspirate weekly during the period of agranulocytosis, if warranted

Infections

If a patient develops fever (≥ 38.5°C) or any sign of infection during the study, deferiprone must be interrupted immediately, and neutrophil count should be obtained and monitored more frequently; every 2 days if ANC <1.5 x 10^9/L (ANC < 1.0 x 10^9/L for a black patient). Therapy with deferiprone can be re initiated once all symptoms have been resolved and it is deemed safe by the investigator

If patients who develop agranulocytosis / neutropenia fail to comply to protocol in laboratory confirmation within 3 days and study drug is not returned back to the study centre within a reasonable period, the general practitioner and the laboratory of the patient will be informed at the same time.

Thus, investigator will be helped by the GP and the biologist of the laboratory to closely monitored the patient for laboratory confirmation to check the stop of the drug and planned the supplementary visit to get back the study drugs.

9.3 Unexpected AEs:

Unexpected adverse event (article R.1123-39 of the French Public Health Act)

Any adverse effect of the medicinal product, the nature, severity or evolution of which does not conform to the information given in the files submitted to the ethics committee for approval or to the relevant authority in application for marketing authorisation.

9.4 Reporting procedure

9.4.1 Procedures for recording AEs

All AEs occurring during the trial or 30 days after the end of the treatment and that are observed by an investigator or reported by the participant will be recorded on the eCRF, regardless of whether or not they are attributed to IMP.

9.4.2 Procedure for reporting SAEs

All SAEs (other than those defined in the protocol as not requiring reporting) that occur during the trial or within 30 days of the end of the treatment must be reported on the SAE reporting form to CHRUL and ApoPharma within 24 hours of the site study team becoming aware of the event.

9.4.3 Responsibilities of the investigator

The investigator shall notify the sponsor immediately without delay when he/she becomes aware of any serious adverse events during the trial period. All serious adverse events must be reported on the form "Serious Adverse Events" present in the case report file. This form must be sent to the sponsor (Notification Team of the Clinical Research Federation) by fax 03 20 44 57 11.

For each adverse event, the investigator assesses the severity and causal link between the adverse event and the protocol.

9.4.4 Responsibilities of the sponsor:

The sponsor will submit expedited and periodic reports to both competent authorities and independent ethics committees as per corporate SOPs and the EU directive 2001/20/EC, while also taking account of specific local requirements.

9.5 Unblinding

A sealed copy of the randomization list will be stored at the CHRUL's Fédération de la Recherche Clinique (FRC) department.
The investigators are responsible for all trial-related medical decisions. The investigator has to be able to unblind the investigational product immediately if he feels it is necessary without prior contact to the coordinator investigator and the Sponsor. However the investigator should promptly document and explain to the sponsor any premature unblinding.
The investigator will have an acces to the IWRS system at the beginning of the study and if he feels necessary to unblind the investigational product, the investigator will connect to the IWRS system with his own login and password.

In case of a serious adverse event possibly or probably related to DFP, the recommendations will be:
- to interrupt the study treatment
- to establish appropriate symptomatic treatments”

9.6 The DSMB advisory board

A Data and Safety Monitoring Board (DSMB) is an independant consultative board asked to express an opinion to the sponsor of the study on the benefit/risk ratio and the management of the clinical trial.

A DSMB will be set up composed of the following members, at least: pharmacologist, haematologist, biostatistician and neurologist not involved in the RCT. On a regular basis, they will review any reported serious and non-serious AEs and any withdrawals due to AEs. They will analyse the potential causal links with DFP and notify frequent and/or unexpected AEs to the Sponsor.

The members must appoint a chairman, which is the main interlocutor of the sponsor. He is in charge with the drafting of reports and the opinions delivered.

The members are nominated and authorized by the sponsor for the duration of the study. They agree on their participation as volunteers as on the respect for the confidentiality of the data.

Composition and meeting modalities are defined in the DSMB Charter.

IX. QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Monitoring quality assurance:

The study's quality assurance approach is based on SOPs. Patients will participate in the research under optimal safety conditions and in compliance with medical and regulatory guidelines. On the technical level, coordination by CHRUL will rely on semi-automated tools for data entry and administrative & operational study management
According to ICH/GCP guidelines, the sponsor should ensure that the trial is adequately monitored. Data monitoring will protect the rights and well-being of patients, ensure that reported trial data are accurate, complete, and verifiable from source documents, and that the trial is being conducted in compliance with the currently approved protocol/amendment(s), GCP, and the applicable regulatory requirements.
To ensure homogeneity and the same quality standards, monitors in all study countries will be trained with the same procedures.
On-site monitoring will be performed by the sponsor for the French sites and ECRIN's national partners for sites in other countries.
Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Monitoring visits will ensure full source data verification.
The investigator or authorized personnel has to record correctly and completely data in the eCRF
The investigator completely and confirm the integrity of the data transferred to the eCRF by signature.

10.2 Data management:

Data collection and data management

An e-CRF for each patient will be completed by authorized personnel. The e-CRF will be developed with FDA-certified Capture System software, which is widely acknowledged in the field of clinical research.
Capture System facilitates the data entry by running uniqueness and consistency tests on the fly, thereby reducing erroneous and missing data. The database will be is as complete and as clean as possible, with instant visibility per centre or overall. Each centre will have access to their patients, and access will be secured by the use of unique personal logins. Each data recording or editing event will be logged in the database to allow better monitoring and database coordination.
Patient data will be anonymized to protect confidentiality; that patients will be identified by an ID number that prevent their identity from being deduced. Each centre will have to manage its own repository to match the ID number with the patients' personal data, in accordance with local data protection requirements.

Records keeping

The Sponsor or his delegates must ensure that data are recorded in the eCRF correctly and completely by authorized personnel. The investigator has to confirm the integrity of the data transferred to the eCRF by signature.

10.2.1 Investigator site file (ISF)

The investigator is responsible for maintaining all records which enable the conduct of the clinical trial at the site to be fully documented, in compliance with ICH GCP filing standard. Timeliness and completeness of the documentation is regularly checked by the clinical monitor. The documentation of the clinical trial including all the relevant correspondence should be kept by the investigator for the minimum period of 15 years.

10.2.2 Obligation to archive (Sponsor)

All completed study related documents (e.g. eCRF, Informed consent forms, drug accountability logs, staff signature lists, Subject identification log, …) must be archived by Sponsor according to regulatory requirements for 30 years.

10.3 Audit and Inspection:

An audit may be performed at any time by people appointed by the sponsor who are independent of those responsible for the study. The aim of an audit is to ensure the good quality of the study, that its results are valid and that the law and regulations in force are being observed.

The investigators agree to comply with the requirements of the sponsor and the relevant authority for an audit or an inspection of the study.

The audit can apply to all stages of the study, from development of the protocol to publication of the results and filing the data used or produced in the study

X. ETHICAL AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with the protocol and ethical principles stated in the Declaration of Helsinki or the applicable guidelines on GCP, and all applicable local laws, rules, and regulations.

11.1 Ethical review

Requirements for ethical review as set forth in Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice (GCP) in the conduct of clinical trials on medicinal products for human use or other relevant local regulations for institutional review will be followed. The Protocol, ICF/PIL, Investigator's Brochure and other required documents must be approved by the EC before enrolment of subjects in the study. The letter of approval from the EC, as well as a list of documents reviewed, will be filed in the Investigator Site File (ISF) and a copy will be filed in the trial master file (TMF) held by the Sponsor.

The Sponsor and his delegates, in collaboration with the investigator, will be responsible for reporting to the EC all changes in research activity, including protocol amendments, updates of Investigator's Brochures, annual safety reports, all unanticipated problems involving risks to human subjects, and study termination.

11.2 Regulatory considerations

In parallel to the submission to the EC, the Sponsor has to obtain an authorisation from the appropriate competent authority (CA) to conduct the clinical study. Subjects must not be entered into the study until the relevant EC has issued its opinion and the CA has given authorisation to conduct the study.
All substantial amendments must be submitted to the EC and/or to the CA for approval.

11.2.1 Responsibilities of the sponsor or his delegates

Prior to initiating the clinical trial, the sponsor or his delegate defines, establishes and allocates all trial-related duties and functions. The sponsor or his delegate ensures that all investigators are provided with instructions and a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the eCRFs.

11.2.2 Responsibilities of the Investigators

The investigators are responsible for the conduct of the clinical trial at the respective site. In signing this protocol, the Investigator accepts to carry out all procedures related to this study according to the laws and guidelines of the EU regarding the conduct of clinical research and any local requirements of the individual EU country. Investigators must allow access to all documents pertinent to the study.

11.2.3 Patient Confidentiality

The personal data gathered during the study will be recorded on an e-CRF and will be anonymized prior to transmission as a computer file for statistical analysis. The principal investigator must ensure that the patient's anonymity is maintained. On the eCRFs or other documents submitted to the Sponsor, subjects should not be identified by their names, but by their assigned identification number. If patient names are included on copies of documents submitted to the Sponsor, the names must be obliterated and replaced with the assigned study patient numbers.

Recording, transmission and storage of subjects' trial-relevant data will be performed according to local secrecy obligations, as well as national and European requirements (Regulation (EU) 2016/679 on the protection of personal data)

Only persons directly involved in the study will be authorized to modify these files.
Study participants are separately informed about data security in the patient information leaflets /informed consent form and have a right to consult and correct their personal data at any time; this right can be exercised by contacting their study physician or the sponsor's data protection officer in accordance with European Regulation (EU) 2016/679 (General Data Protection Regulation).

11.2.4 Amendment

The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor or his delegate and prior review and documented approval of an amendment by the competent authority and the concerned ethics committee, except where necessary to eliminate an immediate hazard to trial participants, or when the change involves only administrative aspects, per European law (Directive 2001/20).

11.2.5 End of the trial

The end of the trial will be notified to concerned ethics committee and competent authority within 90 days, as required by European and local legislations.

The end of the trail is defined as the last visit of the last patient included.

XI. FINANCING AND INSURANCE

13.1 Financing

This study was performed in the frame of the FAIR-PARK II project, which has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 633190

13.2 Insurance

The Sponsor or his delegate will procure insurance for this clinical trial to cover trial related injuries of the participants according to local regulatory requirements.

Clinical trial participants will be provided on request with the conditions of insurance along with the patient information and consent form.

XII. PUBLICATION

The main results will be published by the consortium. We expect further publications from the consortium that will also follow the publication rules described in the consortium agreement.

XIII. REFERENCES

for other references please see the Proposal-SEP-210176699-2

Emre M, Aarsland D, Brown R, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 2007; 22: 1689–707.

Fahn S, Oakes D, Shoulson I, Kieburtz K, Rudolph A, Lang A, Olanow CW, Tanner C, Marek K; Parkinson Study Group. Levodopa and the progression of Parkinson's disease. N Engl J Med. 2004;35:2498-508.

Gibb WRG, Lees AJ. The revalence of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1988; 51: 745–52.

Olanow CW, Rascol O, Hauser R, Feigin PD, Jankovic J, Lang A, Langston W, Melamed E, Poewe.

W, Stocchi F, Tolosa E; ADAGIO Study Investigators. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. N Engl J Med. 2009;361:1268-78.

XIV. ANNEXES

ANNEXE 1: MDS Clinical Diagnostic Criteria for Parkinson's Disease

Having established that the patient has parkinsonism, the MDS-PD criteria will be applied to determine whether the patient meets criteria for PD as the cause of this parkinsonism.

Diagnosis of clinically established PD requires:
1. Absence of absolute exclusion criteria
2. At least two supportive criteria
3. No red flags

Diagnosis of clinically probable PD can be made in:
1. Absence of absolute exclusion criteria
2. Presence of red flags counterbalanced by supportive criteria, ie, if one red flag is present there must also be at least one supportive criterion; if two red flags, at least two supportive criteria are needed. If there are more than two red flags, clinically probable PD cannot be diagnosed.

Supportive Criteria

1. Clear and dramatic beneficial response to dopaminergic therapy. To meet this criterion, during initial treatment, patients should have returned to normal or near-normal level of function.In the absence of clear documentation of initial response (eg, initial treatment with lower-efficacy agents or very low dose), a dramatic response also can be classified as:

a. Marked improvement with dose increases or marked worsening with dose decreases. Mild changes with dose changes do not qualify. This can be documented either objectively (defined as >30% in UPDRS III with change in treatment), or subjectively with a clear history of marked changes provided by a reliable patient or caregiver.

b.Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off.

Note: To meet this criterion, it is not sufficient to document some beneficial response to dopaminergic therapy; the response must be unequivocal and of large amplitude. If treatment response is of modest amplitude, the patient does not meet this criterion.
The requirement of predictable end-of-dose wearing off is to ensure that these are true dopaminergic fluctuations (as opposed to day-to-day variability, for example). The documentation of predictable end-ofdose wearing off can be from retrospective history (ie,
patients do not have to currently be experiencing predictable fluctuations).

2. Presence of levodopa-induced dyskinesia

3. Rest tremor of a limb, documented on clinical examination (in the past, or on current examination)

Note: This is included primarily for two reasons: (1) rest tremor is less common in alternate conditions, and (2) rest tremor may occasionally be less responsive to therapy; if so, criterion 1 may be harder to meet in tremor-predominant PD.

4. Positive results from at least one ancillary diagnostic test having a specificity greater than 80% for differential diagnosis of PD from other parkinsonian conditions. Currently available tests that meet this criterion include:

- Olfactory loss (in the anosmic or clearly hyposmic range, adjusted for age and sex)
- Metaiodobenzylguanidine scintigraphy clearly documenting cardiac sympathetic denervation

Note: To meet these criteria, the marker must have been demonstrated to provide more than 80% specificity in most studies (with a minimum of three studies from different centers).

Absolute Exclusion Criteria

For all absolute exclusion criteria and red flags, the criterion is assumed to not be met because of an alternate unrelated cause. For example, unilateral cerebellar abnormalities attributable to a cerebellar hemisphere stroke, or a wheelchair-bound state attributable to spinal cord injury would not necessarily be exclusion criteria.

The presence of any of these features rules out PD:

1. Unequivocal cerebellar abnormalities on examination, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (eg, sustained gaze-evoked nystagmus, macro square wave jerks, hypermetric saccades)

2. Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades

3. Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia, defined according to consensus criteria31 within the first 5 y of disease

Note: This refers specifically to the frontotemporal type of dementia, which is associated with disorders other than PD (tau deposition disorders, and so forth). Other forms of dementia are not an exclusion criterion for PD. Also note that for this criterion, and for all other criteria with a time component, waiting until the disease duration is 5 y before the criterion is considered as not met is not necessary (ie, if the patient has a 4-y disease duration without frontotemporal dementia and all other criteria are met, this criterion is not met, and one can still diagnose clinically established PD).

4. Parkinsonian features restricted to the lower limbs for more than 3 y

5. Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and timecourse consistent with drug-induced parkinsonism

Note: In application of this criterion, clinical judgment should be applied. For example, if a patient received only a low-dose “highlyatypical” neuroleptic, the evaluator may consider this treatment inconsistent with drug-induced parkinsonism. Or, if parkinsonism clearly persists long after complete medication withdrawal, the investigator might conclude that the dopamine blocker unmasked subclinical PD.

6. Absence of observable response to high-dose levodopa despite at least moderate severity of disease

Note: To meet this criterion, patients must have received a sufficiently high dose of levodopa daily (>600 mg/d). For patients who are untreated, or who have received less than 600 mg levodopa, this criterion cannot be applied. Absence of treatment response should be clearly reported by patient (or reliable witness) or if sequential examinations are available, can be confirmed objectively (ie, improvement >3 points on the MDS-UPDRS Part III). Because mild parkinsonism and tremor may be less clearly responsive to therapy, the patient also must have at least moderate severity parkinsonism (ie, MDS-UPDRS score >2 of one measure of rigidity or bradykinesia) to meet this criterion.

7. Unequivocal cortical sensory loss (ie, graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia

8. Normal functional neuroimaging of the presynaptic dopaminergic system

Note: This criterion does NOT imply that dopaminergic functional imaging is required for diagnosis (nor does the task force wish to imply that this should be performed in diagnosing PD). If no imaging has been performed, this criterion does not apply.

9. Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or the expert evaluating physician, based on the full diagnostic assessment, believes that an alternative syndrome is more likely than PD.

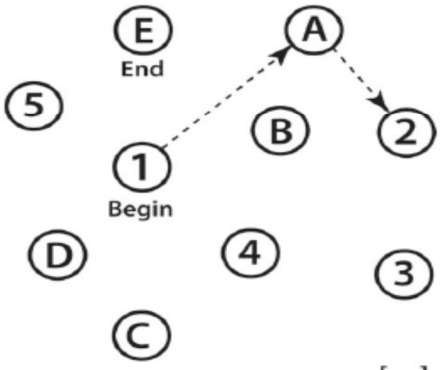
Note: This criterion includes not only rare conditions that can mimic PD, but also can include the more common alternative parkinsonian syndromes (MSA, PSP, and so forth). Note again that dementia with Lewy Bodies is not considered an alternative parkinsonian syndrome according to this criterion.

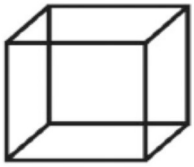
ANNEXE 2: MOCA

MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE





Copy cube

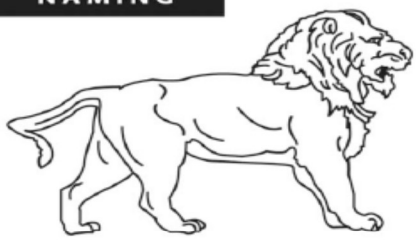
[ ] [ ]

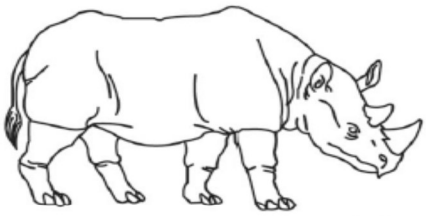
Draw CLOCK (Ten past eleven)
(3 points)

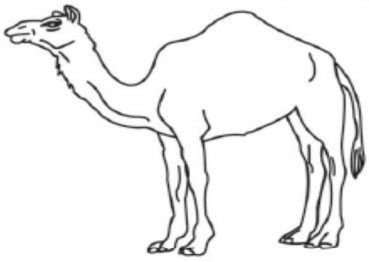
[ ] Contour [ ] Numbers [ ] Hands

POINTS ___/5

NAMING







[ ] [ ] [ ]

___/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2

___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

___/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

___/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ]

___/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

___/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

___/2

DELAYED RECALL

	Has to recall words **WITH NO CUE**	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

___/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

___/6

© Z.Nasreddine MD **www.mocatest.org** Normal ≥26 / 30

TOTAL ___/30

Add 1 point if ≤ 12 yr edu

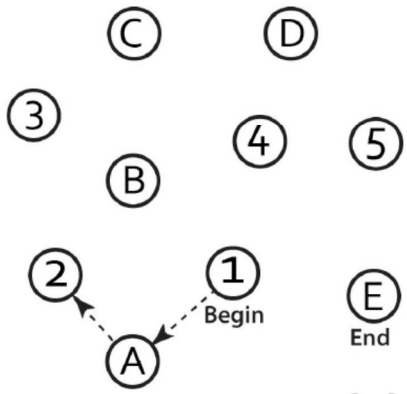
Administered by: _____

MONTREAL COGNITIVE ASSESSMENT (MOCA®)

Version 7.2 Alternative Version

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE



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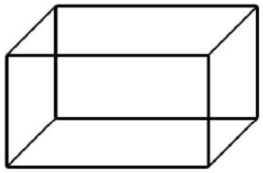
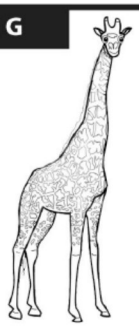


Draw CLOCK (Five past four)
(3 points)

[ ] Contour [ ] Numbers [ ] Hands

POINTS ___/5

NAMING



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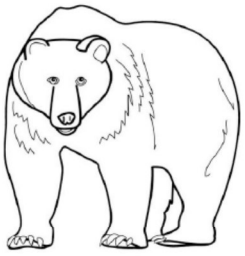

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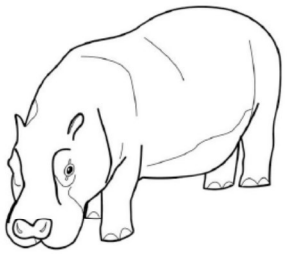


[ ] ___/3

MEMORY

Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	TRUCK	BANANA	VIOLIN	DESK	GREEN
1st trial					
2nd trial					

No points

ATTENTION

Read list of digits (1 digit/ sec.).
Subject has to repeat them in the forward order [ ] 3 2 9 6 5
Subject has to repeat them in the backward order [ ] 8 5 2 ___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B ___/1

Serial 7 subtraction starting at 90 [ ] 83 [ ] 76 [ ] 69 [ ] 62 [ ] 55
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** ___/3

LANGUAGE

Repeat : A bird can fly into closed windows when it's dark and windy. [ ]
The caring grandmother sent groceries over a week ago. [ ] ___/2

Fluency / Name maximum number of words in one minute that begin with the letter S [ ] _____ (N ≥ 11 words) ___/1

ABSTRACTION

Similarity between e.g. carrot - potato = vegetable. [ ] diamond - ruby [ ] cannon - rifle ___/2

DELAYED RECALL

	Has to recall words **WITH NO CUE**	TRUCK [ ]	BANANA [ ]	VIOLIN [ ]	DESK [ ]	GREEN [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

___/5

ORIENTATION

[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City ___/6

Adapted by : Z. Nasreddine MD, N. Phillips PhD, H. Chertkow MD

www.mocatest.org

Normal ≥ 26 / 30

TOTAL ___/30

Add 1 point if ≤ 12 yr edu

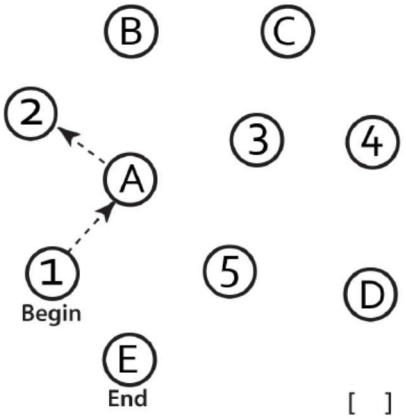
Administered by: _____

MONTREAL COGNITIVE ASSESSMENT (MOCA)

Version 7.3 Alternative Version

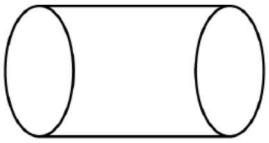
NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE



[ ] [ ]

Copy cylinder

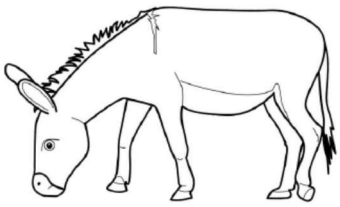


Draw CLOCK (Ten past nine)
(3 points)

[ ] Contour [ ] Numbers [ ] Hands

POINTS ___/5

NAMING



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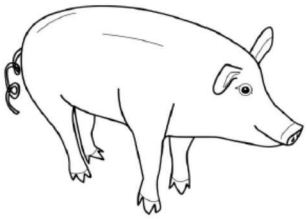

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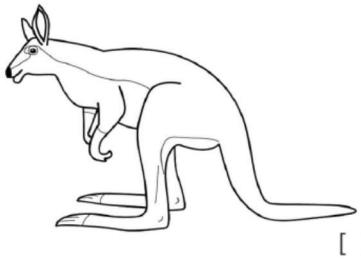

[ ]

___/3

MEMORY

Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	TRAIN	EGG	HAT	CHAIR	BLUE
1st trial					
2nd trial					

No points

ATTENTION

Read list of digits (1 digit/ sec.).
Subject has to repeat them in the forward order [ ] 5 4 1 8 7
Subject has to repeat them in the backward order [ ] 1 7 4

___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

___/1

Serial 7 subtraction starting at 80 [ ] 73 [ ] 66 [ ] 59 [ ] 52 [ ] 45

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

___/3

LANGUAGE

Repeat : She heard his lawyer was the one to sue after the accident. [ ]
The little girls who were given too much candy got stomach aches. [ ]

___/2

Fluency / Name maximum number of words in one minute that begin with the letter B [ ] _____ (N ≥ 11 words)

___/1

ABSTRACTION

Similarity between e.g. banana - orange = fruit [ ] eye – ear [ ] trumpet – piano

___/2

DELAYED RECALL

	Has to recall words **WITH NO CUE**	TRAIN [ ]	EGG [ ]	HAT [ ]	CHAIR [ ]	BLUE [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

___/5

ORIENTATION

[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

___/6

Adapted by : Z. Nasreddine MD, N. Phillips PhD, H. Chertkow MD
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Normal ≥ 26 / 30

TOTAL ___/30
Add 1 point if ≤ 12 yr edu

Administered by: _____

ANNEXE 3: PDQ-39

Please complete the following

Please tick one box for each question

Due to having Parkinson's disease, how often during the last month have you....		Never	Occasionally	Sometimes	Often	Always or cannot do at all
1	Had difficulty doing the leisure activities which you would like to do?	☐	☐	☐	☐	☐
2	Had difficulty looking after your home, e.g. DIY, housework, cooking?	☐	☐	☐	☐	☐
3	Had difficulty carrying bags of shopping?	☐	☐	☐	☐	☐
4	Had problems walking half a mile?	☐	☐	☐	☐	☐
5	Had problems walking 100 yards?	☐	☐	☐	☐	☐
6	Had problems getting around the house as easily as you would like?	☐	☐	☐	☐	☐
7	Had difficulty getting around in public?	☐	☐	☐	☐	☐
8	Needed someone else to accompany you when you went out?	☐	☐	☐	☐	☐
9	Felt frightened or worried about falling over in public?	☐	☐	☐	☐	☐
10	Been confined to the house more than you would like?	☐	☐	☐	☐	☐
11	Had difficulty washing yourself?	☐	☐	☐	☐	☐
12	Had difficulty dressing yourself?	☐	☐	☐	☐	☐
13	Had problems doing up your shoe laces?	☐	☐	☐	☐	☐

*Please check that you have ticked **one box for each question** before going on to the next page*

Questionnaires for patient completion

Due to having Parkinson's disease, how often <u>during the last month</u> have you....		*Please tick <u>one</u> box for each question*				
		Never	**Occasionally**	**Sometimes**	**Often**	**Always** or cannot do at all
14	Had problems writing clearly?	☐	☐	☐	☐	☐
15	Had difficulty cutting up your food?	☐	☐	☐	☐	☐
16	Had difficulty holding a drink without spilling it?	☐	☐	☐	☐	☐
17	Felt depressed?	☐	☐	☐	☐	☐
18	Felt isolated and lonely?	☐	☐	☐	☐	☐
19	Felt weepy or tearful?	☐	☐	☐	☐	☐
20	Felt angry or bitter?	☐	☐	☐	☐	☐
21	Felt anxious?	☐	☐	☐	☐	☐
22	Felt worried about your future?	☐	☐	☐	☐	☐
23	Felt you had to conceal your Parkinson's from people?	☐	☐	☐	☐	☐
24	Avoided situations which involve eating or drinking in public?	☐	☐	☐	☐	☐
25	Felt embarrassed in public due to having Parkinson's disease?	☐	☐	☐	☐	☐
26	Felt worried by other people's reaction to you?	☐	☐	☐	☐	☐
27	Had problems with your close personal relationships?	☐	☐	☐	☐	☐
28	Lacked support in the ways you need from your spouse or partner?	☐	☐	☐	☐	☐
	If you do not have a spouse or partner tick here		☐			
29	Lacked support in the ways you need from your family or close friends?	☐	☐	☐	☐	☐

*Please check that you have ticked **one box for each question** before going on to the next page*

Questionnaires for patient completion

Due to having Parkinson's disease, how often <u>during the last month</u> have you....		***Please tick <u>one</u> box for each question***				
		Never	**Occasionally**	**Sometimes**	**Often**	**Always**
30	Unexpectedly fallen asleep during the day?	☐	☐	☐	☐	☐
31	Had problems with your concentration, e.g. when reading or watching TV?	☐	☐	☐	☐	☐
32	Felt your memory was bad?	☐	☐	☐	☐	☐
33	Had distressing dreams or hallucinations?	☐	☐	☐	☐	☐
34	Had difficulty with your speech?	☐	☐	☐	☐	☐
35	Felt unable to communicate with people properly?	☐	☐	☐	☐	☐
36	Felt ignored by people?	☐	☐	☐	☐	☐
37	Had painful muscle cramps or spasms?	☐	☐	☐	☐	☐
38	Had aches and pains in your joints or body?	☐	☐	☐	☐	☐
39	Felt unpleasantly hot or cold?	☐	☐	☐	☐	☐

*Please check that you have ticked **one box for each question** before going on to the next page*

Thank you for completing the PDQ 39 questionnaire

ANNEXE 4: CGI and PGI

Clinical Global Impressions-Severity Scale (CGI-S)

Severity of Illness

Considering your total clinical experience with this particular population,
how mentally ill is the patient at this time? Severity Score:.....

0 Not assessed

1 Normal, not at all ill

2 Borderline mentally ill

3 Mildly ill

4 Moderately ill

5 Markedly ill

6 Severely ill

7 Among the most extremely ill of subjects

Note: Evaluation should be made as a comparison to baseline

Clinical Global Impressions-Improvement Scale (CGI-I)

Compared to the subject´s condition at baseline,
how much has he/she changed? Improvement Score:.....

0 Not assessed

1 Very much improved

2 Much Improved

3 Minimally Improved

4 No change

5 Minimally worse

6 Much worse

7 Very much worse

Patient global Impression:

Since the start of the study, my overall status is:

1 ☐ Very Much Improved
2 ☐ Much Improved
3 ☐ Minimally Improved
4 ☐ No Change
5 ☐ Minimally Worse
6 ☐ Much Worse
7 ☐ Very Much Worse

ANNEXE 5: MDS-UPDRS

MDS-UPDRS

The Movement Disorder Society (MDS)-sponsored new version of the UPDRS is founded on the critique that was formulated by the Task Force for Rating Scales in Parkinson's disease (Mov Disord 2003;18:738-750). Thereafter, the MDS recruited a Chairperson to organize a program to provide the Movement Disorder community with a new version of the UPDRS that would maintain the overall format of the original UPDRS, but address issues identified in the critique as weaknesses and ambiguities. The Chairperson identified subcommittees with chairs and members. Each part was written by the appropriate subcommittee members and then reviewed and ratified by the entire group. These members are listed below.

The MDS-UPDRS has four parts: Part I (non-motor experiences of daily living), Part II (motor experiences of daily living, Part III (motor examination) and Part IV (motor complications). Part I has two components: IA concerns a number of behaviors that are assessed by the investigator with all pertinent information from patients and caregivers, and IB is completed by the patient with or without the aid of the caregiver, but independently of the investigator. These sections can, however, be reviewed by the rater to ensure that all questions are answered clearly and the rater can help explain any perceived ambiguities. Part II is designed to be a self-administered questionnaire like Part IB, but can be reviewed by the investigator to ensure completeness and clarity. Of note, the official versions of Part IA, Part IB and Part II of the MDS-UPDRS do not have separate on or off ratings. However, for individual programs or protocols the same questions can be used separately for on and off. Part III has instructions for the rater to give or demonstrate to the patient; it is completed by the rater. Part IV has instructions for the rater and also instructions to be read to the patient. This part integrates patient-derived information with the rater's clinical observations and judgments and is completed by the rater.

The authors of this new version are:

Chairperson: Christopher G. Goetz

Part I: Werner Poewe (chair), Bruno Dubois, Anette Schrag

Part II: Matthew B. Stern (chair), Anthony E. Lang, Peter A. LeWitt

Part III: Stanley Fahn (chair), Joseph Jankovic, C. Warren Olanow

Part IV: Pablo Martinez-Martin (chair), Andrew Lees, Olivier Rascol, Bob van Hilten

Development Standards: Glenn T. Stebbins (chair), Robert Holloway, David Nyenhuis

Appendices: Cristina Sampaio (chair), Richard Dodel, Jaime Kulisevsky

Statistical Testing: Barbara Tilley (chair), Sue Leurgans, Jean Teresi,

Consultant: Stephanie Shaftman, Nancy LaPelle

Contact person: Christopher G. Goetz, MD
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1725 W. Harrison Street, Suite 755
Chicago, IL USA 60612

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Email: cgoetz@rush.edu

July 1, 2008

Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)

Overview: This portion of the scale assesses the non-motor impact of Parkinson's disease (PD) on patients' experiences of daily living. There are 13 questions. Part 1A is administered by the rater (six questions) and focuses on complex behaviors. Part 1B is a component of the self-administered Patient Questionnaire that covers seven questions on non-motor experiences of daily living.

Part 1A:

In administering Part IA, the examiner should use the following guidelines:

1. Mark at the top of the form the primary data source as patient, caregiver, or patient and caregiver in equal proportion.

2. The response to each item should refer to a period encompassing the prior week including the day on which the information is collected.

3. All items must have an integer rating (no half points, no missing scores). In the event that an item does not apply or cannot be rated (e.g., amputee who cannot walk), the item is marked UR for Unable to Rate.

4. The answers should reflect the usual level of function and words such as "usually", "generally", "most of the time" can be used with patients.

5. Each question has a text for you to read (Instructions to patients/caregiver). After that statement, you can elaborate and probe based on the target symptoms outlined in the Instructions to examiner. You should NOT READ the RATING OPTIONS to the patient/caregiver, because these are written in medical terminology. From the interview and probing, you will use your medical judgment to arrive at the best response.

6. Patients may have co-morbidities and other medical conditions that can affect their function. You and the patient must rate the problem as it exists and do not attempt to separate elements due to Parkinson's disease from other conditions.

EXAMPLE OF NAVIGATING THROUGH THE RESPONSE OPTIONS FOR PART 1A

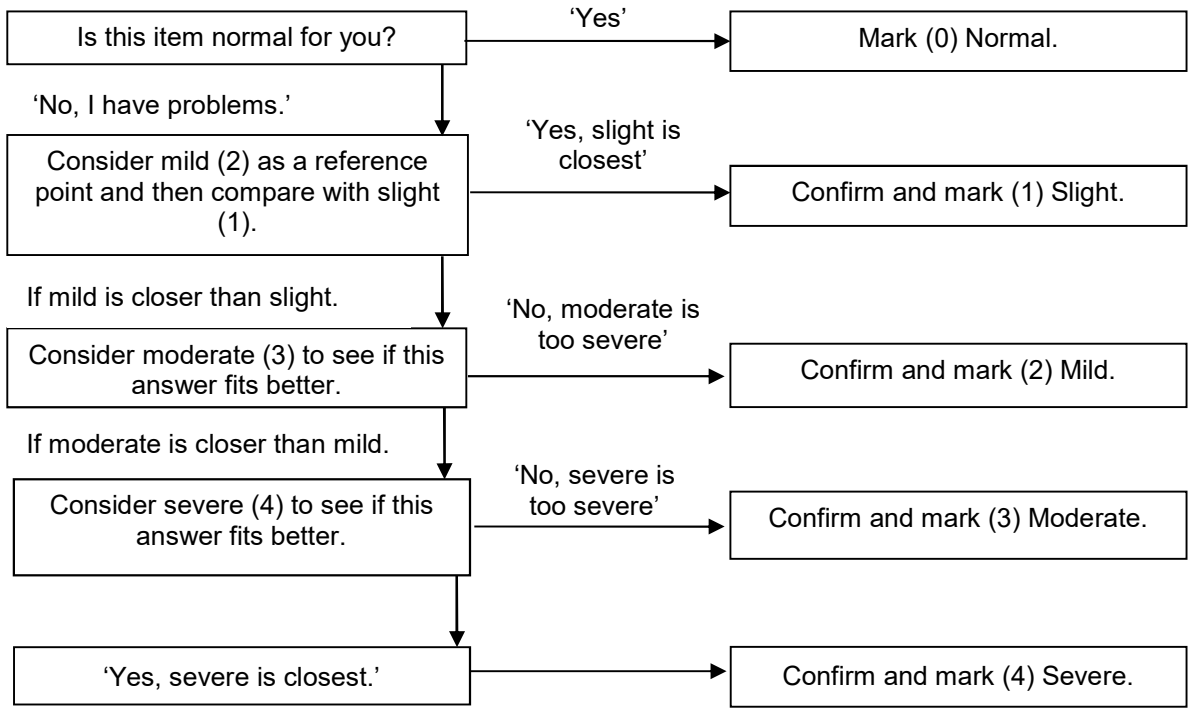
Suggested strategies for obtaining the most accurate answer:

After reading the instructions to the patient, you will need to probe the entire domain under discussion to determine

Normal vs. problematic: If your questions do not identify any problem in this domain, record 0 and move on to the next question.

If your questions identify a problem in this domain, you should work next with a reference anchor at the mid-range (option 2 or Mild) to find out if the patient functions at this level, better or worse. <u>You will not be reading the choices of responses to the patient as the responses use clinical terminology. You will be asking enough probing questions to determine the response that should be coded</u>.

Work up and down the options with the patient to identify the most accurate response, giving a final check by excluding the options above and below the selected response.



MDS-UPRS

Part I : Non-Motor Aspects of Experiences of Daily Living (nM-EDL)

<u>Part IA</u> : Complex behaviors [completed by rater]

Primary source of information:

☐ Patient ☐ Caregiver ☐ Patient and Caregiver in Equal Proportion

To be read to the patient: I am going to ask you six questions about behaviors that you may or may not experience. Some questions concern common problems and some concern uncommon ones. If you have a problem in one of the areas, please choose the best response that describes how you have felt MOST OF THE TIME during the PAST WEEK. If you are not bothered by a problem, you can simply respond NO. I am trying to be thorough, so I may ask questions that have nothing to do with you.

1.1 COGNITIVE IMPAIRMENT	**SCORE**
Instructions to examiner: Consider all types of altered level of cognitive function including cognitive slowing, impaired reasoning, memory loss, deficits in attention and orientation. Rate their impact on activities of daily living as perceived by the patient and/or caregiver. *Instructions to patients [and caregiver]: Over the past week have you had problems remembering things, following conversations, paying attention, thinking clearly, or finding your way around the house or in town?* *[If yes, examiner asks patient or caregiver to elaborate and probes for information]*	
0 : Normal : No cognitive impairment.	
1 : Slight : Impairment appreciated by patient or caregiver with no concrete interference with the patient's ability to carry out normal activities and social interactions	☐

2 : Mild:	Clinically evident cognitive dysfunction, but only minimal interference with the patient's ability to carry out normal activities and social interactions.	
3 : Moderate :	Cognitive deficits interfere with but do not preclude the patient's ability to carry out normal activities and social interactions.	
4 : Severe :	Cognitive dysfunction precludes the patient's ability to carry out normal activities and social interactions.	

1.2 HALLUCINATIONS AND PSYCHOSIS	**SCORE**
Instructions to examiner: Consider both illusions (misinterpretations of real stimuli) and hallucinations (spontaneous false sensations). Consider all major sensory domains (visual, auditory, tactile, olfactory and gustatory). Determine presence of unformed (for example sense of presence or fleeting false impressions) as well as formed (fully developed and detailed) sensations. Rate the patients insight into hallucinations and identify delusions and psychotic thinking. *Instructions to patients [and caregiver]: Over the past week have you seen, heard? smelled or felt things that were not really there? [If yes, examiner asks patient or caregiver to elaborate and probes for information]* 0 : Normal : No hallucinations or psychotic behaviour. 1 : Slight : Illusions or non-formed hallucinations, but patient recognizes them without loss of insight. 2 : Mild: Formed hallucinations independent of environmental stimuli. No loss of insight. 3 : Moderate : Formed hallucinations with loss of insight. 4 : Severe : Patient has delusions or paranoia.	
1.3 DEPRESSED MOOD	**SCORE**
Instructions to examiner: Consider low mood, sadness, hopelessness, feelings of emptiness or loss of enjoyment. Determine their presence and duration over the past week and rate their interference with the patient's ability to carry out daily routines and engage in social interactions. *Instruction to the patient (and caregiver): Over the past week have you felt low, sad, hopeless or unable to enjoy things? If yes, was this feeling for longer than one day at a time? Did it make it difficult for you carry out your usual activities*	

or to be with people? [If yes, examiner asks patient or caregiver to elaborate and probes for information] 0 : Normal : No depressed mood. 1 : Slight : Episodes of depressed mood that are not sustained for more than one day at a time. No interference with patient's ability to carry out normal activities and social interactions. 2 : Mild: Depressed mood that is sustained over days, but without interference with normal activities and social interactions. 3 : Moderate : Depressed mood that interferes with, but does not preclude, the patient's ability to carry out normal activities and social interactions. 4 : Severe : Depressed mood precludes patient's ability to carry out normal activities and social interactions	☐
1.4 ANXIOUS MOOD Instructions to examiner: Determine nervous, tense, worried or anxious feelings (including panic attacks) over the past week and rate their duration and interference with the patient's ability to carry out daily routines and engage in social interactions. *Instructions to patients [and caregiver]: Over the past week have you felt nervous, worried or tense? If yes, was this feeling for longer than one day at a time? Did it make it difficult for you to follow your usual activities or to be with other people*? [If yes, examiner asks patient or caregiver to elaborate and probes for information.] 0 : Normal : No anxious feelings. 1 : Slight :	**SCORE** ☐

	Anxious feelings present but not sustained for more than one day at a time. No interference with patient's ability to carry out normal activities and social interaction.	
2 : Mild:	Anxious feelings are sustained over more than one day at a time, but without interference with patient's ability to carry out normal activities and social interactions.	
3 : Moderate :	Anxious feelings interfere with, but do not preclude, the patient's ability to carry out normal activities and social interactions.	
4 : Severe :	Anxious feelings preclude patient's ability to carry out normal activities and social interactions.	

1.5 APATHY

SCORE

Instructions to examiner: Consider level of spontaneous activity, assertiveness, motivation and initiative and rate the impact of reduced levels on performance of daily routines and social interactions. Here the examiner should attempt to distinguish between apathy and similar symptoms that are best explained by depression.

Instructions to patients (and caregiver): Over the past week, have you felt indifferent to doing activities or being with people? [If yes, examiner asks patient or caregiver to elaborate and probes for information.]

0 : Normal :	No apathy.	
1 : Slight :	Apathy appreciated by patient and/or caregiver, but no interference with daily activities and social interactions.	☐
2 : Mild:	Apathy interferes with isolated activities and social interactions.	

3 : Moderate :	Apathy interferes with most activities and social interactions.	
4 : Severe :	Passive and withdrawn, complete loss of initiative.	

	SCORE
1.6 FEATURES OF DOPAMINE DYSREGULATION SYNDROME Instructions to examiner: Consider involvement in a variety of activities including atypical or excessive gambling (e.g. casinos or lottery tickets), atypical or excessive sexual drive or interests (e.g., unusual interest in pornography, masturbation, sexual demands on partner), other repetitive activities (e.g. hobbies, dismantling objects, sorting or organizing), or taking extra non-prescribed medication for non-physical reasons (i.e., addictive behavior). Rate the impact of such abnormal activities/behaviors on the patient's personal life and on his family and social relations (including need to borrow money or other financial difficulties like withdrawal of credit cards, major family conflicts, lost time from work, or missed meals or sleep because of the activity). *Instructions to patients [and caregiver]: Over the past week, have you had unusually strong urges that are hard to control? Do you feel driven to do or think about something and find it hard to stop?* [Give patient examples such as gambling, cleaning, using the computer, taking extra medicine, obsessing about food or sex, all depending on the patients]. 0 : Normal : No problems present. 1 : Slight : Problems are present but usually do not cause any difficulties for the patient or family/caregiver. 2 : Mild: Problems are present and usually cause a few difficulties in the patient's personal and family life. 3 : Moderate : Problems are present and usually cause a lot of difficulties in the patient's personal and family life. 4 : Severe : Problems are present and preclude the patient's ability to carry out normal activities or social interactions or to maintain previous standards in personal and family life.	☐

The remaining questions in Part I (Non-motor Experiences of Daily Living) [Sleep, Daytime Sleepiness, Pain and Other Sensation, Urinary Problems, Constipation Problems, Lightheadedness on Standing, and Fatigue] are in the **Patient Questionnaire** along with all questions in Part II [Motor Experiences of Daily Living].

Patient Questionnaire:

Instructions :

This questionnaire will ask you about your experiences of daily living.

There are 20 questions. We are trying to be thorough, and some of these questions may therefore not apply to you now or ever. If you do not have the problem, simply mark 0 for NO.

Please read each one carefully and read all answers before selecting the one that best applies to you.

We are interested in your average or usual function over the past week including today.

Some patients can do things better at one time of the day than at others. However, only one answer is allowed for each question, so please mark the answer that best describes what you can do most of the time.

You may have other medical conditions besides Parkinson's disease. Do not worry about separating Parkinson's disease from other conditions. Just answer the question with your best response.

Use only 0, 1, 2, 3, 4 for answers, nothing else. Do not leave any blanks.

Your doctor or nurse can review the questions with you, but this questionnaire is for patients to complete, either alone or with their caregivers.

Who is filling out this questionnaire (check the best answer):

☐ Patient ☐ Caregiver ☐ Patient and Caregiver in Equal Proportion

Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)	
1.7 SLEEP PROBLEMS Over the past week, have you had trouble going to sleep at night or staying asleep through the night ? Consider haw rested you felt after waking up in the morning. 0 : Normal: No problems. 1 : Slight: Sleep problems are present but usually do not cause trouble getting a full night of sleep. 2 : Mild: Sleep problems usually cause some difficulties getting a full night of sleep. 3 : Moderate: Sleep problems cause a lot of difficulties getting a full night of sleep, but I still usually sleep for more than half the night. 4 : Severe: I usually do not sleep for most of the night.	**SCORE**
1.8 DAYTIME SLEEPINESS Over the past week, have you had trouble staying awake during the daytime? 0 : Normal: No daytime sleepiness.	**SCORE**

1 : Slight:	Daytime sleepiness occurs but I can resist and I stay awake.	☐
2 : Mild:	Sometimes I fall asleep when alone and relaxing. For example, while reading or watching TV.	
3 : Moderate:	I sometimes fall asleep when I should not. For example, while eating or talking with other people.	
4 : Severe:	I often fall asleep when I should not. For example, while eating or talking with other people.	

	SCORE
1.9 PAIN AND OTHER SENSATIONS Over the past week, have you had uncomfortable feelings in your body like pain, aches tingling or cramps? 0 : Normal: No uncomfortable feelings. 1 : Slight: I have these feelings. However, I can do things and be with other people without difficulty. 2 : Mild: These feelings cause some problems when I do things or am with other people. 3 : Moderate: These feelings cause a lot of problems, but they do not stop me from doing things or being with other people 4 : Severe: These feelings stop me from doing things or being with other people.	☐
1.10 URINARY PROBLEMS Over the past week, have you had trouble with urine control? For example, an urgent need to urinate, a need to urinate too often, or urine accidents? 0 : Normal: No urine control problems. 1 : Slight: I need to urinate often or urgently. However, these problems do not cause difficulties with my daily activities.	SCORE ☐

2 : Mild:	Urine problems cause some difficulties with my daily activities. However, I do not have urine accidents	
3 : Moderate:	Urine problems cause a lot of difficulties with my daily activities, including urine accidents	
4 : Severe:	I cannot control my urine and use a protective garment or have a bladder tube.	

	SCORE
1.11 CONSTIPATION PROBLEMS Over the past week have you had constipation troubles that cause you difficulty moving your bowels? 0 : Normal: No constipation. 1 : Slight: I have been constipated. I use extra effort to move my bowels. However, this problem does not disturb my activities or my being comfortable. 2 : Mild: Constipation causes me to have some troubles doing things or being comfortable. 3 : Moderate: Constipation causes me to have a lot of trouble doing things or being comfortable. However, it does not stop me from doing anything. 4 : Severe: I usually need physical help from someone else to empty my bowels.	☐
1.12 LIGHT HEADEDNESS ON STANDING Over the past week, have you felt faint, dizzy or foggy when you stand up after sitting or lying down? 0 : Normal: No dizzy or foggy feelings. 1 : Slight: Dizzy or foggy feelings occur. However, they do not cause me troubles doing things.	☐

2 : Mild:	Dizzy or foggy feelings cause me to hold on to something, but I do not need to sit or lie back down.	
3 : Moderate:	Dizzy or foggy feelings cause me to sit or lie down to avoid fainting or falling.	
4 : Severe:	Dizzy or foggy feelings cause me to fall or faint.	

	SCORE
1.13 FATIGUE Over the past week, have you usually felt fatigued? This feeling is <u>not</u> part of being sleepy or sad 0 : Normal: No fatigue. 1 : Slight: Fatigue occurs. However it does not cause me troubles doing things or being with people. 2 : Mild: Fatigue causes me some troubles doing things or being with people. 3 : Moderate: Fatigue causes me a lot of troubles doing things or being with people. However, it does not stop me from doing anything. 4 : Severe: Fatigue stops me from doing things or being with people.	☐

Part II: Motor Aspects of Experiences of Daily Living (M-EDL)

	SCORE
2.1 SPEECH Over the past week, have you had problems with your speech? 0 : Normal: Not at all (no problems). 1 : Slight:	

	My speech is soft, slurred or uneven, but it does not cause others to ask me to repeat myself.	☐
2 : Mild:	My speech causes people to ask me to occasionally repeat myself, but not every day.	
3 : Moderate:	My speech is unclear enough that others ask me to repeat myself every day even though most of my speech is understood.	
4 : Severe:	Most or all of my speech cannot be understood.	

	SCORE
2.2 SALIVA & DROOLING Over the past week, have you usually had too much saliva during when you are awake or when you sleep? 0 : Normal: Not at all (no problems). 1 : Slight: I have too much saliva, but do not drool. 2 : Mild: I have some drooling during sleep, but none when I am awake. 3 : Moderate: I have some drooling when I am awake, but I usually do not need tissues or a handkerchief. 4 : Severe: I have so much drooling that I regularly need to use tissues or a handkerchief to protect my clothes.	☐
2.3 CHEWING AND SWALLOWING Over the past week, have you usually had problems swallowing pills or eating meals? Do you need your pills cut or crushed or your meals to be made soft, chopped or blended to avoid choking? 0 : Normal: No problems. 1 : Slight: I am aware of slowness in my chewing or increased effort at swallowing, but I do not choke or need to have my food specially prepared.	☐

2 : Mild:	I need to have my pills cut or my food specially prepared because of chewing or swallowing problems, but I have not choked over the past week.	
3 : Moderate:	I choked at least once in the past week.	
4 : Severe:	Because of chewing and swallowing problems, I need a feeding tube.	

	SCORE
2.4 EATING TASKS Over the past week, have you usually had troubles handling your food and using eating utensils? For example, do you have trouble handling finger foods or using forks, knifes, spoons, chopsticks? 0 : Normal: Not at all (No problems). 1 : Slight: I am slow, but I do not need any help handling my food and have not had food spills while eating. 2 : Mild: I am slow with my eating and have occasional food spills. I may need help with a few tasks such as cutting meat. 3 : Moderate: I need help with many eating tasks but can manage some alone. 4 : Severe: I need help for most or all eating tasks.	☐
2.5 DRESSING Over the past week, have you usually had problems dressing? For example, are you slow or do you need help with buttoning, using zippers, putting on or taking off your clothes or jewelry? 0 : Normal: Not at all (no problems). 1 : Slight: I am slow but I do not need help. 2 : Mild: I am slow and need help for a few dressing tasks (buttons, bracelets).	☐

3 : Moderate: I need help for many dressing tasks. 4 : Severe: I need help for most or all dressing tasks.	

	SCORE
2.6 HYGIENE Over the past week, have you usually been slow or do you need help with washing, bathing, shaving, brushing teeth, combing your hair or with other personal hygiene? 0 : Normal: Not at all (No problems). 1 : Slight: I am slow but I do not need any help. 2 : Mild: I need someone else to help me with some hygiene tasks. 3 : Moderate: I need help for many hygiene tasks. 4 : Severe: I need help for most or all of my hygiene tasks.	☐
2.7 HANDWRITING Over the past week, have people usually had trouble reading your handwriting? 0 : Normal: Not at all (no problems). 1 : Slight: My writing is slow, clumsy or uneven, but all words are clear. 2 : Mild: Some words are unclear and difficult to read. 3 : Moderate: Many words are unclear and difficult to read. 4 : Severe: Most or all words cannot be read.	☐

2.8 DOING HOBBIES AND OTHER ACTIVITIES	
Over the past week, have you usually had trouble doing your hobbies or other things that you like to do?	
0 : Normal: Not at all (no problems).	☐
1 : Slight: I am a bit slow but do these activities easily.	
2 : Mild: I have some difficulty doing these activities.	
3 : Moderate: I have major problems doing these activities, but still do most.	
4 : Severe: I am unable to do most or all of these activities.	

	SCORE
2.9 TURNING IN BED Over the past week, do you usually have trouble turning over in bed? 0 : Normal: Not at all (No problems). 1 : Slight: I have a bit of trouble turning, but I do not need any help. 2 : Mild: I have a lot of trouble turning and need occasional help from someone else. 3 : Moderate: To turn over I often need help from someone else. 4 : Severe: I am unable to turn over without help from someone else.	☐
2.10 TREMOR Over the past week, have you usually had shaking or tremor? 0 : Normal: Not at all. I have no shaking or tremor. 1 : Slight: Shaking or tremor occurs but does not cause problems with any activities. 2 : Mild: Shaking or tremor causes problems with only a few activities. 3 : Moderate: Shaking or tremor causes problems with many of my daily activities. 4 : Severe: Shaking or tremor causes problems with most or all activities.	☐

2.11 GETTING OUT OF BED, A CAR, OR A DEEP CHAIR	
Over the past week, have you usually had trouble getting out of bed, a car seat, or a deep chair?	
0 : Normal: Not at all (no problems).	☐
1 : Slight: I am slow or awkward, but I usually can do it on my first try.	
2 : Mild: I need more than one try to get up or need occasional help.	
3 : Moderate: I sometimes need help to get up, but most times I can still do it on my own.	
4 : Severe: I need help most or all of the time.	

	SCORE
2.12 WALKING AND BALANCE Over the past week, have you usually had problems with balance and walking? 0 : Normal: Not at all (No problems). 1 : Slight: I am slightly slow or may drag a leg. I never use a walking aid. 2 : Mild: I occasionally use a walking aid, but I do not need any help from another person. 3 : Moderate: I usually use a walking aid (cane, walker) to walk safely without falling. However, I do not usually need the support of another person. 4 : Severe: I usually use the support of another persons to walk safely without falling.	☐
2.13 FREEZING Over the past week, on your usual day when walking, do you suddenly stop or freeze as if your feet are stuck to the floor; 0 : Normal: Not at all (no problems). 1 : Slight: I briefly freeze but I can easily start walking again. I do not need help from someone else or a walking aid (cane or walker) because of freezing. 2 : Mild: I freeze and have trouble starting to walk again, but I do not need someone's help or a walking aid (cane or walker) because of freezing.	☐

3 : Moderate:	When I freeze I have a lot of trouble starting to walk again and, because of freezing, I sometimes need to use a walking aid or need someone else's help.	
4 : Severe:	Because of freezing, most or all of the time, I need to use a walking aid or someone's help.	

This completes the questionnaire. We may have asked about problems you do not even have, and may have mentioned problems that you may never develop at all. Not all patients develop all these problems, but because they can occur, it is important to ask all the questions to every patient. Thank you for your time and attention in completing this questionnaire.

Part III: Motor Examination

Overview: This portion of the scale assesses the motor signs of PD. In administering Part III of the MDS-UPDRS the examiner should comply with the following guidelines:

At the top of the form, mark whether the patient is on medication for treating the symptoms of Parkinson's disease and, if on levodopa, the time since the last dose.

Also, if the patient is receiving medication for treating the symptoms of Parkinson's Disease, mark the patient's clinical state using the following definitions:

ON is the typical functional state when patients are receiving medication and have a good response.

OFF is the typical functional state when patients have a poor response in spite of taking medications.

The investigator should "rate what you see". Admittedly, concurrent medical problems such as stroke, paralysis, arthritis, contracture, and orthopedic problems such as hip or knee replacement and scoliosis may interfere with individual items in the motor examination. In situations where it is absolutely impossible to test (e.g., amputations, plegia, limb in a cast), use the notation "**UR**" for Unable to Rate. Otherwise, rate the performance of each task as the patient performs in the context of co-morbidities.

All items must have an integer rating (no half points, no missing ratings).

Specific instructions are provided for the testing of each item. These should be followed in all instances. The investigator demonstrates while describing tasks the patient is to perform and rates function immediately thereafter.

For Global Spontaneous Movement and Rest Tremor items (3.14 and 3.17), these items have been placed purposefully at the end of the scale because clinical information pertinent to the score will be obtained throughout the entire examination.

At the end of the rating, indicate if dyskinesia (chorea or dystonia) was present at the time of the examination, and if so, whether these movements interfered with the motor examination.

3a Is the patient on medication for treating the symptoms of Parkinson's disease? ☐ No ☐ Yes

3b If the patient is receiving medication for treating the symptoms of Parkinson's Disease,

mark the patient's clinical state using the following definitions:

☐ ON: On is the typical functional state when patients are receiving medication and have a good response.

☐ OFF: Off is the typical functional state when patients have a poor response in spite of taking medications.

3c Is the patient on Levodopa? ☐ No ☐ Yes

3.C1 If yes, minutes since last levodopa dose: _____

SCORE

3.1 SPEECH

Instructions to examiner: Listen to the patient's free-flowing speech and engage in conversation if necessary. Suggested topics: ask about the patient's work, hobbies, exercise, or how he got to the doctor's office. Evaluate volume, modulation (prosody) and clarity, including slurring, palilalia (repetition of syllables) and tachyphemia (rapid speech, running syllables together).

0 : Normal:	No speech problems.	☐
1 : Slight:	Loss of modulation, diction or volume, but still all words easy to understand.	
2 : Mild:	Loss of modulation, diction, or volume, with a few words unclear, but the overall sentences easy to follow.	
3 : Moderate:	Speech is difficult to understand to the point that some, but not most, sentences are poorly understood	

4 : Severe:	Most speech is difficult to understand or unintelligible.	

3.2 FACIAL EXPRESSION

Instructions to examiner: Observe the patient sitting at rest for 10 seconds, without talking and also while talking. Observe eye-blink frequency, masked facies or loss of facial expression, spontaneous smiling and parting of lips.

0 : Normal:	Normal facial expression.	☐
1 : Slight:	Minimal masked facies manifested only by decreased frequency of blinking.	
2 : Mild:	In addition to decreased eye-blink frequency, Masked facies present in the lower face as well, namely fewer movements around the mouth, such as less spontaneous smiling, but lips not parted.	
3 : Moderate:	Masked facies with lips parted some of the time when the mouth is at rest.	
4 : Severe:	Masked facies with lips parted most of the time when the mouth is at rest.	

	SCORE
3.3 RIGIDITY Instructions to examiner: Rigidity is judged on slow passive movement of major joints with the patient in a relaxed position and the examiner manipulating the limbs and neck. First, test without an activation maneuver. Test and rate neck and each limb separately. For arms, test the wrist and elbow joints simultaneously. For legs, test the hip and knee joints simultaneously. If no rigidity is detected, use an activation maneuver such as tapping fingers, fist opening/closing, or heel tapping in a limb not being tested. Explain to the patient to go as limp as possible as you test for rigidity. 0 : Normal: No rigidity. 1 : Slight: Rigidity only detected with activation maneuver. 2 : Mild: Rigidity detected without the activation maneuver, but full range of motion is easily achieved. 3 : Moderate: Rigidity detected without the activation maneuver; full range of motion is achieved with effort. 4 : Severe: Rigidity detected without the activation maneuver and full range of motion not achieved.	☐ Neck ☐ RUE ☐ LUE ☐ RLE ☐ LLE
3.4 FINGER TAPPING Instructions to examiner: Each hand is tested separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to tap the index finger on the thumb 10 times as quickly AND as big as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0 : Normal: No problems. 1 : Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) the amplitude decrements near the end of the 10 taps. 2 : Mild:	☐ R

	Any of the following: a) 3 to 5 interruptions during tapping; b) mild slowing; c) the amplitude decrements midway in the 10-tap sequence.	
3 : Moderate:	Any of the following: a) more than 5 interruptions during tapping or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st tap.	☐
4 : Severe:	Cannot or can only barely perform the task because of slowing, interruptions or decrements.	L

3.5 HAND MOVEMENTS		**SCORE**
Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to make a tight fist with the arm bent at the elbow so that the palm faces the examiner. Have the patient open the hand 10 times as fully AND as quickly as possible. If the patient fails to make a tight fist or to open the hand fully, remind him/ her to do so. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.		☐
0 : Normal:	No problem.	R
1 : Slight:	Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the task	
2 : Mild:	Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the task.	☐
3 : Moderate:	Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st open-and-close sequence.	L
4 : Severe:	Cannot or can only barely perform the task because of slowing, interruptions or decrements.	

3.6 PRONATION-SUPINATION MOVEMENTS OF HANDS

Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to extend the arm out in front of his/her body with the palms down; then to turn the palm up and down alternately 10 times as fast and as fully as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

0 : Normal:	No problems.	
1 : Slight:	Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the sequence.	☐
2 : Mild:	Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the sequence.	R
3 : Moderate:	Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing c) the amplitude decrements starting after the 1st supination-pronation sequence.	☐
4 : Severe:	Cannot or can only barely perform the task because of slowing, interruptions or decrements.	L

SCORE

3.7 TOE TAPPING

Instructions to examiner: Have the patient sit in a straight-backed chair with arms, both feet on the floor. Test each foot separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the heel on the ground in a comfortable position and then tap the toes 10 times as big and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

0 : Normal:	No problem.
1 : Slight:	

	Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) amplitude decrements near the end of the ten taps.	☐
2 : Mild:	Any of the following: a) 3 to 5 interruptions during the tapping movements; b) mild slowing; c) amplitude decrements midway in the task.	R
3 : Moderate:	Any of the following: a) more than 5 interruptions during the tapping movements or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) amplitude decrements after the first tap.	
4 : Severe:	Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐
		L

3.8 LEG AGILITY

Instructions to examiner: Have the patient sit in a straight-backed chair with arms. The patient should have both feet comfortably on the floor. Test each leg separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the foot on the ground in a comfortable position and then raise and stomp the foot on the ground 10 times as high and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

0 : Normal:	No problems.	
1 : Slight:	Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) amplitude decrements near the end of the task.	
2 : Mild:	Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowness; c) amplitude decrements midway in the task..	☐
3 : Moderate:	Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing in speed; c) amplitude decrements after the first tap.	R
4 : Severe:	Cannot or can only barely perform the task because of slowing, interruptions or decrements.	

	L
3.9 ARISING FROM CHAIR Instructions to examiner: Have the patient sit in a straight-backed chair with arms, with both feet on the floor and sitting back in the chair (if the patient is not too short). Ask the patient to cross his/her arms across the chest and then to stand up. If the patient is not successful, repeat this attempt a maximum up to two more times. If still unsuccessful, allow the patient to move forward in the chair to arise with arms folded across the chest. Allow only one attempt in this situation. If unsuccessful, allow the patient to push off using his/her hands on the arms of the chair. Allow a maximum of three trials of pushing off. If still not successful, assist the patient to arise. After the patient stands up, observe the posture for item 3.13 0 : Normal: No problem. Able to arise quickly without hesitation. 1 : Slight: Arising is slower than normal; or may need more than one attempt; or may need to move forward in the chair to arise. No need to use the arms of the chair. 2 : Mild: Pushes self up from arms of chair without difficulty. 3 : Moderate: Needs to push off, but tends to fall back; or may have to try more than one time using arms of chair, but can get up without help. 4 : Severe: Unable to arise without help.	**SCORE**
3.10 GAIT	

Instructions to examiner: Testing gait is best performed by having the patient walking away from and towards the examiner so that both right and left sides of the body can be easily observed simultaneously. The patient should walk at least 10 meters (30 feet), then turn around and return to the examiner. This item measures multiple behaviors: stride amplitude, stride speed, height of foot lift, heel strike during walking, turning, and arm swing, but not freezing. Assess also for "freezing of gait" (next item 3.11) while patient is walking. Observe posture for item 3.13 0 : Normal: No problems. 1 : Slight: Independent walking with minor gait impairment. 2 : Mild: Independent walking but with substantial gait impairment. 3 : Moderate: Requires an assistance device for safe walking (walking stick, walker) but not a person. 4 : Severe: Cannot walk at all or only with another person's assistance.	☐
3.11 FREEZING OF GAIT Instructions to examiner: While assessing gait, also assess for the presence of any gait freezing episodes. Observe for start hesitation and stuttering movements especially when turning and reaching the end of the task. To the extent that safety permits, patients may NOT use sensory tricks during the assessment. 0 : Normal: No freezing. 1 : Slight: Freezes on starting, turning or walking through doorway with a single halt during any of these events, but then continues smoothly without freezing during straight walking. 2 : Mild: Freezes on starting, turning or walking through doorway with more than one halt during any of these activities, but continues smoothly without freezing during straight walking. 3 : Moderate: Freezes once during straight walking.	**SCORE** ☐

4 : Severe:	Freezes multiple times during straight walking.	

3.12 POSTURAL STABILITY

Instructions to examiner: The test examines the response to sudden body displacement produced by a quick, forceful pull on the shoulders while the patient is standing erect with eyes open and feet comfortably apart and parallel to each other. Test retropulsion. Stand behind the patient and instruct the patient on what is about to happen. Explain that s/he is allowed to take a step backwards to avoid falling. There should be a solid wall behind the examiner, at least 1-2 meters away to allow for the observation of the number of retropulsive steps. The first pull is an instructional demonstration and is purposely milder and not rated. The second time the shoulders are pulled briskly and forcefully towards the examiner with enough force to displace the center of gravity so that patient MUST take a step backwards. The examiner needs to be ready to catch the patient, but must stand sufficiently back so as to allow enough room for the patient to take several steps to recover independently. Do not allow the patient to flex the body abnormally forward in anticipation of the pull. Observe for the number of steps backwards or falling. Up to and including two steps for recovery is considered normal, so abnormal ratings begin with three steps. If the patient fails to understand the test, the examiner can repeat the

test so that the rating is based on an assessment that the examiner feels reflects the patient's limitations rather than misunderstanding or lack of preparedness. Observe standing posture for item 3.13

0 : Normal:	No problems: Recovers with one or two steps.	
1 : Slight:	3-5 steps, but subject recovers unaided.	
2 : Mild:	More than 5 steps, but subject recovers unaided.	
3 : Moderate:	Stands safely, but with absence of postural response; falls if not caught by examiner.	
4 : Severe:	Very unstable, tends to lose balance spontaneously or with just a gentle pull on the shoulders.	

SCORE

3.13 POSTURE

Instructions to examiner: Posture is assessed with the patient standing erect after arising from a chair, during walking, and while being tested for postural reflexes. If you notice poor posture, tell the patient to stand up straight and see if the posture improves (see option 2 below). Rate the worst posture seen in these three observation points. Observe for flexion and side-to-side leaning.

0 : Normal:	No problems.	

1 : Slight:	Not quite erect, but posture could be normal for older person.	☐
2 : Mild:	Definite flexion, scoliosis or leaning to one side, but patient can correct posture to normal posture when asked to do so.	
3 : Moderate:	Stooped posture, scoliosis or leaning to one side that cannot be corrected volitionally to a normal posture by the patient.	
4 : Severe:	Flexion, scoliosis or leaning with extreme abnormality of posture.	

3.14 GLOBAL SPONTANEITY OF MOVEMENT (BODY BRADYKINESIA)

Instructions to examiner: This global rating combines all observations on slowness, hesitancy, and small amplitude and poverty of movement in general, including a reduction of gesturing and of crossing the legs. This assessment is based on the examiner's global impression after observing for spontaneous gestures while sitting, and the nature of arising and walking.

0 : Normal:	No problems.	☐
1 : Slight:	Slight global slowness and poverty of spontaneous movements.	
2 : Mild:	Mild global slowness and poverty of spontaneous movements.	
3 : Moderate:	Moderate global slowness and poverty of spontaneous movements.	
4 : Severe:	Severe global slowness and poverty of spontaneous movements.	

3.15 POSTURAL TREMOR OF THE HANDS

Instructions to examiner: All tremor, including re-emergent rest tremor, that is present in this posture is to be included in this rating. Rate each hand separately. Rate the highest amplitude seen. Instruct the patient to stretch the arms out in front of the body with palms down. The wrist should be straight and the fingers comfortably separated so that they do not touch each other. Observe this posture for 10 seconds.

0 : Normal:	No tremor.	☐ R
1 : Slight:	Tremor is present but less than 1 cm in amplitude.	
2 : Mild:	Tremor is at least 1 but less than 3 cm in amplitude.	☐
3 : Moderate:	Tremor is at least 3 but less than 10 cm in amplitude.	

4 : Severe: Tremor is at least 10 cm in amplitude.	L
3.16 KINETIC TREMOR OF THE HANDS Instructions to examiner: This is tested by the finger-to-nose maneuver. With the arm starting from the outstretched position, have the patient perform at least three finger-to-nose maneuvers with each hand reaching as far as possible to touch the examiner's finger. The finger-to-nose maneuver should be performed slowly enough not to hide any tremor that could occur with very fast arm movements. Repeat with the other hand, rating each hand separately. The tremor can be present throughout the movement or as the tremor reaches either target (nose or finger). Rate the highest amplitude seen. 0 : Normal: No tremor. 1 : Slight: Tremor is present but less than 1 cm in amplitude. 2 : Mild: Tremor is at least 1 but less than 3 cm in amplitude. 3 : Moderate: Tremor is at least 3 but less than 10 cm in amplitude. 4 : Severe: Tremor is at least 10 cm in amplitude.	**SCORE** ☐ R ☐ L
3.17 REST TREMOR AMPLITUDE Instructions to examiner: This and the next item have been placed purposefully at the end of the rater to gather observations on rest tremor that may appear at any time during the exam, including when quietly sitting, during walking and during activities when some body parts are moving but others are at rest. Score the maximum amplitude that is seen at any time as the final score. Rate only the amplitude and not the persistence or the intermittency of the tremor. As part of the rating, the patient should sit quietly in a chair with the hands placed on the arms of the chair (not in the lap) and the feet comfortably supported on the floor for 10 seconds with no other directives. Rest tremor is assessed separately for all four limbs and also for the lip/jaw. Rate only the maximum amplitude that is seen at any time as the final rating. **Extremity ratings** 0 : Normal: No tremor. 1 : Slight: < 1 cm in maximal amplitude. 2 : Mild: > 1 cm but < 3 cm in maximal amplitude. 3 : Moderate: 3 - 10 cm in maximal amplitude.	☐ RUE ☐ LUE ☐ RLE

4 : Severe:	> 10 cm in maximal amplitude.	
Lip/Jaw ratings		
0 : Normal:	No tremor.	LLE
1 : Slight:	< 1 cm in maximal amplitude.	
2 : Mild:	> 1 cm but < 2 cm in maximal amplitude.	
3 : Moderate:	> 2 cm but < 3 cm in maximal amplitude.	Lip/Jaw
4 : Severe:	> 3 cm in maximal amplitude.	

3.18 CONSTANCY OF REST TREMOR		**SCORE**
Instructions to examiner: This item receives one rating for all rest tremor and focuses on the constancy of rest tremor during the examination period when different body parts are variously at rest. It is rated purposefully at the end of the examination so that several minutes of information can be coalesced into the rating.		
0 : Normal:	No tremor.	
1 : Slight:	Tremor at rest is present < 25% of the entire examination period.	
2 : Mild:	Tremor at rest is present 26-50% of the entire examination period.	
3 : Moderate:	Tremor at rest is present 51-75% of the entire examination period.	
4 : Severe:	Tremor at rest is present > 75% of the entire examination period.	

DYSKINESIA IMPACT ON PART III RATINGS

A. Were dyskinesias (chorea or dystonia) present during examination? □ No □ Yes

B. If yes, did these movements interfere with your ratings? □ No □ Yes

HOEHN AND YAHR STAGE

0: Asymptomatic.

1: Unilateral involvement only.

2: Bilateral involvement without impairment of balance.

3: Mile to moderate involvement; some postural instability but physically independent; needs assistance to recover from pull test.

4: Severe disability; still able to walk or stand unassisted.

5: Wheelchair bound or bedridden unless aided.

Part IV: Motor Complications

Overview and Instructions: In this section, the rater uses historical and objective information to assess two motor complications, dyskinesias and motor fluctuations that include OFF-state dystonia. Use all information from patient, caregiver, and the examination to answer the six questions that summarize function over the past week including today. As in the other sections, rate using only integers (no half points allowed) and leave no missing ratings. If the item cannot be rated, place UR for Unable to Rate. You will need to choose some answers based on percentages, and therefore you will need to establish how many hours generally are awake hours and use this figure as the denominator for “OFF” time and Dyskinesias. For “OFF dystonia”, the total “Off” time will be the denominator.

Operational definitions for examiner’s use.

Dyskinesias: Involuntary random movements

Words that patients often recognize for dyskinesias include “irregular jerking”, “wiggling”, “twitching”. It is essential to stress to the patient the difference between dyskinesias and tremor, a common error when patients are assessing dyskinesias.

Dystonia: contorted posture, often with a twisting component:

Words that patients often recognize for dystonia include “spasms”, “cramps”, “posture”.

Motor fluctuation: Variable response to medication:

Words that patients often recognize for motor fluctuation include “wearing out”, “wearing off”, “roller-coaster effect”, “on-off”, “uneven medication effects”.

OFF: Typical functional state when patients have a poor response in spite of taking mediation or the typical functional response when patients are on NO treatment for parkinsonism. Words that patients often recognize include “low time”, “bad time”, “shaking time”, “slow time”, “time when my medications don’t work.”

ON: Typical functional state when patients are receiving medication and have a good response:

Words that patients often recognize include “good time”, “walking time”, “time when my medications work.”

A . DYSKINESIAS [exclusive of OFF-state dystonia]

SCORE

4.1 TIME SPENT WITH DYSKINESIAS

Instructions to examiner: Determine the hours in the usual waking day and then the hours of dyskinesias. Calculate the percentage. If the patient has dyskinesias in the office, you can point them out as a reference to ensure that patients and caregivers understand what they are rating. You may also use your own acting skills to enact the dyskinetic movements you have seen in the patient before or show them dyskinetic movements typical of other patients. Exclude from this question early morning and nighttime painful dystonia.

Instructions to patient [and caregiver]. Over the past week, how many hours do you usually sleep on a daily basis, including nighttime sleep and daytime napping? Alright, if you sleep ___ hrs, you are awake ____ hrs. Out of those awake hours, how many hours in total do you have wiggling, twitching or jerking movements? Do not count the times when you have tremor, which is a regular back and forth shaking or times when you have painful foot cramps or spasms in the early morning or at nighttime. I will ask about those later. Concentrate only on these types of wiggling, jerking and irregular movements. Add up all the time during the waking day when these usually occur. How many hours ____ (use this number for your calculation).

0 : Normal: No dyskinesias.

1 : Slight: ≤ 25% of waking day.

2 : Mild: 26 - 50% of waking day.

3 : Moderate: 51 - 75% of waking day.

1. Total Hours awake: _____

2. Total hours with dyskinesia: _____

4 : Severe:	> 75% of waking day.	3. % Dyskinesia = ((2/1)*100): _____	

4.2 FUNCTIONAL IMPACT OF DYSKINESIAS **SCORE**

Instructions to examiner: Determine the degree to which dyskinesias impact on the patient's daily function in terms of activities and social interactions. Use the patient's and caregiver's response to your question and your own observations during the office visit to arrive at the best answer.

Instructions to patient [and caregiver]: Over the past week, did you usually have trouble doing things or being with people when these jerking movements occurred? Did they stop you from doing things or from being with people?

0 : Normal:	No dyskinesias or no impact by dyskinesias on activities or social interactions.	
1 : Slight:	Dyskinesias impact on a few activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods.	
2 : Mild:	Dyskinesias impact on many activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods.	☐
3 : Moderate:	Dyskinesias impact on activities to the point that the patient usually does not perform some activities or does not usually participate in some social activities during dyskinetic episodes.	
4 : Severe:	Dyskinesias impact on function to the point that the patient usually does not perform most activities or participate in most social interactions during dyskinetic episodes.	

B. MOTOR FLUCTUATIONS

4.3 TIME SPENT IN THE OFF STATE

Instructions to examiner: Use the number of waking hours derived from 4.1 and determine the hours spent in the "OFF" state. Calculate the percentage. If the patient has an OFF period in the office, you can point to this state as a reference. You may also use your knowledge of the patient to describe a typical OFF period. Additionally you may use your own acting skills to enact an OFF period you have seen in the patient before or show them OFF function typical of other patients. Mark down the typical number of OFF hours, because you will need this number for completing 4.6.

Instructions to patient [and caregiver]: Some patients with Parkinson's disease have a good effect from their medications throughout their awake hours and we call that "ON" time. Other patients take their medications but still have some hours of low time, bad time, slow time or shaking time. Doctors call these low periods "OFF" time. Over the past week, you told me before that you are generally awake ____ hrs each day. Out of these awake hours, how many hours in total do you usually have this type of low level or OFF function ____ (Use this number for your calculations).

0 : Normal:	No OFF time.		
1 : Slight:	≤ 25% of waking day.		
		1. Total Hours awake: _____	
2 : Mild:	26 - 50% of waking day.		
		2. Total hours OFF: _____	
3 : Moderate:	51 - 75% of waking day.		
		3. % OFF = ((2/1)*100): _____	☐
4 : Severe:	> 75% of waking day.		

4.4 FUNCTIONAL IMPACT OF FLUCTUATIONS		**SCORE**
Instructions to examiner: Determine the degree to which motor fluctuations impact on the patient's daily function in terms of activities and social interactions. This question concentrates on the difference between the ON state and the OFF state. If the patient has no OFF time, the rating must be 0, but if patients have very mild fluctuations, it is still possible to be rated 0 on this item if no impact on activities occurs. Use the patient's and caregiver's response to your question and your own observations during the office visit to arrive at the best answer.		
Instructions to patient [and caregiver]: Think about when those low or "OFF" periods have occurred over the past week. Do you usually have more problems doing things or being with people than compared to the rest of the day when you feel your medications working? Are there some things you usually do during a good period that you have trouble with or stop doing during a low period?		
0 : Normal:	No fluctuations or No impact by fluctuations on performance of activities or social interactions.	
1 : Slight:	Fluctuations impact on a few activities, but during OFF, the patient usually performs all activities and participates in all social interactions that typically occur during the ON state.	☐
2 : Mild:	Fluctuations impact many activities, but during OFF, the patient still usually performs all activities and participates in all social interactions that typically occur during the ON state.	
3 : Moderate:	Fluctuations impact on the performance of activities during OFF to the point that the patient usually does not perform some activities or participate in some social interactions that are performed during ON periods.	
4 : Severe:	Fluctuations impact on function to the point that, during OFF, the patient usually does not perform most activities or participate in most social interactions that are performed during ON periods.	

4.5 COMPLEXITY OF MOTOR FLUCTUATIONS

Instructions to examiner: Determine the usual predictability of OFF function whether due to dose, time of day, food intake or other factors. Use the information provided by the patients and caregiver and supplement with your own observations. You will ask if the patient can count on them always coming at a special time, mostly coming at a special time (in which case you will probe further to separate slight from mild), only sometimes coming at a special time or are they totally unpredictable? Narrowing down the percentage will allow you to find the correct answer.

Instructions to patient [and caregiver]: For some patients, the low or "OFF" periods happen at certain times during day or when they do activities like eating or exercising. Over the past week, do you usually know when your low periods will occur? In other words, do your low periods always come at a certain time? Do they mostly come at a certain time? Do they only sometimes come at a certain time? Are your low periods totally unpredictable?"

0 : Normal:	No motor fluctuations.
1 : Slight:	OFF times are predictable all or almost all of the time (> 75%).
2 : Mild:	OFF times are predictable most of the time (51-75%).
3 : Moderate:	OFF times are predictable some of the time (26-50%).
4 : Severe:	OFF episodes are rarely predictable. (< 25%).

C. "OFF" DYSTONIA

4.6 PAINFUL OFF-STATE DYSTONIA

Instructions to examiner: For patients who have motor fluctuations, determine what proportion of the OFF episodes usually includes painful dystonia? You have already determined the number of hours of "OFF" time (4.3). Of these hours, determine how many are associated with dystonia and calculate the percentage. If there is no OFF time, mark 0.

Instructions to patient [and caregiver]: In one of the questions I asked earlier, you said you generally have ___ hours of low or "OFF" time when your Parkinson's disease is under poor control. During these low or "OFF" periods, do you usually have painful cramps or spasms? Out of the total ____ hrs of this low time, if you add up all the time in a day when these painful cramps come, how many hours would this make?

0 : Normal:	No dystonia OR NO OFF TIME.
1 : Slight:	< 25% of time in OFF state.
2 : Mild:	26-50% of time in OFF state.
3 : Moderate:	51-75% of time in OFF state.

4 : Severe: > 75% of time in OFF state. 1. Total hours Off: _____ 2. Total Off Hours w/Dystonia: _____ 3. % Off Dystonia = ((2/1)*100): _____		☐

Summary statement to patient: READ TO PATIENT

This completes my rating of your Parkinson's disease. I know the questions and tasks have taken several minutes, but I wanted to be complete and cover all possibilities. In doing so, I may have asked about problems you do not even have, and I may have mentioned problems that you may never develop at all. Not all patients develop all these problems, but because they can occur, it is important to ask all the questions to every patient. Thank you for your time and attention in completing this scale with me.

_____	___ ___ ___	__ __ - __ __ - __ __ __ __	___ ___ ___
Patient Name or Subject ID	Site ID	(mm-dd-yyyy) Assessment date	Investigator's Initials

MDS UPDRS Score Sheet

1.A.	Source of information	☐ Patient ☐Caregiver ☐ Patient + Caregiver	3.3b	Rigidity– RUE	
			3.3c	Rigidity– LUE	
Part I			3.3d	Rigidity– RLE	
1.1	Cognitive impairment		3.3e	Rigidity– LLE	
1.2	Hallucinations and psychosis		3.4a	Finger tapping– Right hand	
1.3	Depressed mood		3.4b	Finger tapping– Left hand	
1.4	Anxious mood		3.5a	Hand movements–	
1.5	Apathy		3.5b	Hand movements–	
1.6	Features of DDS		3.6a	Pronation- supination movements– Right hand	
1.6a	Who is filling out questionnaire	☐ Patient ☐Caregiver ☐ Patient + Caregiver	3.6b	Pronation- supination movements– Left hand	
			3.7a	Toe tapping–Right foot	
1.7	Sleep problems		3.7b	Toe tapping–Left foot	
1.8	Daytime sleepiness		3.8a	Leg agility– Right leg	
1.9	Pain and other sensations		3.8b	Leg agility– Left leg	
1.10	Urinary problems		3.9	Arising from chair	
1.11	Constipation problems		3.10	Gait	
1.12	Light headedness on standing		3.11	Freezing of gait	
1.13	Fatigue		3.12	Postural stability	
Part II			3.13	Posture	
2.1	Speech		3.14	Global spontaneity of movement	
2.2	Saliva and drooling		3.15a	Postural tremor– Right hand	
2.3	Chewing and swallowing		3.15b	Postural tremor– Left hand	
2.4	Eating tasks		3.16a	Kinetic tremor– Right hand	
2.5	Dressing		3.16b	Kinetic tremor– Left hand	
2.6	Hygiene		3.17a	Rest tremor amplitude– RUE	
2.7	Handwriting		3.17b	Rest tremor amplitude– LUE	
2.8	Doing hobbies and other activities		3.17c	Rest tremor amplitude– RLE	

2.9	Turning in bed		3.17d	Rest tremor amplitude– LLE	
2.10	Tremor		3.17e	Rest tremor amplitude– Lip/jaw	
2.11	Getting out of bed		3.18	Constancy of rest	
2.12	Walking and balance			Were dyskinesias present	☐No ☐Yes
2.13	Freezing			Did these movements interfere with ratings?	☐No ☐Yes
3a	Is the patient on medication?	☐No ☐Yes		Hoehn and Yahr Stage	
3b	Patient's clinical state	☐Off ☐On	**Part IV**		
3c	Is the patient on Levodopa?	☐No ☐Yes	4.1	Time spent with dyskinesias	
3.C1	If yes, minutes since last dose:		4.2	Functional impact of dyskinesias	
Part III			4.3	Time spent in the OFF state	
3.1	Speech		4.4	Functional impact of fluctuations	
3.2	Facial expression		4.5	Complexity of motor fluctuations	
3.3a	Rigidity– Neck		4.6	Painful OFF-state dystonia	

FAIRPARK

Patient / Caregiver Questionnaire

Patient ID:

(Please fill in patient ID of the Minimal Data Set)

THIS PAGE TO BE KEPT AT STUDY CENTER

(Please fill in patient ID of the Minimal Data Set)

Patient ID ☐☐☐☐☐☐

FAIRPARK

Patient Questionnaire

Dear Patient,

Dear Caregiver,

Thank you very much for your support. After your physician has explained the observational study to you he is asked to fill in a short questionnaire regarding your clinical data.

Moreover, we would like to ask you to fill in this questionnaire. The questionnaire is concerned with the course of your illness and the financial burden of the disease. Additionally we would like to ask you to provide information regarding your quality of life.

If you should have any further questions, please do not hesitate to contact us.

Thank you very much for your cooperation!

Persons for contact:

Ms Dr. _____ Mr _____

Phone: _____ Phone: _____

_____

Address:

Personal data of the patient (e.g. health insurance, profession)

Marital status of the patient

- ☐ Married / in relationship
- ☐ Divorced / living apart
- ☐ Single
- ☐ Widowed

What type of health insurance do you have?

- ☐ Compulsory health insurance
- ☐ Private health insurance

Are you free from co-payments (e.g. for medication)?

- ☐ No
- ☐ Yes

Are you classified within the compulsory long term care insurance?

- ☐ No
- ☐ Yes, if yes please tick box

- ☐ Level of caring 0
- ☐ Level of caring 1
- ☐ Level of caring 2
- ☐ Level of caring 3

What is your current employment situation (patient)?

- ☐ Employee full time
- ☐ Employee part time, _____hours/week
- ☐ Worker full time
- ☐ Worker part time, _____hours/week
- ☐ Self-employed
- ☐ Housewife/househusband

- ☐ Unable to work due to Parkinson's disease and its subsequent illnesses, starting ☐☐☐☐ *m m y y*

☐ Unable to work due to other reasons, starting ☐☐☐☐ m m y

☐ Unemployed due to Parkinson's disease and its subsequent illnesses, starting ☐☐☐☐ m m y

☐ Unemployed due to other reasons, starting ☐☐☐☐ m m y

☐ Early retirement due to Parkinson's disease and its subsequent illnesses, starting ☐☐☐☐ m m y

☐ Early retirement due to other reasons, starting ☐☐☐☐ m m y

☐ Old age pensioner, starting ☐☐☐☐ m m y

Please specify the patient's current living accommodation.

☐ Own home (owner occupied or rented)

☐ Intermediate forms of accommodation

☐ Residential acomodation

☐ Long-term institutional care

☐ Other

During the last 30 days, if the patient temporarily changed living accommodations (i.e. moved to a new location for more than 24 hours and then back to the original location), please specify the number of nights spent in this temporary living accommodation.

Number of nights

Own home (owner occupied or rented) ___

Intermediate forms of accommodation ___

Dementia-specific residential accommodation ___

Long-term institutional care ___

Other ___

For each service listed below, please specify the number of times the service was received since the last 30 days and the average number of hours per visit.

☐ The patient did not receive any of these services during the last 30 days

Service	Number of visits since the last visit	Number of hours per visit
District nurse		
Home aid/orderly		
Food delivery		N/A
Day care		
Transportation (care related)		N/A
Other (e.g. please specify)		

Have you been absent from work during the past 3 months due to Parkinson's disease?

IMPORTANT: If you were treated in hospital as an in-patient or were on a cure please do not include these days!

☐ No

☐ Yes Number of days*: ___ in 3 Months

IMPORTANT: * Please do also include single hours per working day (e.g. 4 hours Working days)

Consultation of Physicians

Is your primary physician for Parkinson's disease a General Practitioner or has she/he specialised in another medical field?

General Practitioner ☐

Specialist for internal medicine ☐

Neurologist ☐

Others, *please specify* _____ ☐
(e.g. Geriatrician)

How often did you see your primary physician during the past 3 months due to Parkinson's disease?

If so, how much did you pay yourself? (you did not get reimbursed)

Number of visits	Amount paid by yourself per visit
☐☐ visits	☐☐☐ Euro *(no Cents)*

Did you see further doctors/specialists in addition to seeing your primary physician who is treating you for Parkinson's disease during the past 3 months due to Parkinson's disease? *If so, how much did you pay yourself? (you did not get reimbursed)*

Physician / Specialist	Number of visits	Amount paid by yourself per visit
☐ Specialist for internal medicine	☐☐ visits	☐☐☐ Euro *(no Cents)*
☐ Psychologist	☐☐ visits	☐☐☐ Euro *(no Cents)*
☐ Physician for natural treatment	☐☐ visits	☐☐☐ Euro *(no Cents)*
☐ Homeopath/non-medical	☐☐ visits	☐☐☐ Euro *(no Cents)*
☐ Specialist in _____	☐☐ visits	☐☐☐ Euro *(no Cents)*
☐ Specialist in _____	☐☐ visits	☐☐☐ Euro *(no Cents)*
☐ Specialist in _____	☐☐ visits	☐☐☐ Euro *(no Cents)*
☐ Physiotherapist	☐☐ visits	☐☐☐ Euro *(no Cents)*
☐ Nutrition consultant	☐☐ visits	☐☐☐ Euro *(no Cents)*

Did you receive further therapy during the past 3 months due to Parkinson's disease?

If so, how much did you pay yourself? (you did not get reimbursed)

Therapy	Number of visits	Amount paid by yourself per visit
☐ Physiotherapy	☐☐ visits	☐☐☐ Euro *(no Cents)*
☐ massage	☐☐ visits	☐☐☐ Euro *(no Cents)*
☐ occupational therapy	☐☐ visits	☐☐☐ Euro *(no Cents)*
☐ speech training	☐☐ visits	☐☐☐ Euro *(no Cents)*
☐ others, which ones _____	☐☐ visits	☐☐☐ Euro *(no Cents)*
☐ others, which ones _____	☐☐ visits	☐☐☐ Euro *(no Cents)*
☐ others, which ones _____	☐☐ visits	☐☐☐ Euro *(no Cents)*
☐ others, which ones _____	☐☐ visits	☐☐☐ Euro *(no Cents)*
☐ others, which ones _____	☐☐ visits	☐☐☐ Euro *(no Cents)*

Out-patient treatment in hospital

Did you have an out-patient hospital treatment during the past 3 months (without overnight stay)?

☐ No

☐ Yes If "yes", how often? ____ times

Due to Parkinson's Disease? Yes ☐ No ☐

In-patient treatment in hospital

Were you treated as an in-patient in hospitals during the past 3 months (at least one night) due to Parkinson's disease?

If so, please indicate the reason and the length of the hospital stay as well as the description of the ward.

Reason for hospital stay	**Was your hospitalisation related to Parkinson's disease ?**		**Specification of ward** (e.g. internal ward)	**Length of stay** (e.g. 10 days) *e.g.: 1 0 days*		
	Yes	**No**				
						days
						days
						days
						days

Within the framework of the above-mentioned hospital stay, did you have to pay for the costs yourself?

☐ No

☐ Yes

If „yes", what and how much did you have to pay?

Costs			Amount paid by you (Euro)
Co-payments	☐ Yes	☐ No	
Travel costs:	☐ Yes	☐ No	
- travelled with own car	☐ Yes	☐ No	km travelled (one way): km

- by public transport	☐ Yes	☐ No	_____
Others	☐ Yes	☐ No	_____

Did you stay at a rehabilitation facility during the past 3 months ?

☐ No

☐ Yes

If ”yes”, how many days did you spend as an in-patient (at least one night) or as an out-patient in a rehabilitation facility ? Please do also count the day of admittance and the day of discharge as a full day.

In-patient	**Out-patient**	**Length of stay (in days)**
☐	☐	_____ days
☐	☐	_____ days
☐	☐	_____ days

Did you have to pay for the costs within the framework of the above-mentioned rehabilitation?

☐ No

☐ Yes

If „yes“, what and how much did you have to pay?

Costs			Amount paid by you (Euros)
Co-payment for stay	☐ Yes	☐ No	
Co-payment for food	☐ Yes	☐ No	
Co-payment for therapeutic measures	☐ Yes	☐ No	
Travel costs:	☐ Yes	☐ No	
- travelled with own car	☐ Yes	☐ No	km travelled (one way): km
- by public transport	☐ Yes	☐ No	
Stay	☐ Yes	☐ No	
Food	☐ Yes	☐ No	
Others	☐ Yes	☐ No	

Did you take any medication during the past 3 months which was without prescription (not prescribed by a physician and paid for by yourself) ? (Please include all sorts of medication, also e.g. vitamins such as vitamin C or vitamin E, herbal medicines, enzymes etc.)

Name of the medication	**Approximately how much did you spend on this medication during the past 3 months?**

Indications to the additional financial burden for medical devices etc. during the past 3 months

Did you get any medical devices during the past 3 months ?

Yes ☐ No ☐

Medical devices	Number	co-payment by patient	by compulsory health insurance	by private health insurance	Date Month and year
Crutch	☐	_____	_____	_____	☐☐☐☐ *m m y y*
Walking vehicle	☐	_____	_____	_____	☐☐☐☐ *m m y y*
Handrail	☐	_____	_____	_____	☐☐☐☐ *m m y y*
Special bed	☐	_____	_____	_____	☐☐☐☐ *m m y y* *m m y y*
Others _____	☐	_____	_____	_____	☐☐☐☐ *m m y y*
Others _____	☐	_____	_____	_____	☐☐☐☐

m m y y

Were there any other financial burdens due to Parkinson's disease within the past 3 months which were not covered by the questionnaire? Please feel free to use this space for your comments.

Patient: Health Questionnaire EQ-5D

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking around ❑

I have some problems in walking around ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

Iam unble to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

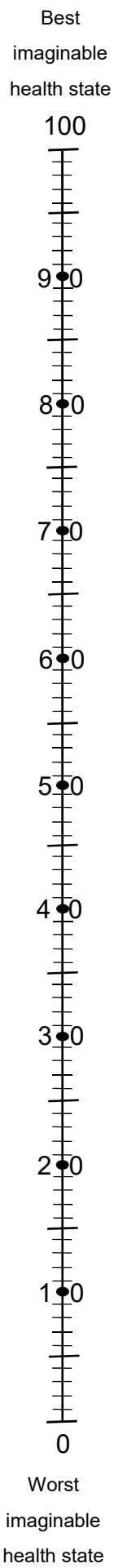
I am moderately anxious or depressed ❑

I am extermely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today

Your own health state today



Assistant Persons - Caregivers

Sociodemographic data of assistant person/caregiver

Age: __ __ years

Gender: ☐ male ☐ female

What relationship do you have to the person?

Spouse ☐

Sibling ☐

Child ☐

Others : _____

Do you live together with the patient?

Yes ☐ No ☐

Does the patient need help in your daily life from assistant persons/caregivers?

Yes ☐

if yes, please answer the following questions

Who assists you?

care service / day ☐ , ☐☐ hours

private persons / day ☐ , ☐☐ hours

No ☐

if no, please continue with question &&

How many other assistant persons/caregivers help with the care of the patient?

0 ☐

1 ☐

2 ☐

3 ☐

4 or more ☐

Among all assistant persons/caregivers what is your level of contribution?

1-20% ☐

21-40% ☐

41-60% ☐

61-80% ☐

81-100% ☐

On a typical care day during the last 30 days, how much time per day and night did you spend asleep?

☐☐ hours and ☐☐ minutes per day and night

On a typical care day during the last 30 days, how much time per day did you assist the

patient with tasks such as toilet visits, eating, dressing, grooming, walking and bathing?

☐☐ hours and ☐☐ minutes per day and night

During the last 30 days, how many days did you spend providing these services to the patient?

☐☐ days

On a typical care day during the last 30 days, how much time per day did you assist the patient with tasks such as shopping, food preparation, housekeeping, laundry, transportation, taking medication and managing financial matters?

☐☐ hours and ☐☐ minutes per day

During the last 30 days, how many days did you spend providing these services to the patient?

☐☐ days

On a typical care day during the last 30 days, how much time per day did you spend supervising (that is, prevent dangerous events) the patient?

☐☐ hours and ☐☐ minutes per day

During the last 30 days, how many days did you spend providing these services to the patient?

☐☐ days

In which employment is the assistant person/caregiver?

Does the assistant person work?	Yes ☐ No ☐ if no, please continue with question &&	
Is the assistant person part-time or full time working	part-time ☐	full-time ☐
Part time due to Parkinson's disease of the cared person? ☐ yes ☐ no	*If part-time working:* When did the assistant person start part-time work ?	since ☐☐☐☐ *m m y y*

How many hours per week? ☐☐

hours/week

Has working been stopped due to Parkinson's disease of the cared person?

☐ yes ☐ no

In case the person stopped working:

When did the assistant person stop working ?

since: ☐☐☐☐

m m y y

Was there any change due to Parkinson's disease?

no ☐

release ☐

early retirement ☐

others (retraining) ☐ _____

Has the assistant person/caregiver been absent from work during the past 3 months due to caregiving to the patient?

IMPORTANT: If you were treated in hospital as an in-patient or were on a cure please do not include these days!

☐ No

☐ Yes Number of days*: ☐☐☐ in 3 Months

IMPORTANT: * Please do also include single hours per working day (e.g. 4 hours Working days)

Yes ☐ No ☐

Which ones? _____

_____

_____

_____

Are there any known diseases the assistant person suffers from?

How often did the assistant person/caregiver visit your primary physician during the past 3 months?

If so, how much did you pay yourself? (you did not get reimbursed)

Number of visits	Amount paid by yourself per visit
☐☐ visits	☐☐☐ Euro *(no Cents)*

Did assistant person/caregiver see further doctors/specialists in addition to seeing your primary physician during the past 3 months? ***If so, how much did you pay yourself? (you did not get reimbursed)***

Physician / Specialist	Number of visits	Amount paid by yourself per visit
☐ Specialist for internal medicine	☐☐ visits	☐☐☐ Euro *(no Cents)*
☐ Psychologist	☐☐ visits	☐☐☐ Euro *(no Cents)*
☐ Physician for natural treatment	☐☐ visits	☐☐☐ Euro *(no Cents)*
☐ Homeopath/non-medical	☐☐ visits	☐☐☐ Euro *(no Cents)*
☐ Specialist in _____	☐☐ visits	☐☐☐ Euro *(no Cents)*
☐ Specialist in _____	☐☐ visits	☐☐☐ Euro *(no Cents)*
☐ Physiotherapist	☐☐ visits	☐☐☐ Euro *(no Cents)*
☐ Nutrition consultant	☐☐ visits	☐☐☐ Euro *(no Cents)*

Did the assistant person/caregiver receive further therapy during the past 3 months?

If so, how much did you pay yourself? (you did not get reimbursed)

Therapy	Number of visits	Amount paid by yourself per visit
☐ Physiotherapy	☐☐ visits	☐☐☐ Euro *(no Cents)*
☐ massage	☐☐ visits	☐☐☐ Euro *(no Cents)*
☐ occupational therapy	☐☐ visits	☐☐☐ Euro *(no Cents)*
☐ speech training	☐☐ visits	☐☐☐ Euro *(no Cents)*
☐ others, which ones _____	☐☐ visits	☐☐☐ Euro *(no Cents)*
☐ others, which ones _____	☐☐ visits	☐☐☐ Euro *(no Cents)*

Out-patient treatment in hospital

Did assistant person/caregiver have an out-patient *hospital* treatment during the past 3 months (without overnight stay)?

☐ No

☐ Yes If "yes", how often? ☐☐ times

Due to Parkinson's Disease? Yes ☐ No ☐

In-patient treatment in hospital

Were the assistant person/caregiver treated as an in-patient in hospitals during the past 3 months (at least one night)?

If so, please indicate the reason and the length of the hospital stay as well as the description of the ward.

Reason for hospital stay	**Was your hospitalisation related to Parkinson's disease ?**		**Specification of ward** (e.g. internal ward)	**Length of stay** (e.g. 10 days)
	Yes	**No**		*e.g.: 1 0 days*
				days
				days
				days
				days

Within the framework of the above-mentioned hospital stay, did you have to pay for the costs yourself?

☐ No

☐ Yes

If „yes", what and how much did you have to pay?

Costs			Amount paid by you (Euro)
Co-payments	☐ Yes	☐ No	
Travel costs:	☐ Yes	☐ No	
- travelled with own car	☐ Yes	☐ No	km travelled (one way): km
- by public transport	☐ Yes	☐ No	
Others	☐ Yes	☐ No	

3.10. Did the assistant person/caregiver stay at a rehabilitation facility during the past 3 months?

☐ No

☐ Yes

If "yes", how many days did you spend as an in-patient (at least one night) or as an out-patient in a rehabilitation facility ? Please do also count the day of admittance and the day of discharge as a full day.

In-patient	**Out-patient**	**Length of stay (in days)**
☐	☐	_____ days
☐	☐	_____ days
☐	☐	_____ days

Did the assistant person/caregiver have to pay for the costs within the framework of the above-mentioned rehabilitation?

☐ No

☐ Yes

If „yes", what and how much did you have to pay?

Costs			Amount paid by you (Euros)
Co-payment for stay	☐ Yes	☐ No	
Co-payment for food	☐ Yes	☐ No	
Co-payment for therapeutic measures	☐ Yes	☐ No	
Travel costs:	☐ Yes	☐ No	
- travelled with own car	☐ Yes	☐ No	km travelled (one way): km
- by public transport	☐ Yes	☐ No	
Stay	☐ Yes	☐ No	
Food	☐ Yes	☐ No	
Others	☐ Yes	☐ No	

Please fill in all medication which was prescribed to the assistant person/caregiver by a physician during the past 3 months

☐ I am not taking any medication currently.

Name indicated on the package	Dose	Application form *please tick box or fill in application form in case of other form (e.g. injection)*			Co-payment per package by patient (in Euro)	Duration of application *(if you currently still take the drug, please tick the box "ongoing", if you do not take the drug anymore, please fill in the date of last intake)*
		tablets	capsules	Other (e.g. injections)		
		☐	☐		_____	Application since: ☐☐☐☐ *m m y y* Ongoing: ☐ Stopped at: ☐☐☐☐ *m m y y*
		☐	☐		_____	Application since: ☐☐☐☐ *m m y y* Ongoing: ☐ Stopped at: ☐☐☐☐ *m m y y*

Did the assistant person/caregiver take any medication during the past 3 months which was without prescription (not prescribed by a physician and paid for by yourself) ? (Please include all sorts of medication, also e.g. vitamins such as vitamin C or vitamin E, herbal medicines, enzymes etc.)

Name of the medication	**Approximately how much did you spend on this medication during the past 3 months?**

Caregiver: Health Questionnaire EQ-5D

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking around ❑

I have some problems in walking around ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

Iam unble to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

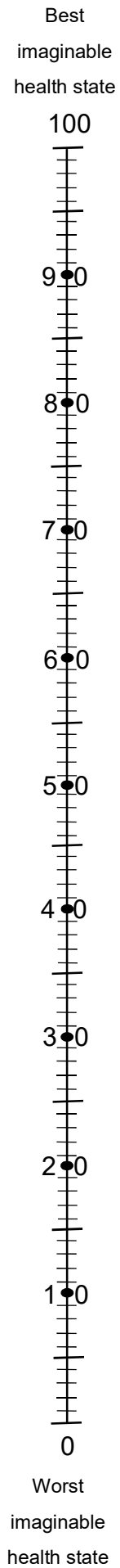
I am moderately anxious or depressed ❑

I am extermely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today

Your own health state today



ANNEXE 7: Columbia Suicide Severity Rating Scale

COLUMBIA-SUICIDE SEVERITY
RATING SCALE
(C-SSRS)

Baseline/Screening Version

Version 14/01/2009

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale (C-SSRS) are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behaviour depends on the judgment of the individual administering the scale.

Definitions of behavioural suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behaviour: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; enquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to the "Suicidal Behaviour" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete the "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or a wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes No** ☐ ☐	**Yes No** ☐ ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life / commit suicide (e.g. "*I've thought about killing myself*") without thoughts of ways to kill oneself / associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes No** ☐ ☐	**Yes No** ☐ ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different from a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, "*I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it… and I would never go through with it*". ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes No** ☐ ☐	**Yes No** ☐ ☐
4. Active Suicidal Ideation with Some Intent to Act, Without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to "*I have the thoughts but I definitely will not do anything about them*". ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes No** ☐ ☐	**Yes No** ☐ ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes No** ☐ ☐	**Yes No** ☐ ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e. 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** ***Type # (1-5)*** ***Description of Ideation*** Past X Months - ***Most Severe Ideation:*** ***Type # (1-5)*** ***Description of Ideation***	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

SUICIDAL BEHAVIOUR *(Tick all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behaviour was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behaviour or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/storey). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent maybe inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behaviour without suicidal intent) If yes, describe:	**Yes** ☐ **No** ☐ Total # of Attempts _____	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behaviour?	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (*if not for that, actual attempt would have occurred*). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed towards self, gun is taken away by someone else, or he/she is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of Interrupted _____	**Yes** ☐ **No** ☐ Total # of Interrupted _____
Aborted Attempt: When person begins to take steps towards making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behaviour. Examples are similar to interrupted attempts, except that the individual stops him/herself instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of Aborted _____	**Yes** ☐ **No** ☐ Total # of Aborted _____
Preparatory Acts or Behaviour: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalisation or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Suicidal Behaviour: Suicidal behaviour was present during the assessment period?	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech, first degree burns, mild bleeding, sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive, second degree burns, bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalisation and likely intensive care required (e.g. comatose with reflexes intact, third degree burns less than 20% of body, extensive blood loss but can recover, major fractures). 4. Severe physical damage; *medical* hospitalisation with intensive care required (e.g. comatose without reflexes, third degree burns over 20% of body, extensive blood loss with unstable vital signs, major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality = 0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun failed to fire so no medical damage; lay on train tracks with oncoming train but pulled away before run over). 0 = Behaviour not likely to result in injury 1 = Behaviour likely to result in injury but not likely to cause death 2 = Behaviour likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

COLUMBIA-SUICIDE RATING (C-SSRS)

SEVERITY SCALE

Since Last Visit

Version 14/01/2009

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

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For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; enquiries and training requirements contact posnerk@nyspi.columbia.edu

C-SSRS-Since Last Visit - United Kingdom/English - Version of 07 Apr 14 - Mapi.
ID7651 / C-SSRS-SinceLastVisit_AU5.1_eng-GB.doc

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to the "Suicidal Behaviour" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete the "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or a wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
If yes, describe:
Yes ☐ **No** ☐

2. Non-Specific Active Suicidal Thoughts
General non-specific thoughts of wanting to end one's life / commit suicide (e.g. "*I've thought about killing myself*") without thoughts of ways to kill oneself / associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
If yes, describe:
Yes ☐ **No** ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different from a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, "*I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it… and I would never go through with it*".
Have you been thinking about how you might do this?
If yes, describe:
Yes ☐ **No** ☐

4. Active Suicidal Ideation with Some Intent to Act, Without Specific Plan
Active suicidal thoughts of killing one self and subject reports having some intent to act on such thoughts, as opposed to "*I have the thoughts but I definitely will not do anything about them*".
Have you had these thoughts and had some intention of acting on them?
If yes, describe:
Yes ☐ **No** ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
If yes, describe:
Yes ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e. 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe

Most Severe Ideation: _____ _____

Type # (1-5) ***Description of Ideation***

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others.
(2) Mostly to get attention, revenge or a reaction from others.
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling).
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling).
(0) Does not apply
____

SUICIDAL BEHAVIOUR *(Tick all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die*, as a result of act*. Behaviour was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behaviour or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/storey). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from _____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behaviour without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behaviour?**	**Yes** ☐ **No** ☐ Total # of Attempts _____ **Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (*if not for that, actual attempt would have occurred*). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed towards self, gun is taken away by someone else, or he/she is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of Interrupted _____
Aborted Attempt: When person begins to take steps towards making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behaviour. Examples are similar to interrupted attempts, except that the individual stops him/herself instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of Aborted _____
Preparatory Acts or Behaviour: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalisation or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behaviour: Suicidal behaviour was present during the assessment period?	**Yes** ☐ **No** ☐
Suicide:	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech, first degree burns, mild bleeding, sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive, second degree burns, bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalisation and likely intensive care required (e.g. comatose with reflexes intact, third degree burns less than 20% of body, extensive blood loss but can recover, major fractures). 4. Severe physical damage; *medical* hospitalisation with intensive care required (e.g. comatose without reflexes, third degree burns over 20% of body, extensive blood loss with unstable vital signs, major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality = 0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun failed to fire so no medical damage; lay on train tracks with oncoming train but pulled away before run over). 0 = Behaviour not likely to result in injury 1 = Behaviour likely to result in injury but not likely to cause death 2 = Behaviour likely to result in death despite available medical care	*Enter Code* _____