A PHASE IIA, RANDOMIZED, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND EFFICACY OF DA-9805 IN SUBJECTS WITH PARKINSON'S DISEASE

Protocol Number:	**DA-9805-PD-001**
Version Number:	**Version 3.0**
Version Date	**12 Jul2017**
Development Phase:	**Phase IIa**
Investigational Compound:	**DA-9805**
Control:	**Placebo**

Sponsor: Dong-A ST Co., Ltd.
Protocol Prepared By: Amarex Clinical Research, LLC
20201 Century Blvd, 4th Floor
Germantown, MD 20874
USA

Confidentiality Statement

This protocol is provided for conducting a clinical research study. The information contained in this document is confidential and, except to the extent necessary to obtain informed consent or IEC/IRB approval, cannot be disclosed unless required by governmental regulation. Persons to whom any portion of the contents of this document is disclosed must be informed that the information is confidential and may not be further disclosed by them.

PROTOCOL APPROVAL PAGE

Protocol Number: **DA-9805-PD-001**
Version: **Version 3.0**
Date: **12 Jul2017**

We, the undersigned, have reviewed this protocol and agree that it contains all relevant information required to meet FDA, GCP and all applicable regulatory guidelines and statutes.

PROTOCOL APPROVAL FOR USE

Anandkrishnan Balasubramanian; B.Pharm (Hons); Amarex Clinical Research, LLC Project Manager	Date
Shide Badri, MD; Amarex Clinical Research, LLC. Medical Monitor	Date
Hana Mekonnen, MA; Amarex Clinical Research, LLC. Biometrics	Date
Jin Seok Jeong; Dong-A ST Co., Ltd. Research Scientist, Strategic Project Team	Date

INVESTIGATOR'S SIGNATURE PAGE

Protocol Number:	**DA-9805-PD-001**
Version:	**Version 3.0**
Date:	**12 Jul2017**

I have read the protocol specified above and agree to participate in and comply with the procedures, as outlined herein for the conduct of this clinical trial. I also agree to comply with US Food and Drug Administration (FDA) regulations and Investigational Review Board/Institutional Ethics (IRB/IEC) requirements for testing on human subjects. I agree to ensure that the requirements for obtaining informed consent are met.

Principal Investigator's Signature _____ Date _____

Print Name _____

Site Number _____

STUDY SPONSOR INFORMATION

Dong-A ST Co., Ltd.

Primary Contact: Dong-A ST Co., Ltd.
64, Cheonho-daero
Dongdaemun-gu
Seoul, Korea
E-mail: treadwheel@donga.co.kr

CLINICAL RESEARCH ORGANIZATION INFORMATION

Amarex Clinical Research, LLC (Amarex)

Amarex Office: Amarex Clinical Research, LLC.
20201 Century Boulevard, 4th Floor
Germantown, MD 20878 USA

Project Manager: **Anandkrishnan Balasubramanian**
Telephone number: +1 (301) 956-2531
Fax number: +1 (301) 528-2300
E-mail: anandb@amarexcro.com

Medical Monitor: **Shide Badri, MD**

Telephone number: +1 (240) 454-6844
Fax number: +1 (240) 454-6602
E-mail: saereporting@amarexcro.com

LIST OF ABBREVIATIONS

TERM	DEFINITION
%	Percent
ADR	Angelica dahurica root
AE	Adverse Event
ALT	Alanine Aminotransferase
Amarex	Amarex Clinical Research, LLC.
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
BCRP	Breast Cancer Resistance Protein
BMI	Body Mass Index
BF	Bupleurum Root
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CI	Confidence Interval
CNS	Central Nervous System
COX-2	Cyclooxygenase-2
CRF	Case Report Form
CFR	Code of Federal Regulations
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology criteria for Adverse events
CV	Curriculum vitae
DAT	Dopamine Transporter
DSMC	Data Safety and Monitoring Committee
DSM-V	Diagnostic and Statistical Manual of Mental Disorder-Version 5
ECG	Electrocardiogram
EOT	End of Treatment
ER	Endoplasmic reticulum
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
g/dL	grams/deciliter
GCP	Good Clinical Practices
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practices
HDL	High Density Lipoprotein
HEENT	Head, Ears, Eyes, Nose, and Throat
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart Rate

TERM	DEFINITION
H&Y	Hoehn and Yahr
IA	Interim Analysis
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IL-B	Interleukin-1b
iNOS	Inducible Nitric Oxide Synthase
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intra Uterine Device
IWRS	Interactive Web Based Response System
Kg	Kilograms
LDH	Lactate Dehydrogenase
LPS	Lipopolysaccharides
MAO-B	MonoAmine Oxidase type B inhibitors
MAPK	Mitogen-activated protein serine/threonine kinase
MC	Moutan Root Bark
MCV	Mean corpuscular volume
MDS-UPDRS	Movement Disorder Society - Unified Parkinson Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MFDS	Ministry of Food and Drug Safety
Mg	Milligrams
mg/dL	Milligram/deciliter
mmol/L	Millimole/Liter
MMRM	Mixed Model Repeated Measures
MMSE	Mini-Mental State Examination
MPP^+	1-methyl-4 phenylpyridinium
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
Msec	Milliseconds
MC	Moutan Root Bark
NF-κB	Nuclear Factor Kappa B
OAT	Organic Anion Transporter
OATP	Organic Anion Transporter Polypeptide
OCT	Organic Cation Transporter
OECD	Organization for Economic Co-operation and Development
OHDA	Neurotoxin 6-hydroxydopamine
PD	Parkinson’s Disease
PDE	Phosphodiesterase
PDQ	Parkinson's Disease Questionnaire
PP	Per Protocol
RBC	Red Blood Cells

TERM	DEFINITION
RR	Respiration Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SD	Standard Deviation
SOP	Standard Operating Procedures
SN	Substantia Nigra
SNpc	Substantia Nigra pars compacta
ST	Striatum
S&E	Schwab and England
TEAE	Treatment Emergent Adverse Event
TH	Tyrosine Hydroxylase
TID	ter in die (Three times daily)
TNF	Tumor Necrosis Factor
TV	Treatment Visit
U/L	Units/Liter
UGT	Uridine 5'-diphospho-Glucuronosyltransferase
USA	United States of America
WBC	White Blood Cells
WHO	World Health Organization
µL	Microliter

PROTOCOL SYNOPSIS

Name of Sponsor/Company: **Dong-A ST Co. Ltd**	
Name of Study Product: DA-9805 tablet **Comparator Product**: Placebo tablet	
Protocol Number: DA-9805-PD-001	**Indication:** Parkinson's Disease
Title of Study: A Phase IIa, Randomized, Multicenter, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability and Efficacy of DA-9805 in Subjects With Parkinson's Disease.	
Study Center: Up to 10 research sites in USA	
Planned Number of Subjects: 60 Subjects (20 subjects per arm)	**Study Development Phase:** IIa
Indication for Use: Parkinson's Disease	
Objectives: **Primary Objective:** To evaluate the safety and tolerability of DA-9805 at 45mg, 90mg compared to Placebo (0 mg) in subjects with Parkinson's Disease. **Secondary Objective:** To evaluate DA-9805 at 45mg, 90mg compared to Placebo (0 mg), in terms of efficacy in subjects with Parkinson's Disease.	
Study Outcomes: **Primary Outcome Measure:** • Change in motor MDS-Unified Parkinson Disease Rating Scale (MDS-UPDRS) total score from baseline at week 12. **Secondary Outcome Measures:** • Change in total MDS- UPDRS total score from baseline at week 12. • Change in MDS-UPDRS subscale scores from baseline at week 12. • Change in Schwab and England (S&E) Scale total score from baseline at week 12. • Change in Parkinson's Disease Questionnaire (PDQ-39) total score from baseline at week 12. • Change in Hoehn and Yahr (H&Y) scale total score from baseline at week 12. • Change in Clinical Global Impression-Severity (CGI-S) and Clinical Global Impression-	

Name of Sponsor/Company: **Dong-A ST Co. Ltd**	
Name of Study Product: DA-9805 tablet **Comparator Product**: Placebo tablet	
Protocol Number: DA-9805-PD-001	**Indication:** Parkinson's Disease

Improvement (CGI-I) scale score from baseline at week 12.

Safety Assessments:

- Incidence of Treatment-Emergent Adverse Events (AEs).
- Incidence of withdrawals due to AEs.
- Change/shifts in laboratory values.
- Change in vital signs.
- Change in Electrocardiogram (ECG) parameters.
- Change in Columbia-Suicide Severity Rating Scale (C-SSRS) from baseline at week 12.

Trial Design:

This is a phase IIa, first in human, randomized, double-blind, multicenter study to evaluate the safety, tolerability and efficacy of DA-9805 at 45mg, 90mg versus placebo in subjects diagnosed with early Parkinson's disease.

The study will include three parts: a 2-week Screening part, a 12-week Double-Blind Treatment part, and a 4-week Follow-up part. The Schedule of Events is provided in Table 4-1.

Screening part (Day -14 to Day -1), up to 14 days:

Screening part is designed to determine subject's eligibility to proceed to Randomization and the Treatment Phase of the study. During this part, a series of assessments will be performed to determine subject eligibility as per inclusion and exclusion criteria (Refer to Section 3.1.2 and Section 3.1.3).

At the Screening Visit, prior to any study-related procedures, a written informed consent will be obtained from the subject by the Investigator or suitable qualified personnel. Screening procedures will be conducted per the study schedule of events. All screening information will be documented in the case report forms.

Subjects who meet eligibility criteria, but have some abnormal laboratory values, based on PI review a repeat laboratory sample may be collected. The repeat laboratory reports should be reviewed by the PI to confirm eligibility prior to randomization.

Subjects who fail to meet eligibility criteria during the Screening part will be considered screen failures and will be exited from the study. Subjects who meet the eligibility criteria will be scheduled for randomization visit.

Double-Blind Treatment Part (12 weeks):

Subjects who have successfully completed the Screening part will enter the Double-Blind treatment

Name of Sponsor/Company: **Dong-A ST Co. Ltd**	
Name of Study Product: DA-9805 tablet **Comparator Product**: Placebo tablet	
Protocol Number: DA-9805-PD-001	**Indication:** Parkinson's Disease

part of the study. Treatment part followed by randomization will last for 12 weeks. Subjects will take the assigned randomized treatment, DA-9805 at 45mg, 90mg or placebo for 12 weeks. DA-9805 and matching placebo are oral tablets that will be taken three times daily during this study.

Randomization/Treatment Visit 0 (TV0): On Day 0 prior to randomization, the subject's continued eligibility will be evaluated (Refer to Section 3.1.2 and Section 3.1.3). Subjects who continue to be eligible will be randomized in a 1:1:1 ratio to one of the following treatment groups and assigned the study treatment kit:

- Group 1: DA-9805 45mg tablet
- Group 2: DA-9805 90mg tablet
- Group 3: placebo tablet (0 mg DA-9805)

Treatment Visits 1 (TV1) through 3 (TV3):

Clinic treatment visits TV1 through TV3 will be conducted every four (4) week (± window periods). During each of these visits, study evaluations will be conducted per the study schedule of events (Refer to Section 4.1.3), and sufficient supply of DA-9805 or placebo till the next treatment visit will be dispensed.

Treatment Visit 3 (TV3) will be the end of treatment (EOT) clinic visit. Study evaluations, review of the adverse events, concomitant medications and final study treatment accountability will be conducted.

Follow-up Part (4 weeks ± 3 days)

The follow-up part will consist of a follow-up visit at the end of the Double-Blind Treatment part. The detailed study schedule and assessments in each visit are provided in Section 4.1 of the protocol.

Name of Sponsor/Company: **Dong-A ST Co. Ltd**	
Name of Study Product: DA-9805 tablet **Comparator Product**: Placebo tablet	
Protocol Number: DA-9805-PD-001	**Indication:** Parkinson's Disease

Duration of Screening Part: 2 weeks

Duration of Double-Blind Treatment Part: 12 weeks

Duration of follow-up Part: 4 weeks

Total Study Duration: 18 weeks

Inclusion Criteria:

Subjects will be eligible for enrollment in the study only if they meet ALL of the following criteria:

1. Male or female subjects who are between 30 and 79 years old inclusive with a clinical diagnosis of Parkinson's disease as per UK Brain Bank Criteria for two (2) years or less at screening.
2. Hoehn and Yahr I or II at screening.
3. Subjects who are newly diagnosed & currently not on any Parkinson's disease medication (or) subjects who are on stable doses for at least 4 weeks prior to screening on Amantadine or anticholinergics for treatment of Parkinson's disease
    (1) Note: Subjects that had anti-parkinsonian medication (including levodopa, dopamine agonists, entacapone and monoamine oxidase-B inhibitors) discontinued at least 60 days prior to screening, e.g., for intolerance, may be considered eligible if all other eligibility requirements are met.
4. Women of child-bearing potential should use reliable contraception. Acceptable methods of contraception include: surgical sterilization (e.g. bilateral tubal ligation), hormonal contraception (implantable, patch, and oral), and double-barrier methods (condom, diaphragm and spermicide are each considered a barrier). Women of child-bearing potential are defined as women physiologically capable of becoming pregnant, UNLESS they meet the following criteria:
    (1) Post-menopausal: 12 months of natural (spontaneous) amenorrhea or 6 months of spontaneous amenorrhea with serum Follicle Stimulating Hormone (FSH) levels > 40mIU/m, OR;
    (2) 6 weeks post surgical bilateral oophorectomy with or without hysterectomy
5. If a male and heterosexually active with a female of childbearing potential, the subject must agree to use a double barrier method of birth control (or must have been surgically sterilized) and to not donate sperm during the study.
6. Without clinically significant abnormalities in physical exam, neurological exam and laboratory assessments (urine/blood routine, biochemical tests and ECG) which would exclude the subject from the study in the opinion of the Investigator. For Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) the screening levels should be ≤ 2 times

Name of Sponsor/Company: **Dong-A ST Co. Ltd**	
Name of Study Product: DA-9805 tablet **Comparator Product**: Placebo tablet	
Protocol Number: DA-9805-PD-001	**Indication:** Parkinson's Disease

upper limit normal.

7. Subject is capable of providing informed consent and is willing to sign the ICF prior to study Screening and agrees to comply with the study protocol requirements.

Exclusion Criteria:

Subjects will be eligible for enrollment in the study only if they meet NONE of the following criteria:

1. Subject has an atypical parkinsonian syndrome or secondary parkinsonism (e.g., due to drugs, metabolic neurogenetic disorders, encephalitis, cerebrovascular disease or degenerative disease).
2. Subjects with history of neurosurgical intervention for Parkinson's disease.
3. Subjects who meet the DSM-V criteria at screening for bipolar disorder, major depressive disorder, psychotic disorders, or any other comorbid mental disorders that in the opinion of the Investigator may interfere with study conduct and results interpretation.
4. Subjects with clinical diagnosis of dementia (MMSE score <24) as determined by the investigator using Mini–Mental State Examination (MMSE).
5. Female subjects who are pregnant or breast feeding.
6. Initiation of any anti-parkinsonian medication (including levodopa, dopamine agonists, entacapone and monoamine oxidase-B inhibitors) for the duration of the trial.
7. Initiation of Amantadine or anticholinergics for newly diagnosed subjects or change in the dosage of Amantadine or anticholinergics during the trial for subjects who were on stable doses for 4 weeks prior to screening.
8. Subjects who used investigational drugs or devices within 60 days prior to screening or investigational biologics within the last 6 months prior to screening.
9. Subjects with a clinically significant medical or surgical condition, including major surgeries within 28 days prior to enrollment.

Statistical Considerations:

Sample Size Determination and Rationale

The sample size of 60 subjects (20 subjects per group) will be used in this trial. Early Parkinson's disease subjects will be randomized in this trial. This sample size is selected on the basis of clinical judgment and not based on statistical power calculation; it is deemed adequate to provide clinically meaningful descriptive results consistent with the study objectives.

Interim Analysis

There is no interim analysis planned for this study.

Name of Sponsor/Company: **Dong-A ST Co. Ltd**	
Name of Study Product: DA-9805 tablet **Comparator Product**: Placebo tablet	
Protocol Number: DA-9805-PD-001	**Indication:** Parkinson's Disease

Analysis Populations

Intent-to-Treat (ITT) population

The Intent-to-Treat (ITT) population is defined as all randomized subjects who have received at least one dose of study treatment and undergone at least one post-randomization efficacy assessment.

Per Protocol (PP) Population

The Per Protocol (PP) population is defined as the set of subjects who meet the ITT population requirements, and were not associated with a major protocol violation. This population will be identified before the database lock, and before the treatment assignments are revealed.

Safety Population

The Safety population is defined as all subjects receiving at least one dose of the treatment after randomization.

Analysis Methods:

The primary analysis of the primary and secondary endpoints will be conducted using the PP population.

Efficacy Analysis:

For analysis of the primary and secondary endpoints the following will be considered:

- For endpoints that are continuous in nature
  - Number of observations, mean, median, minimum and maximum, and standard deviation (SD) values will be presented as descriptive summary.
  - For inferential statistics:
    - If the Normality assumption is met, t-test or ANCOVA using the baseline value as a covariate will be used.
    - If the Normality assumption is not met, a rank –ANCOVA analysis i.e., an ANCOVA analysis on rank-transformed data or other non-parametric methods will be used.
- For endpoints that are categorical in nature:
  - Frequency counts and percentages will be presented as descriptive summary.
  - Chi-square test or Logit model will be used for inferential statistics.

To assess the consistency of the Primary Analysis results, a supportive analysis will be conducted using the ITT population. Statistical methodology for the supportive analyses will be the same as that of the primary analysis, with the exception of the analysis population.

Name of Sponsor/Company: **Dong-A ST Co. Ltd**	
Name of Study Product: DA-9805 tablet **Comparator Product**: Placebo tablet	
Protocol Number: DA-9805-PD-001	**Indication:** Parkinson's Disease

Safety Analysis:

The Safety population will be used for the analysis of all safety parameters or measurements.

Adverse events will be coded using the most recent version of MedDRA. Treatment-Emergent AEs (TEAE) are defined as events with an onset on or after the first randomized treatment. TEAEs will be summarized by treatment group, System Organ Class, and preferred term.

Summary statistics of raw data and change from baseline values for each laboratory parameter will be presented by treatment group and time point. Data will be summarized as appropriate to the variable type (i.e. continuous or categorical variables).

Individual subject changes will be identified through shift tables. Shift tables will be presented for each laboratory parameter with counts and percentages of subjects, by treatment group and time point, for shift from baseline, using the normal ranges.

In addition, all the data from physical examination, 12 Lead ECG and vital signs will also be descriptively summarized.

TABLE OF CONTENTS

List of Tables

List of Figures

1 INTRODUCTION

1.1 STATEMENT OF INTENT

The design, conduct and reporting of this trial will be in compliance with the protocol, International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) and all appropriate regulatory requirements. The protocol will follow 21 Code of Federal Regulations (CFR) 50, subpart D and will provide all the necessary safeguards for study subjects. All of the Investigators will have documented training in GCP. Independent monitoring of the trial will be accomplished by utilizing Amarex Clinical Research as the Contract Research Organization (CRO).

1.2 BACKGROUND

Parkinson's disease (PD) is recognized as one of the most common neurologic disorders, affecting approximately 1% of individuals older than 60 years. There are 2 major neuropathologic findings:

- the loss of pigmented dopaminergic neurons in the substantia nigra pars compacta (SNpc) and
- the presence of Lewy bodies.

Most cases of Parkinson's disease are hypothesized to be due to a combination of genetic and environmental factors. However, no environmental cause of Parkinson's disease has yet been proven. A known genetic cause can be identified in approximately 10% of cases, and these are more common in younger-onset patients.

The classic motor features of Parkinson's disease typically start insidiously and emerge slowly over weeks or months, with tremor being the most common initial symptom. The 3 cardinal signs of Parkinson's disease are resting tremor, rigidity, and bradykinesia. Postural instability (balance impairment) is sometimes listed as the fourth cardinal feature. However, balance impairment in Parkinson's disease is a late phenomenon.

Parkinson's disease affects an estimated 1.5 million persons in the United States, with over ten million affected worldwide, and these estimates are expected to increase substantially in the next few decades. Despite the increasing prevalence, the approved agents for the early management of Parkinson's disease have changed little in the past decade; however, there have been advances in drug delivery, dosing, and the use of combination therapy in an attempt to reduce adverse events. The available treatments continue to focus on the dopaminergic system and include primarily carbidopa/levodopa, monoamine oxidase type B (MAO-B) inhibitors, and dopamine agonists. Current research on the early management of Parkinson's disease focuses on improved and more consistent drug delivery systems, targeting alternate neurotransmitter systems and the identification of neuroprotective therapies for Parkinson's disease. There has also been an increased interest in earlier intervention with various forms of exercise in addition to pharmacological treatments.

The most important, unmet medical need in targeting Parkinson's disease is developing agents with neuroprotective potential. So far, no drug has been shown to reduce or slow down the progression of PD.

1.3 DA-9805

DA-9805 is a botanical drug product composed of three main raw herbal materials; Moutan Root Bark [MC], Bupleurum Root [BF] and Angelica dahurica root [ADR]. The main active ingredients are Paeonol, Saikosaponin A and Imperatorin respectively. All the three herbal raw materials are listed in the Japanese, Korean and Chinese Pharmacopoeias. DA-9805 reduces neuronal loss by:

1. Protection of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) induced nigrostriatal dopamine neuron degeneration.
2. Restoration of 6-OHDA (neurotoxin 6-hydroxydopamine) induced nigrostriatal dopamine neuron degeneration.
3. Inhibition of Rotenone induced α-synuclein accumulation in substantial niagra (SN).
4. Inhibition of LPS induced microglial/astrocyte activation in substantial niagra/striatum(ST).

It is expected that DA-9805 will help treat PD by prevention of dopaminergic neurodegeneration via recovery of mitochondrial dysfunction, anti-inflammatory effect and relief from Endoplasmic reticulum (ER) stress and oxidative stress.

1.4 SUMMARY OF PRIOR PRE-CLINICAL STUDIES

The botanical components of DA-9805 (Moutan Root Bark [MC], Bupleurum Root [BF] and Angelica dahurica root [ADR]) have a long history of human use and have been tested individually and in various combinations in animal models. Based on available published information, MC has been attributed anti-depression, prevention of dementia, improvement of cognitive functions, and anti-inflammatory, neuroregenerative, anti-oxidant, anti-cancer and hypoglycemic effects. Similarly, BF is attributed therapeutic effects in brain damage and depression, and has also shown neuroprotective, neuroregenerative, anti-cancer, anti-allergy effects. Based on published literature, ADR is attributed anti-depression, prevention of dementia, improvement of cognitive function and anti-inflammatory, antioxidant and anti-asthmatic effects.

All three botanicals listed in KP, Chinese Pharmacopoeia (CP) and Japanese Pharmacopoeia (JP) as well as other pre-existing oriental medicine books as over-the-counter (OTC) medicines and approved drugs in Korea, China and Japan. However, none of these consist of individual components of DA-9805 alone, but rather a various combinations with other botanicals. DA-9805 will be the first botanical mixture comprising of all three botanical ingredients.

In addition to Korea, China and Japan, MC, BF and/or ADR containing products can also be found in US, Canada, Australia, Taiwan, Europe and Southeast Asia. These products are not only available as prescription drugs, but also as herbal OTC medicinal products and dietary/food supplements. MC containing products have been used in central nervous system disorders, indigestion, cough, dental care, anemia, and constipation, among other indications. BF containing products have been used in headache, cold, insomnia, enterogastritis, constipation, neurosis and other indications. Finally, ADR containing products are used in fever, headache, antiemetic, cold, insect bites, rhinitis and other indications.

The current market status on products that contain MC, BF and ADR, individually or in combination, in various countries is briefly summarized below.

- In Korea, there are hundreds of products containing MC (115), BF (162) or ADR (67), which are all approved and released as medicinal products by MFDS. MC, BF or ADR are prohibited as raw materials for food in Korea.
- In China, MC, BF or ADR are approved as raw materials for health food and they are found in many of the nutritional products that are approved by the China Food and Drug Administration. The Chinese Pharmacopoeia has listed 29, 22 and 47 regulated products of Traditional Patent Medicine containing MC, BF and ADR, respectively.
- In Japan, out of the 233 common herbal prescriptions and 148 medicinal herbal prescriptions approved by the government, MC is found in 18 products, BF is found in 38 products and ADR is found in 18 products.
- In Taiwan, out of the 200 Chinese medicinal prescriptions listed in the Taiwan Herbal Pharmacopoeia, 12 products contained MC, 25 products contained BF and 14 products contained ADR.
- In US, there are some dietary supplements that contain MC, BF or ADR but they have not been registered or regulated.
- In Canada, MC, BF and ADR are listed as acceptable traditional Chinese medicine ingredients for natural health products in Canada. Traditional Chinese medicine (TCM) products containing MC, BF or ADR are registered marketed as dietary supplements in Canada by various Chinese pharmaceutical companies.
- In Australia, traditional Chinese medicine (TCM) products containing MC, BF or ADR are registered and marketed as complementary medicine by various Chinese pharmaceutical companies.
- In Southeast Asia, countries such as Vietnam, Malaysia, Singapore and Indonesia allow imports of TCM products containing MC, BF or ADR from China.
- In Hong Kong, there are some traditional medicinal products and foods containing MC, BF and ADR.
- In Europe, a few traditional Chinese patent medicines containing MC and ADR are marketed in England and Belgium as dietary supplements.

Dong-A conducted a number of nonclinical studies with DA-9805 and its individual botanical components, as well as with proposed purified active ingredients. Dong-A DA-9805 nonclinical studies were conducted in compliance with the Ministry of Food and Drug Safety (MFDS) (Notification No. 2013-232 'The Standards of Pharmacology Study for Medicinal Products' [Oct 30, 2013] and Notification No. 2014-67 'Good Laboratory Practice [GLP]' [Feb 12, 2014]) and Organization for Economic Co-operation and Development (OECD) GLP requirements and also comply with the current International Conference on Harmonization (ICH) guidelines, including ICH guideline S7A 'Safety Pharmacology Studies for Human Pharmaceuticals' (Nov 08, 2000).

DA-9805 has not undergone any clinical testing in the US or anywhere else in the world; the study proposed under this IND is the first-in-human study. Non-clinical study data summarized below provides safety data for conducting the first DA-9805 in-human study. The NOAEL of DA-9805 in rats was determined at 2000 mg/kg in males and 1000 mg/kg in females with stomach being the affected organ. Based on the FDA guidance on Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers (2005), the human equivalent dose (HED) can be estimated from animal NOAEL using conversion factors based on body surface area, in which the

maximum recommended starting dose (MRSD) is then derived from by applying a safety factor. 1000 mg/kg NOAEL rat dose is equivalent to HED 161 mg/kg, or 9677 mg for a 60 kg adult. The proposed starting doses selected for the first in human clinical trial are 45 mg/day and 90 mg/day; highest selected dose, 90 mg/day, is not expected to result in safety issues based on the animal data and the applied safety factor of 100.

Primary Pharmacology studies evaluated the effects of individual extracts of botanical components of DA-9805, various ratios of botanicals in the final drug substance mixture as well as the DA-9805 final formulation. **MC extract** was shown to have neuroprotective effect, including increased dopamine availability, promoted dopaminergic neuron survival and recovery, and inhibition of mitochondrial dysfunction and mitochondria-mediated apoptosis after MPTP and MPP+ - induced damage in cell culture and in mice. **BF extract** effects, as well as effects of individual isolated BF components (saikosaponins B3, B4 and D) were studied in LPS-induced inflammatory dopaminergic neurodegeneration mouse model. BF extract and its individual saikosaponins components showed the potential to inhibit the apoptosis of dopamine neurons in microglial cells through inhibiting the NF-κB-mediated inflammatory pathway. **ADR extract** effects were studied in multiple models. In spinal cord injury model *in vitro* (LPS-activation of microglial cell culture) and *in vivo*, ADR decreased the levels of pro-inflammatory factors such as tumor necrosis factor-a (TNF-α), interleukin (IL)-1b, IL-6, inducible nitric oxide synthase (iNOS), ROS and cyclooxygenase-2 (COX-2), and subsequently alleviated oxidative stress. In endoplasmic reticulum (ER) stress model, pre-treatment with ADR in human neuroblastoma cell line was found to partially protect cells from thapsigargin and tunicamycin cytotoxicity, reduce intracellular ATP levels, and decrease mRNA levels of markers of ER stress suggesting potential to decrease neuronal damage by inhibiting ER stress. In MPTP-induced PD mouse model, ADR alleviated behavioral impairments and protected against MPTP effect on tyrosine hydroxylase (TH), a rate-limiting enzyme in brain catecholamine biosynthesis. Various **MC, BF and ADR ratios** were screened *in vitro* (MPP+-induced mitochondrial dysfunction model in human neuroblastoma cells) and *in vivo* (MPTP-induced mouse PD model). 1:1:1 ratio was selected for the DA-9805 composition as the one with the optimal pharmacological effect. Proposed **active ingredients** of botanicals MC, BF and ADR (paeonol, saikosaponin A and imperatorin) were shown to improve levels of TH in Substantia Nigra pars compacta (SNpc) of MPTP-induced mice at doses corresponding to 10 mg/kg DA-9805. Based on the results from the above studies, it was concluded that all three selected botanical components of DA-9805 contributed to the neuroprotective effect of DA-9805 and the optimal ratio of the botanicals was 1:1:1.

DA-9805 pharmacological effect was investigated in multiple *in vitro* and *in vivo* models of PD as well as compared to effects of individual components in order to confirm synergistic effects. In *in vitro* studies, pre-treatment of DA-9805 was found to alleviate MPP+-induced mitochondrial dysfunctions, decrease endogenous indicators of ER stress induced by Tunicamycin or Thapsigargin as well as attenuate NO production and NF-kB activation induced by LPS. DA-9805 was also shown to inhibit PDE enzymatic activities and subsequently convey protective properties against dopaminergic neuronal cell lose and α-synuclein accumulation by autophagy activation. *In vitro* binding and inhibition profile showed that DA-9805 inhibited COX-2, MAO-B, PDE1, JNK1 and DAT - enzymes and receptors known to be involved in the pathogenesis of PD and targeted by current PD therapies. Based on additional studies, the inhibitory effect of DA-9805 on MAO-B can at least in part be attributed to paeonol from MC; the inhibitory effects on MAO-B, PDE1, and DAT can at least in part be attributed to imperatorin from ADR.

In *in vivo* studies, DA-9805 provided significant protection against MPTP-induced PD motor symptoms and exhibited a positive effect on TH levels in DA neurons in the SNpc. Both effects were stronger than those of individual botanical extracts alone confirming synergistic effect. Neuroprotective effect of DA-9805 was further confirmed in 6-OHDA-lesion mouse model of PD, in rotenone PD rat model, LPS-induced neuroinflammatory PD mouse model. Neuroprotective effects were shown to be stronger than those of rasagiline. Optimal DA-9805 dose from MPTP-induced PD mouse study was established to be 10 and 20 mg/kg.

Safety Pharmacology studies evaluated the effects of DA-9805 on body temperature and general behavior in mice and respiration rate and volume in rats after single oral administration. NOAEL for both studies was concluded to be the highest tested dose, 1000 mg/kg. A dog telemetry study showed that single oral administration of DA-9805 up to 250 mg/kg (highest tested dose) did not affect the blood pressure, heart rate and electrocardiogram parameters in male beagle dogs. Additional safety pharmacology study, effects of DA-9805 on the cardiovascular hERG in CHO cells, is currently ongoing and results will be provided to the IND when available.

Pharmacokinetic studies investigated the effect of DA-9805 on metabolizing enzymes in liver microsomes and human hepatocyte culture showed that DA-9805 co-administration is not expected to result in clinically significant drug interactions with CYP2C8, CYP2C9, CYP2E1, UGT1A1, UGT1A4, UGT1A9, UGT2B7, and SULT2A1 substrates. Higher doses of DA-9805 (5 and 10 µg/mL) suggested possible interactions with CYP3A4, CYP1A2 and CYP2B6 substrates in the *in vitro* studies. Inhibitory activity was shown to be attributed to imperatorin and paeonol. Drug-drug interactions were further investigated in vivo and no significant inhibitory effects on the enzymatic activities of CYP1A2, CYP2B6, and CYP3A were observed in SD rats that were administered single or multiple oral doses of DA-9805 (60 mg/kg/day). DA-9805 is not expected to cause drug interactions due to inhibition of UGT1A1, UGT1A3, UGT1A4, UGT1A9, and UGT2B7 enzyme activities.

DA-9805 effect was further evaluated on uptake and influx hepatic transporters. DA-9805 inhibited the transport activity of OCT1, OCT2, OAT1, OAT3, OATP1B1, and OATP1B3 with IC_{50} values of 74.8, 70.1, 24.6, 9.5, 40.1, and 45.3 µg/mL, respectively. DA-9805 did not inhibit the efflux of digoxin via P-gp upto 200 µg/mL in LLC-PK1-MDR1 cells, but DA-9805 inhibited the transport activity of BCRP with IC_{50} value of 20.6 µg/mL in LLC-PK1-BCRP cells. These results suggest that DA-9805 has a potential for drug interactions through inhibition of the transport activity of OAT1, OAT3, and BCRP.

Toxicology studies with DA-9805 showed an overall favorable profile. **Acute oral toxicity** in rats at 2000 mg/kg dose showed transient symptoms such as salivation, decrease in locomotor activity, incomplete eyelid opening, crouching position, panting and decreased respiration rate in most of the animals. Those symptoms were resolved within 3 hours of drug administration. The Approximate Lethal Dose of DA-9805 is considered to be higher than 2000 mg/kg for both sexes. Repeat dose toxicity study for 13 weeks in rats concluded NOAEL of DA-9805 to be 2000 mg/kg/day in males and 1000 mg/kg/day in females, with stomach being the target organ in females. The only toxicologically significant changes were erosion/ulceration in glandular and non-glandular stomach revealed in histopathological examination in female rats in the 2000 mg/kg/day group. Other histopathological changes were normalized after completion of dosing and were not considered toxicologically

significant. Repeat dose toxicity was further evaluated in a 4-week dog study to determine dosages for chronic toxicity studies and 750 mg/kg/day was selected.

Chronic oral toxicity for 26 weeks in rats at doses ≥ 500 mg/kg/day showed salivation right after dosing. Transient microscopic changes that are related to DA-9805 but not considered adverse were observed in the liver and thyroids in both sexes at ≥ 500 mg/kg/day, stomach and duodenum in both sexes at 1000 and/or 2000 mg/kg/day, and bone marrow in both sexes at 2000 mg/kg/day. The NOAEL of this study was considered to be the highest dose at 2000 mg/kg/day in box sexes in rats. The 39-week chronic oral toxicity study in dogs showed decrease in body weight and food consumption after dosing in both sexes at the highest dose of 720 mg/kg/day. These observations were considered adverse. Microscopic examination showed changes in the liver of females at 720 mg/kg/day with increased liver weight, which were considered not adverse and symptoms were reversed after recovery. The NOAEL of this study was considered to be 240 mg/kg/day for both sexes in dogs.

Genotoxicity of DA-9805 was evaluated in Ames test, Chromosome Aberration Test and Mouse Bone Marrow Micronucleus Assay. Neither of the studies showed any signs of the genetic toxicity.

1.5 STUDY DESIGN RATIONALE

This Phase IIa study is designed to establish the safety and tolerability of DA-9805 compared to placebo in subjects with PD. This study will also seek to determine the effectiveness of DA-9805 in subjects with PD, which will provide information for subsequent clinical trials with DA-9805.

1.6 RISKS AND BENEFITS

The safety monitoring practices employed by this protocol are adequate to protect the subjects' safety and should detect all Treatment Emergent Adverse Events (TEAEs). The approximate volume of blood (~ 60-75 mL) planned for collection from each subject over the course of the entire study presents no undue risk to the participants. An indirect health benefit to the subjects enrolled in this trial is the free medical tests received at screening and during the study.

2 STUDY OBJECTIVES

- To evaluate the safety and tolerability of DA-9805 at 45mg, 90mg compared to Placebo (0 mg) in subjects with Parkinson's disease.
- To evaluate DA-9805 at 45mg, 90mg compared to Placebo (0 mg), in terms of efficacy in subjects with Parkinson's disease.

3 STUDY DESIGN

This is a phase IIa, first in human, randomized, double-blind, multicenter study to evaluate the safety, tolerability and efficacy of DA-9805 at 45mg, 90mg versus placebo in subjects with early diagnosed Parkinson's disease.

The study will include three parts: a 2-week Screening part, a 12-week Double-Blind Treatment part, and a 4-week Follow-up part. The Schedule of Events is provided in Table 4-1.

Study Visits:

- **Screening Visit** (Day -14 to Day -1), up to 14 days:

Screening part is designed to determine subject's eligibility to proceed to Randomization and the Treatment Phase of the study. During this part, a series of assessments will be performed to determine subject eligibility as per inclusion and exclusion criteria.

At the Screening Visit, prior to any study-related procedures, a written informed consent will be obtained from the subject by the Investigator or suitable qualified personnel. Screening procedures will be conducted per the study schedule of events (Refer to section 4.1.1). All screening information will be documented in the case report forms.

Subjects who meet eligibility criteria, but have some abnormal laboratory values, based on PI review a repeat laboratory sample may be collected. The repeat laboratory reports should be reviewed by the PI to confirm eligibility prior to randomization.

Subjects who fail to meet eligibility criteria during the Screening part will be considered screen failures and will be exited from the study. Subjects who have successfully completed the Screening part will enter the Double-Blind treatment part of the study. Treatment part followed by randomization will last for 12 weeks. Subjects will take the randomized treatment, DA-9805 at 45mg, 90mg or placebo for 12 weeks.

- **Visit 0: Randomization/Baseline Visit** (Day 0) (TV0)**:** On Day 0 prior to randomization, the subject's continued eligibility will be evaluated (Refer to section 4.1.2). Subjects who continue to be eligible will be randomized in a 1:1:1 ratio to one of the following treatment groups and assigned the study treatment kit:

    - Group 1: DA-9805 45mg tablet
    - Group 2: DA-9805 90mg tablet
    - Group 3: placebo (0 mg DA-9805) tablet

DA-9805 and matching placebo are oral tablets that will be taken three times daily during this study.

- **Treatment Visits 1 (TV1) through Treatment Visit 3 (TV3)**:

Clinic treatment visits TV1 through TV3 will be conducted every four (4) week (± 3 days). During each of these visits, study evaluations will be conducted per the study schedule of events (Refer to section 4.1.3), and sufficient supply of DA-9805 or placebo till the next treatment visit will be dispensed.

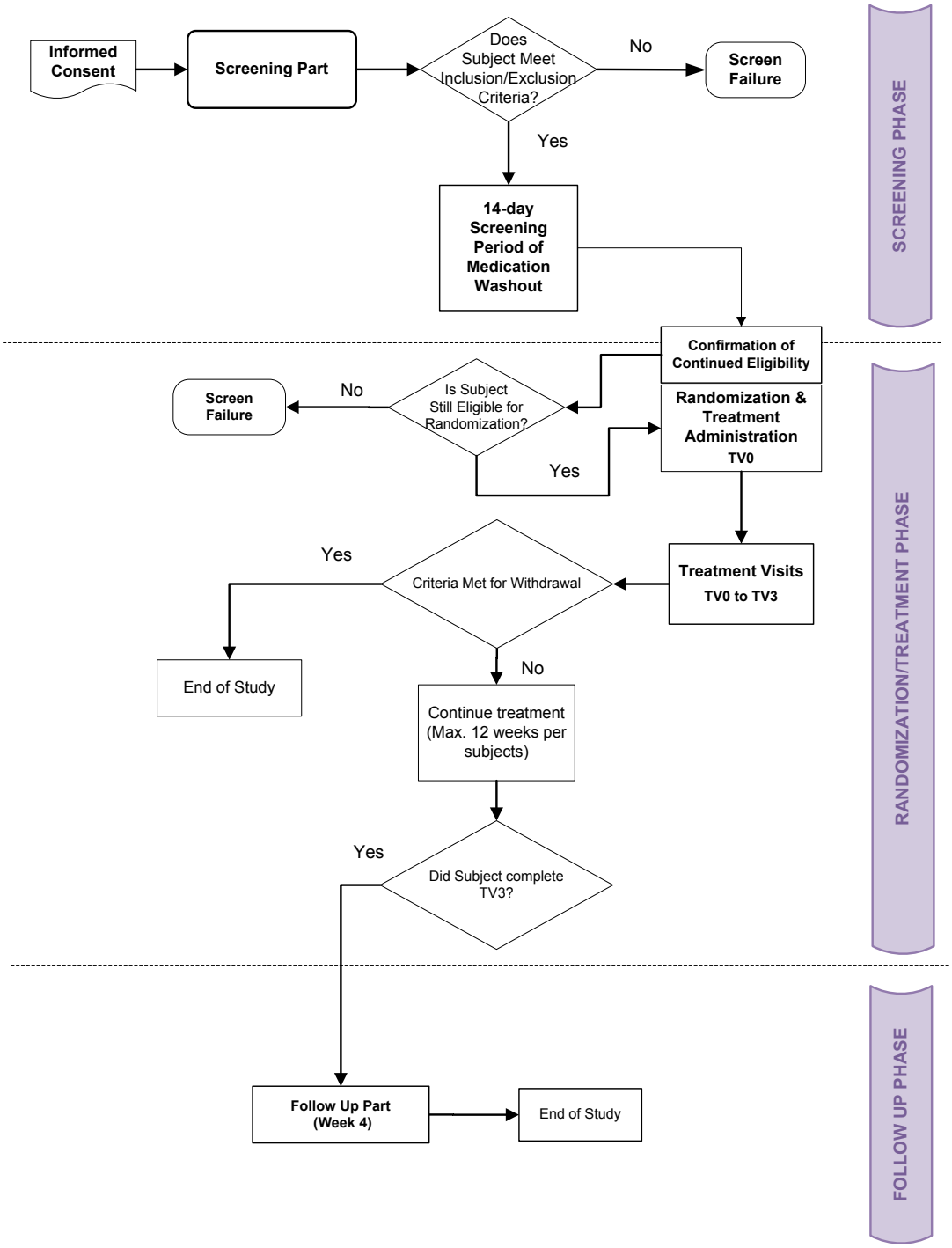
Treatment Visit 3 (TV3) will be considered the end of treatment (EOT) clinic visit. Study evaluations, review of the adverse events and concomitant medications and final study treatment accountability will be conducted.

- **Follow-up Part (4 weeks ± 3 days)**

The follow-up part will consist of a follow-up visit at the end of the Double-Blind Treatment part.

The detailed study schedule and assessments in each visit are provided in Section 4.1 of the protocol.

Figure 3-1: Study Flow Diagram



3.1 STUDY POPULATION

3.1.1 NUMBER OF SUBJECTS

A total of 60 subjects will be randomized to this study from up to 10 Centers within the USA.

3.1.2 INCLUSION CRITERIA

Subjects will be eligible for enrollment in the study only if they meet ALL of the following criteria:

1. Male or female subjects who are between 30 and 79 years old inclusive with a clinical diagnosis of Parkinson's disease as per UK Brain Bank Criteria for two (2) years or less at screening.
2. Hoehn and Yahr I or II at screening.
3. Subjects who are newly diagnosed & currently not on any Parkinson's disease medication (or) subjects who are on stable doses for at least 4 weeks prior to screening on Amantadine or anticholinergics for treatment of Parkinson's disease.
    1. Note: Subjects that had anti-parkinsonian medication (including levodopa, dopamine agonists, entacapone and monoamine oxidase-B inhibitors) discontinued at least 60 days prior to screening, e.g., for intolerance, may be considered eligible if all other eligibility requirements are met.
4. Women of child-bearing potential should use reliable contraception. Acceptable methods of contraception include: surgical sterilization (e.g. bilateral tubal ligation), hormonal contraception (implantable, patch, and oral), and double-barrier methods (condom, diaphragm and spermicide are each considered a barrier). Women of child-bearing potential are defined as women physiologically capable of becoming pregnant, UNLESS they meet the following criteria:
    1. Post-menopausal: 12 months of natural (spontaneous) amenorrhea or 6 months of spontaneous amenorrhea with serum Follicle Stimulating Hormone (FSH) levels > 40mIU/m, OR;
    2. 6 weeks post surgical bilateral oophorectomy with or without hysterectomy
5. If a male and heterosexually active with a female of childbearing potential, the subject must agree to use a double barrier method of birth control (or must have been surgically sterilized) and to not donate sperm during the study.
6. Without clinically significant abnormalities in physical exam, neurological exam and laboratory assessments (urine/blood routine, biochemical tests and ECG) which would exclude the subject from the study in the opinion of the Investigator. For Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) the screening levels should be ≤ 2 times upper limit normal.
7. Subject is capable of providing informed consent and is willing to sign the ICF prior to study Screening and agrees to comply with the study protocol requirements.

3.1.3 EXCLUSION CRITERIA

Subjects will be eligible for enrollment in the study only if they meet NONE of the following criteria:

1. Subject has an atypical parkinsonian syndrome or secondary parkinsonism (e.g., due to drugs, metabolic neurogenetic disorders, encephalitis, cerebrovascular disease or degenerative disease).
2. Subjects with history of neurosurgical intervention for Parkinson's disease.
3. Subjects who meet the DSM-V criteria at screening for bipolar disorder, major depressive disorder, psychotic disorders, or any other comorbid mental disorders that in the opinion of the Investigator may interfere with study conduct and results interpretation.
4. Subjects with clinical diagnosis of dementia (MMSE score <24) as determined by the investigator using Mini–Mental State Examination (MMSE).
5. Female subjects who are pregnant or breast feeding.

6. Initiation of any anti-parkinsonian medication (including levodopa, dopamine agonists, entacapone and monoamine oxidase-B inhibitors) for the duration of the trial.
7. Initiation of Amantadine or anticholinergics for newly diagnosed subjects or change in the dosage of Amantadine or anticholinergics during the trial for subjects who were on stable doses for 4 weeks prior to screening.
8. Subjects who used investigational drugs or devices within 60 days prior to screening or investigational biologics within the last 6 months prior to screening.
9. Subjects with a clinically significant medical or surgical condition, including major surgeries within 28 days prior to enrollment.

4 STUDY SCHEDULE

The schedules for the protocol-specified assessments and procedures for this study are detailed in this section. Day 0 is used as the day of Randomization/baseline and first randomized study treatment administration. See Table 4-1.

Table 4-1: Study Schedule of Events

Study Parts	**Screening Part** (2 weeks)	**Double-Blind Treatment Part** (12 weeks)					**Follow-up Part Follow-up Visit**(4 weeks)
Treatment Visits		**TV0 Randomization**		**TV1**	**TV2**	**TV3**	**FUV**
Weeks from Randomization Date (window period: ± days)	**- 2**	**Day 0**		**+ 4** (± 3)	**+ 8** (± 3)	**+ 12** (± 3)	**+ 16** (± 3)
		Pre-	**Post-**				
Written Informed Consent	X						
Inclusion/Exclusion Criteria	X						
Schedule Randomization Day	X						
Continued Eligibility		X					
Randomization		X					
Demographics	X						
Medical History	X	X					
Physical Examination	X	X		X	X	X	
Vital Signs	X	X	X	X	X	X	
Height[1] and Weight	X	X				X	
ECG	X	X		X		X	
Serum Hematology[2]	X			X	X	X	
Serum Chemistry[2]	X			X	X	X	
Urine Analysis[2]	X			X	X	X	
Urine Pregnancy Test[3]	X	X				X	
MDS-UPDRS		X		X	X	X	
H & Y	X	X		X	X	X	
S & E		X		X	X	X	
PDQ-39		X		X	X	X	
CGI-S and CGI-I[4]	X	X		X	X	X	
C-SSRS	X	X		X	X	X	
MMSE	X	X					
Dispense the DA-9805 or placebo[5]			X	X	X		
DA-9805 or Placebo first dose administration			X				
Study treatment accountability				X	X	X	

Study Parts	**Screening Part** (2 weeks)	**Double-Blind Treatment Part** (12 weeks)					**Follow-up Part Follow-up Visit**(4 weeks)
Treatment Visits		**TV0 Randomization**		**TV1**	**TV2**	**TV3**	**FUV**
Weeks from Randomization Date (window period: ± days)	**- 2**	**Day 0**		**+ 4** (± 3)	**+ 8** (± 3)	**+ 12** (± 3)	**+ 16** (± 3)
		Pre-	**Post-**				
Adverse Events			X	X	X	X	X
Concomitant medications	X	X		X	X	X	X

[1] Height only at Screening.

[2] Subjects who meet eligibility criteria, but have some abnormal laboratory values, based on PI review a repeat laboratory sample may be collected. The repeat laboratory reports should be reviewed by the PI to confirm eligibility prior to randomization.

[3] Only for female subjects of childbearing potential.

[4] CGI-I will be done only at Treatment Visit 1 to Treatment Visit 3

[5] Dispense the DA-9805 or placebo at each of the clinic treatment visit, except TV3 which is the End of Treatment visit (EOT).

4.1 SCREENING AND RANDOMIZATION

4.1.1 SCREENING VISIT (DAY -14TO DAY -1), UP TO 14 DAYS

The subject will sign and date the ICF, and Health Insurance Portability and Accountability Act (HIPAA) authorization (according to site practices) prior to any study-related procedures. A subject number will be assigned to each subject in successive order of consent signing at each center, beginning with 001 at each site. Each study site will receive a unique numeric designation, and will precede the subject number (e.g. at study center 01 the first two consented subjects would be 01-001 and 01-002; at study center 02 the first two consented subjects would be 02-001 and 02-002).

Screening Visit procedures are per below:

- Informed Consent will be obtained prior to any study-related procedures. (Refer to Section 8.1)
- Eligibility assessment per the inclusion and exclusion criteria and diagnosis confirmation (Refer to Section 3.1.2 and Section 3.1.3).
- Subject demographics (Refer to Section 8.3)
- Medical history (Refer to Section 8.4)
- Vital signs (Refer to Section 8.5)
- Height, Weight and BMI (Refer to Section 8.6)
- Physical examination (Refer to Section 8.7)
- List concomitant medications (Refer to Section 7)
- Laboratory assessments (hematology, biochemistry and urine analysis) (Refer to Section 8.8)
- Electrocardiogram (Refer to Section 8.9)
- Urine pregnancy test (Refer to Section 8.10)
- Hoehn and Yahr (H&Y) Scale (Refer to Section 8.12)
- Columbia-Suicide Severity Rating Scale (C-SSRS) (Refer to Section 8.16)
- Clinical Global Impression-Severity (CGI-S) scale (Refer to Section 8.14)
- Mini-Mental State Examination (MMSE) (Refer to Section 8.17)
- Schedule randomization visit

4.1.2 TREATMENT VISIT 0 (TV0): RANDOMIZATION/BASELINE VISIT (DAY 0)

If continued to be eligible for the study at TV0, the subject will proceed to be randomized. All entrance criteria must be met prior to randomization of a subject into the protocol. The following assessments will be performed:

Treatment Visit 0 (TV0) – Prior to Randomization: Perform the following baseline assessments

- Assessment of continued eligibility (Refer to Section 3.1.2 and Section 3.1.3)
- Medical history (Refer to Section 8.4)
- Vital signs (Refer to Section 8.5)
- Body Weight (Refer to Section 8.6)
- Physical Examination (Refer to Section 8.7)
- Electrocardiogram (Refer to Section 8.9)
- Urine pregnancy test (Refer to Section 8.10)

- MDS-UPDRS Scale (Refer to Section 8.11)
- Hoehn and Yahr (H&Y) Scale (Refer to Section 8.12)
- Schwab and England (S&E) Scale (Refer to Section 8.15)
- Parkinson's Disease Questionnaire (PDQ-39) total score (Refer to Section 8.13)
- Clinical Global Impression-Severity (CGI-S) scale (Refer to Section 8.14)
- List concomitant medications (Refer to Section 7)
- Columbia-Suicide Severity Rating Scale (C-SSRS) (Refer to Section 8.16)
- Mini-Mental State Examination (MMSE) (Refer to Section 8.17)
- Randomization (Refer to Section 9.4)

Treatment Visit 0 (TV0) – Post Randomization: Perform the following assessments
- Vital signs (Refer to Section 8.5)
- Study treatment dispensation (Refer to Section 6.7)
- Study treatment first dose administration (Refer to Section 6.7)
- Adverse events evaluation after first dose (Refer to Section 10)

4.1.3 TREATMENT VISIT 1 (TV1) (WEEK 4: DAY 28±3), TREATMENT VISIT 2 (TV2) (WEEK 8: DAY 56±3), TREATMENT VISIT 3 (TV3) (WEEK 12: DAY 84±3)

The following assessments will be performed:

- Vital signs (Refer to Section 8.5)
- Weight and BMI (Refer to Section 8.6) (Only at TV3)
- Physical examination (Refer to Section 8.7)
- Laboratory assessments (hematology, biochemistry and urine analysis) (Refer to Section 8.8)
- Electrocardiogram (Refer to Section 8.9) (This is done ONLY at TV1 and TV3)
- Urine pregnancy test (Refer to Section 8.10) (This is done ONLY at TV3)
- MDS-UPDRS Scale (Refer to Section 8.11)
- Hoehn and Yahr (H&Y) Scale (Refer to Section 8.12)
- Schwab and England (S&E) Scale (Refer to Section8.15)
- Parkinson's Disease Questionnaire (PDQ-39) total score (Refer to Section 8.13)
- Clinical Global Impression-Severity (CGI-S) and Clinical Global Impression-Improvement (CGI-I) scale (Refer to Section 8.16)
- List concomitant medications (Refer to Section 7)
- Columbia-Suicide Severity Rating Scale (C-SSRS) (Refer to Section 8.16)
- Adverse events evaluation (Refer to Section 10)
- Study treatment dispensation (This is done ONLY at TV1 and TV2) (Refer to Section 6.7)
- Study treatment accountability (Refer to Section 6.9)

4.2 FOLLOW-UP

4.2.1 FOLLOW-UP VISIT (WEEK 16: DAY 112±3)

The following assessments will be performed:

- List concomitant medications (Refer to Section 7)
- Adverse events evaluation (Refer to Section 10)

4.3 UNSCHEDULED VISITS

Unscheduled visits may be required in addition to the scheduled visits per the Investigator's discretion. The details of these unscheduled visits with subjects will be recorded in the medical records and on the Case Report Form (CRF).

4.4 MISSED VISITS

If a subject misses a visit, the site is to make every effort to have the subject return as soon as possible to make up the visit. Once the subject is seen, he/she is to return to his/her original visit schedule.

5 SUBJECT COMPLETION AND WITHDRAWAL

5.1 SUBJECT COMPLETION

A subject who completes TV3 will be considered to have completed the study.

5.2 SUBJECT PREMATURE WITHDRAWAL FROM THE STUDY

A subject who is randomized into the study, but who does not complete the study will be considered prematurely discontinued.

All subjects have the right to withdraw at any point during the study without prejudice. It will be documented whether or not each subject completed the clinical study. If for any subject, study treatment or observations were discontinued, the reason(s) will be recorded and the Sponsor should be notified promptly. All efforts must be made to collect data and report records and tests as completely as possible. Reasons for subject withdrawal/discontinuation may constitute one of the following:

- Subject withdrew consent
- Subject chooses to withdraw
- Subject is withdrawn due to an AE
- Pregnancy
- Lost to follow-up
- Subject is treated with or takes a prohibited medication
- The Investigator determines that it is in the subject's best interest
- Excessive protocol deviations, as determined by the Investigator or the Sponsor
- Discontinuation of study by the Sponsor

For subjects who withdraw/are discontinued prematurely, TV3 assessments will be performed as the end of study evaluations. For all withdrawn/discontinued subjects the Follow-up visit will happen 4 weeks ±3 days after the end of study Visit evaluations.

Important Notes:

1. Subjects may drop out or be withdrawn at their own request. Although subjects do not need to give a reason for requesting withdrawal from the trial, the Investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.
2. Any subjects reporting Serious Adverse Events (SAEs) that have not resolved by their last study visit will be followed to resolution or until 30 days after the subject completes the study.
3. Every attempt should be made to collect follow-up information. The reason for withdrawal from the study (if known) will be recorded in the source documents and on the appropriate page of the CRF.
4. Before a subject is identified as lost-to-follow-up, the site should make all reasonable efforts to contact the subject. These attempts must be documented and should include at a minimum one phone call and one follow-up certified letter.

5.3 SCREEN FAILURES

A subject who has signed the consent form but is not randomized is classified as a screen failure. Subject number, demographic information, and reason for screen failure will be collected.

6 STUDY TREATMENTS

6.1 METHOD FOR ASSIGNING ELIGIBLE SUBJECTS TO TREATMENT

Study eligible subjects will be randomized based on a randomization schedule prepared by Amarex Clinical Research, as the contracted CRO. Details of the randomization and assignment of the subject number are provided in Section 4.1 and Section 9.4.

At Baseline/Randomization visit (Treatment Visit 0, Day 0), all eligible subjects will be randomized 1:1:1 to receive DA-9805 at 45mg, 90mg or Placebo for 12 weeks.

After a subject has been determined to be eligible for the treatment in the study, a randomization number will be assigned. Once the randomization number is assigned, it cannot be re-assigned even if the subject is subsequently deemed ineligible or withdraws consent.

A subject who is randomized to study treatment becomes part of the Intent-to-Treat (ITT) population. Once a subject is randomized to study treatment, the subject must either complete the protocol or withdraw from the protocol (with reason specified). Randomized subjects may not be considered screen failures.

6.2 TEST TREATMENT

Test treatment for this trial is defined as DA-9805 45mg or 90mg. DA-9805 is an oral tablet that will be taken three times daily during this study.

- Group 1: DA-9805 45mg tablet (15 mg TID)
- Group 2: DA-9805 90mg tablet (30 mg TID)
- Group 3: placebo tablet (0 mg DA-9805 TID)

The ingredients in each DA-9805 tablet are included in Table 6-1 below.

6.3 CONTROL TREATMENT

The control treatment is Placebo, which will look, and will be packaged and maintained exactly the same way as the test treatment. The ingredients in each placebo tablet are included in Table 6-1.

Table 6-1: Study Treatment Ingredients

	Ingredient(mg/tablet)	DA-9805 45mg (15mg TID)	DA-9805 90mg (30 mg TID)	Placebo 0mg (0mg TID)
	Moutan Root Bark ・Bupleurum Root・Angelica Dahurica Root (1:1:1) 90% Ethanol Soft Extract	15	30	0
	Copovidone	2.5	2.5	2.5
	Magnesium Aluminometasilicate	20	40	20

	Lactose Hydrate	39	21.5	39
	Microcrystalline Cellulose	39	21.5	54
	Croscarmellose Sodium	7.5	7.5	7.5
	Magnesium Stearate	2	2	2
	Opadry White	3.75	3.75	3.75
	Opadry Pink	5	5	5
	Carnauba Wax	0.05	0.05	0.05
Total weight		133.8mg	133.8mg	133.8mg

6.4 STUDY TREATMENT LABELING AND PACKAGING

Both DA-9805 and placebo tablets will be provided under appropriate investigational product labeling. For the Double-Blind phase of the study, investigational product will be provided as blister packs. Each blister pack will contain 10 tablets of DA-9805 or placebo.

6.5 STUDY TREATMENT STORAGE

All study treatments will be stored at temperatures up to 25℃ and protected from direct light (Storage: Up to 25℃). Access to study treatment will be restricted to authorized personnel only.

6.6 STUDY TREATMENT ADMINISTRATION

All subjects, after signing the Informed Consent Form (ICF), will be assessed during the screening phase. Eligible subjects who have completed the screening phase will proceed with randomization and the double-blind treatment phase of the study.

- Subjects randomized to the active treatment groups (45mg or 90mg) will take one tablet three times daily with water.
- Subjects randomized to the Placebo treatment group will take one Placebo tablet three times daily with water.

Placebo tablets, as described in Section 6.3will be identical in appearance to the DA-9805 tablets.

6.7 STUDY TREATMENT DISPENSATION

At Treatment Visits 0, 1 and 2 of the study, sufficient randomized study treatments will be dispensed to each randomized subject for the period of time between the current clinic visit and the next clinic visit. Investigational products will be provided as blister packs. Each blister pack will contain 10 tablets of DA-9805 or placebo. For the active treatment group, 11 blister packs of active tablets (DA-9805 45mg or DA-9805 90mg as per treatment assignment) will be dispensed at each of these visits. For the placebo group, 11 blister packs of placebo tablets will be dispensed at each of these visits.

6.8 STUDY TREATMENT ACCOUNTABILITY

The Investigator or designee will verify the contents of each shipment against the shipping documents. Verification of study treatment receipt will be documented according to the Sponsor's requirements.

A study treatment accountability log will be provided to the site for use by the Investigator to maintain current and accurate inventory records (batch, expiry, and quantity) covering the receipt, dispensing and the destruction of all the study treatments.

At the conclusion of the study, or other situations as applicable (ex. site closure, IP expiry, etc.) the Investigator must agree to return or destroy all study materials as instructed by the Sponsor.

6.9 STUDY DRUG COMPLIANCE

Subjects will be instructed to bring used/unused study treatment blister packs. At each of these visits, tablet counts of returned study treatments will be conducted to determine if the subject has taken the study treatment per the protocol. If the number of dispensed tablets minus the number of remaining tablets (<80%) indicates that the subject is not taking their study treatment according to the study protocol, this will be recorded as a study drug non-compliance and the subject will be re-instructed on proper dosing. If the subject continues to be non-compliant with the dosing regimen the subject might be withdrawn from the study per the PI and/or the Sponsor's discretion. During Visits 1 to 3 subjects are required to report the date and time for the last daily dose of study treatment taken since the last visit.

7 CONCOMITANT AND PROHIBITED MEDICATIONS

Initiation of any new Parkinson's treatment during the study is prohibited.

Subjects must be questioned at each study visit concerning any new medications or changes in current medications including over-the-counter medication and topical medication. All medications and therapies administered or taken by the subject beginning 30 days prior to signing the ICF and throughout the study will be recorded in the source documents and on the appropriate page of the CRF.

For each medication and non-study treatment, the following will be documented:

- Medication/treatment name (generic name may be used if trade name is unknown)
- Dose, unit, and frequency of dosing (individual dosages, not total daily dose). Note: Each new dose of medication should be recorded as a separate entry, with the exception of medications that are given on a sliding scale. For these, it is acceptable to enter the range of the dosage, including the start and stop dates for which the specified dosage range was used.
- Route of dosing
- Indication for use
- The start date
- The stop date (if medication/therapy is not ongoing)

7.1 PROHIBITED MEDICATION

The following treatments and medications are prohibited throughout the study

1. Initiation of any anti-parkinsonian medication (including levodopa, dopamine agonists, entacapone and monoamine oxidase-B inhibitors) for the duration of the trial.
2. Initiation of Amantadine or anticholinergics for newly diagnosed subjects or change in the dosage of Amantadine or anticholinergics during the trial for subjects who were on stable doses for 4 weeks prior to screening.

8 DESCRIPTION OF PROTOCOL ASSESSMENTS AND PROCEDURES

8.1 INFORMED CONSENT

Written informed consent will be obtained for this study by the Investigator or suitably qualified designee from all subjects before the performance of any protocol-specific procedure. This study will be conducted in accordance with the provisions of the Declaration of Helsinki.

In obtaining and documenting informed consent, the Investigator must comply with applicable regulatory requirements and must adhere to GCP. The Investigator, or designee, must fully inform subjects of all pertinent aspects of the study. Before informed consent may be obtained, the Investigator, or a person designated by the Investigator, must provide the subject ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the trial. All questions about the trial must be answered to the satisfaction of the subject. Prior to the subject's participation in the trial, the written informed consent must be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

8.2 ELIGIBILITY ASSESSMENT

The eligibility assessment will be done as per inclusion and exclusion criteria of this Protocol as described in Section 3.1.2 and Section 3.1.3.

8.3 SUBJECT DEMOGRAPHICS

For the purposes of this study, demographic information will include:

- Date of birth
- Gender
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Pacific Islander, Caucasian, or other)
- Ethnicity (Hispanic/Latino or Not Hispanic/Latino)

8.4 MEDICAL HISTORY

All ongoing and any prior medical conditions that have resolved in the past year will be recorded at the Screening Visit.

Events that are reported prior to the first randomized dose administration at Treatment Visit 0 (TV0) will be recorded as part of the medical history and not as AEs. Aside from being used to determine subject eligibility, this information will permit the Investigator to record the nature, duration and severity of any ongoing baseline medical conditions prior to receiving study treatment.

Medical histories will be recorded using the body system categories outlined below:

- Psychiatric
- Neurological
- HEENT
- Respiratory
- Cardiovascular
- Gastrointestinal
- Genitourinary
- Musculoskeletal
- Endocrine
- Substance Abuse
- Integumentary
- Other

For each relevant history, the following will be documented:

- Disease/disorder/condition
- Date of onset/diagnosis
- History status (resolved or ongoing)
- Date of resolution, if applicable

8.5 VITAL SIGNS

The following vital signs will be collected in the CRF and should be in the subject's medical records:

- Blood Pressure (systolic and diastolic)*
- Heart Rate (HR)
- Respiration Rate (RR)
- Temperature

**Note: Blood Pressure will be assessed in "Sitting Position" after 5 minutes' rest.*

8.6 HEIGHT, WEIGHT AND BMI

Measurements will be taken in street clothing with jacket/coat and shoes removed. Body mass index (BMI) will be calculated from the height and weight measurements using the following formulas:

- Metric: BMI = Weight (kg) / $[\text{Height (m)}]^2$

  Or,

- Imperial: BMI= Weight (lb) / $[\text{Height (in)}]^2$ x 703

8.7 PHYSICAL EXAM

The physical examination will include routine examinations, not including rectal or genitourinary examinations. All clinically significant abnormalities will be recorded in subject's medical record and on the physical exam CRF page. Any abnormality that, in the opinion of the Investigator, is relevant to the safety of the subject or could impact safety or efficacy results for the subject will be considered as "clinically significant". After administration of the first dose of study treatment, each physical exam abnormality that is clinically significant will be recorded as an AE.

8.8 LABORATORY ASSESSMENTS

The subjects are not required to be fasting. The following lab measurements will be obtained (as part of the subject's medical record) and recorded:

- Biochemistry:
  - AST (U/L)
  - ALT (U/L)
  - ALP (U/L)
  - Bilirubin, direct and total (mg/dL)
  - LDH (U/L)
  - BUN (mg/dL)
  - GGT (U/L)
  - Serum creatinine (mg/dL)
  - Uric acid (mg/dL)
  - Sodium (mmol/L)
  - Potassium (mmol/L)
  - Chloride (mmol/L)
  - Serum triglycerides (mg/dL)
  - HDL (mg/dL)
  - Blood glucose (mg/dL)
- Hematology:
  - Red blood cell (RBC) count (millions/µL)
  - White blood cell (WBC) count (thousands/µL)
  - Platelet count (thousands/µL)
  - Hemoglobin (g/dL)
  - Hematocrit (%)
  - Mean Corpuscular Volume (MCV) (fL)
  - WBC differential including percentages of total WBC and absolute counts:
    - Neutrophils (i.e., segmented neutrophils)
    - Immature neutrophils
    - Lymphocytes
    - Monocytes
    - Eosinophils
    - Basophils
- Urine analysis:
  - Color
  - Specific gravity
  - pH
  - Semi-quantitative (dipstick) assessments for:
    - Blood
    - Glucose (mg/dL)
    - Protein (mg/dL)

- If abnormality is detected, microscopic assessment:
  - RBC (number per High Power Field [HPF])
  - WBC (number per HPF)
  - Epithelial cells (number per HPF)
  - Cast (number per HPF)
  - Crystals (number per HPF)

8.9 ELECTROCARDIOGRAM (ECG)

ECG will be performed per the site standard procedures. The following parameters will be recorded (as part of the subject's medical record) and recorded on the appropriate page of the CRF: ventricular rate (beats per minute), PR interval (msec), QRS interval (msec), QT interval (msec), and QTc interval (msec). Additionally, the Investigator will record the overall results of the ECG reading as either normal or abnormal, and if abnormal, as either "not clinically significant" or "clinically significant." If abnormalities are observed, each will be recorded. Each treatment-emergent abnormality that is clinically significant will be recorded as an AE. Each ECG should be signed by a physician.

8.10 URINE PREGNANCY TEST

The result must be documented on the source documents and in the CRF. Subjects who are found to be pregnant during the screening period will be considered a screen failure. If pregnancy occurs during the course of the study, the subject will be withdrawn from the study and the pregnancy will be followed up to term for safety purposes. Relevant safety information collected after the study has completed will be reported as supplemental information.

8.11 MDS- UNIFIED PARKINSON DISEASE RATING SCALE (MDS-UPDRS)

The MDS-UPDRS is a multimodal scale assessing both impairment and disability and is separated into 4 subscales (Parts I-IV). The MDS-UPDRS includes components assessed by the study investigator as well as sections completed by the subject. Every effort should be made to have the same investigator perform the ratings for an individual subject throughout the course of the study.

- Part I: This assesses non-motor experiences of daily living and is comprised of two components:
  - Part IA contains 6 questions that are assessed by the Investigator and focuses on complex behaviors.
  - Part IB contains 7 questions that are part of the Patient Questionnaire completed by the subject.
- Part II: This assesses motor experiences of daily living. There are an additional 13 questions that are also part of the Patient Questionnaire completed by the subject.
- Part III: This assesses the motor signs of PD and is administered by the Investigator.
- Part IV: This assesses motor complications, dyskinesias and motor fluctuations using historical and objective information. The Investigator will complete this assessment at each visit once a subject has started PD medication.

8.12 HOEHN AND YAHR STAGE

The Hoehn and Yahr is a commonly used system for describing how the symptoms of Parkinson's disease progress. The scale allocates stages from 0 to 5 to indicate the relative level of disability. This scale is included within the MDS-UPDRS and will be completed for all subjects.

- Stage zero: No symptoms.
- Stage one: Symptoms on one side of the body only.
- Stage two: Symptoms on both sides of the body. No impairment of balance.
- Stage three: Balance impairment. Mild to moderate disease. Physically independent.
- Stage four: Severe disability, but still able to walk or stand unassisted.
- Stage five: Wheelchair-bound or bedridden unless assisted.

8.13 PARKINSON'S DISEASE QUESTIONNAIRE (PDQ 39)

Parkinson's disease questionnaire (PDQ-39) is the most widely used patient reported rating scale in Parkinson's disease. PDQ 39 has questions relating to mobility, activities of daily living, emotional well-being, social support, cognition, communication and bodily discomfort. Subjects will be asked to answer the questions related to the last month.

8.14 CLINICAL GLOBAL IMPRESSION

The CGI measures global severity of illness at a given point in time, and the improvement from baseline at visits following the initial baseline visit. At the screening and baseline visit, the investigator will assess the severity on a seven-point scale. At subsequent visits, the investigator will assess the subject's severity and improvement relative to baseline.

Severity of Illness (CGI-S)

Rating should account for severity of the patient's illness.

0 = Not assessed
1 = Normal, not at all ill
2 = Borderline ill
3 = Mildly ill
4 = Moderately ill
5 = Markedly ill
6 = Severely ill
7 = Extremely ill

Global Improvement (CGI-I)

Compared to the patient's condition at the baseline of this study, how much has the patient's illness improved or worsened? (Circle one)

Rating should account for severity of the patient's illness.

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

8.15 SCHWAB AND ENGLAND ACTIVITIES OF DAILY LIVING SCALE

The Schwab & England Activities of Daily Living (ADL) scale reflects the speed, ease, and independence with which an individual performs daily activities, or personal chores, such as eating, toileting, and dressing. This scale uses a rating scale from 0% to 100%, with 100% representing complete independence in performing daily activities and 0% representing a vegetative, bedridden state.

8.16 COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

The Columbia Suicide Severity Rating Scale (C-SSRS) is a widely used suicidal ideation/suicidal behavior assessment tool (Posner, 2011). The C-SSRS assesses both suicidal ideation and suicidal behavior using questions in eleven (11) categories: five (5) for suicidal ideation, five (5) for suicidal behavior, and one (1) for self-injurious behavior without suicidal intent. There is a binary response (yes/no) for each question. For the purpose of this study, the "Lifetime/Recent" version of the C-SSRS, including questions spanning subjects' lifetime as well as the one (1) month prior to screening will be used as the baseline evaluation. On the following visits the "Since Last Visit" version of the C-SSRS will be used to assess the treatment-emergent suicidal ideation/behavior under study treatment. Suicidal ideation or behavior is defined as a "yes" answer to any one of the 10 suicidal ideation or behavior questions on the C-SSRS. All ratings will be done by a trained interviewer and ideally by the same individual at each study site. Examples for both versions of the C-SSRS to be used are depicted in the text Figure 18-1 and text Figure 18-2.

8.17 MINI-MENTAL STATE EXAMINATION

The MMSE is a commonly used tool to evaluate cognition (Folstein et al., 1975). It comprises of 11 items within different categories (orientation, registration, attention and calculation, recall, language and complex commands). The total score can range between 0 and 30. The example scoring of the tool is presented in text

Example Mini-Mental State Exam (MMSE)

Maximum	Score	
5		*What is the (year) (season) (date) (day) (month)?*

5	*Where are we (state) (country) (town) (hospital) (floor)?*
3	*Name 3 objects: 1 second to say each. Then ask the patient all 3 after you have said them. Give 1 point for each correct answer. Then repeat them until he/she learns all 3. Count trials and record.*
5	*Serial 7's. 1 point for each correct answer. Stop after 5 answers. Alternatively spell "world" backward.*
3	*Ask for the 3 objects repeated above. Give 1 point for each correct answer.*
2	*Name a pencil and watch*
1	*Repeat the following "No ifs, ands, or buts"*
3	*Follow a 3-stage command: "Take a paper in your hand, fold it in half, and put it on the floor."*
1	*Read and obey the following: CLOSE YOUR EYES*
1	*Write a sentence.*
1	*Copy the design shown.*

9 STATISTICAL CONSIDERATIONS

This section presents general information about statistical considerations and concepts such as randomization, covariates, sample size, and a brief discussion on analysis methodology, as well as some data conventions. Detailed descriptions of the statistical analysis methods and data conventions will be included in a separate document; i.e., the Statistical Analysis Plan (SAP).

9.1 TREATMENT GROUPS

The following treatment groups will be assessed:

Group	Description
1	DA-9805 (45 mg/day – 15mg TID) for 12 weeks
2	DA-9805 (90 mg/day – 30mg TID) for 12 weeks
3	Placebo (0 mg/day) for 12 weeks

9.2 DESCRIPTION OF STUDY ENDPOINTS

9.2.1 SAFETY OUTCOME MEASURES

- Incidence of Treatment-Emergent Adverse Events (AEs).
- Incidence of withdrawals due to AEs.
- Change/shifts in laboratory values.
- Change in vital signs.
- Change in Electrocardiogram (ECG) parameters.
- Change in Columbia- Suicide Severity Rating Scale from baseline at week 12.

9.2.2 PRIMARY EFFICACY OUTCOME MEASURE

- Change in motor MDS-Unified Parkinson Disease Rating Scale (MDS-UPDRS) total score from baseline at week 12.

9.2.3 SECONDARY EFFICACY OUTCOME MEASURES

- Change in total MDS- UPDRS total score from baseline at week 12.
- Change in MDS-UPDRS subscale scores from baseline at week 12.
- Change in Schwab and England (S&E) Scale total score from baseline at week 12.
- Change in Parkinson's Disease Questionnaire (PDQ-39) total score from baseline at week 12.
- Change in Hoehn and Yahr (H&Y) scale total score from baseline at week 12.
- Change in Clinical Global Impression-Severity (CGI-S) and Clinical Global Impression-Improvement (CGI-I) scale score from baseline at week 12.

9.3 SAMPLE SIZE DETERMINATION

It is planned to randomize a total of 60 subjects (20 subjects per group) with early Parkinson’s disease in this trial. This sample size is selected on the basis of clinical judgment and not based on statistical

power calculation; it is deemed adequate to provide clinically meaningful descriptive results consistent with the study objectives.

9.4 RANDOMIZATION

Treatment assignment will be based on randomization schedule. An individual, independent of the clinical trial team, will develop the randomization schedules. The actual randomization assignment will be made through an Interactive Web Based Response System (IWRS) called WebView®. Subjects who have provided written informed consent and have met all the inclusion criteria and none of the exclusion criteria will be randomized to one of the treatment groups.
The randomization in this multi-center study will be applied centrally across the sites and will use a mixed block size of 3 and 6 with a 1:1:1 ratio of DA-9805 (45mg/day), DA-9805 (90mg/day) and Placebo Treatment groups.

9.5 BLINDING AND PREVENTION OF BIAS

The subjects, Investigators and their staff, and all Sponsor/CRO personnel involved in the management, and data collection in this study will be blinded to the treatment assignments.

Treatment un-blinding for the study will occur after all clinical data have been received, data inconsistencies have been resolved, and the database is locked, except for safety reasons on a case-by-case basis (i.e., emergency unblinding).

9.6 INTERIM ANALYSIS (IA)

There is no interim analysis planned for this study.

9.7 GENERAL STATISTICAL CONSIDERATIONS

All collected study data will be presented in subject data listings. Statistical analyses will be performed using SAS® for Windows, version 9.3 or later.

9.8 ANALYSIS POPULATIONS

The details of the analysis population to be used for the study are described below:

9.8.1 INTENT-TO-TREAT (ITT) POPULATION

The Intent-to-Treat (ITT) population is defined as all randomized subjects who have received at least one dose of study treatment and undergone at least one post-randomization efficacy assessment.

9.8.2 PER PROTOCOL (PP) POPULATION

The Per Protocol (PP) population is defined as the set of subjects who meet the ITT population requirements, and were not associated with a major protocol violation. This population will be identified before the database lock, and before the treatment assignments are revealed.

9.8.3 SAFETY POPULATION

The Safety population is defined as all subjects receiving at least one dose of the treatment after randomization.

9.9 STATISTICAL METHODS

A Statistical Analysis Plan (SAP) will be developed and approved before the database is locked. The SAP will present the detailed statistical methodology to be used in analyzing the efficacy and tabulating the safety data from this trial. All inferential statistical analyses will be based on a two-sided test with a Type I error rate of 0.05.

9.9.1 SUBJECT DISPOSITION

The disposition of all subjects who sign an ICF will be provided. The numbers of subjects screened, randomized, completed, and discontinued during the study, as well as the reasons for all post-randomization discontinuations will be summarized by treatment group. Disposition and reason for study discontinuation will also be provided as a by-subject listing.

9.9.2 DEMOGRAPHICS AND BASELINE CHARACTERISTICS ANALYSIS

Demographics and baseline characteristics will be summarized by treatment group using appropriate descriptive statistics.

9.9.3 CONCOMITANT MEDICATIONS/THERAPIES

Concomitant medications/therapies will be summarized separately for the Safety population. All prior and concomitant medications recorded in the case report form will be coded to all matching Anatomic Therapeutic Classification codes using the most recent version of WHO Drug. Descriptive summaries, by treatment group and stage of the study, will be prepared using the coded term. All concomitant medications/therapies recorded in the case report form will be listed.

9.9.4 MEDICAL HISTORY

The medical history will be summarized and/or listed descriptively.

9.9.5 STUDY TREATMENT COMPLIANCE

The study treatment compliance data will be summarized and/or listed descriptively.

9.10 SAFETY OUTCOME ANALYSES

Analyses of safety outcomes will be conducted using the safety population.

9.10.1 ADVERSE EVENTS

Adverse events will be coded using MedDRA. Treatment Emergent AE's (TEAE) are defined as events with an onset on or after the first randomized treatment. TEAEs will be summarized by treatment group and by stage of the study, System Organ Class, and preferred term. The following TEAE summaries will be provided:

- TEAEs by severity grade
- TEAEs by relationship to study treatment.

In addition, separate summaries of serious adverse events, and adverse events resulting in discontinuation of study treatment will be presented.

9.10.2 COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

All the data from C-SSRS will be listed and descriptive summaries will be presented for each of the subscales (i.e. Suicidal Ideation and Suicidal Behavior).

9.10.3 CLINICAL LABORATORY DATA

All laboratory values will be listed. Laboratory measurements will also be summarized and presented by treatment group and time point.

9.10.4 VITAL SIGN AND WEIGHT

All changes in vital signs and weight will be listed and summarized over time.

9.10.5 ECG

All changes in ECG will be listed and summarized over time.

9.10.6 PHYSICAL EXAMINATION

All results for physical examination will be listed and summarized.

9.11 EFFICACY OUTCOME ANALYSES

The primary analysis of the primary and secondary endpoints will be conducted using the PP population.

For the efficacy endpoints the data will be summarized and compared according to the variable type.
Continuous data summaries will include:

- Descriptive summary of number of observations, mean, standard deviation, median, and minimum and maximum values.
- Inferential statistics include:
  - t-test or ANCOVA using the baseline value as a covariate , if the Normality assumption is met
  - rank –ANCOVA analysis i.e., an ANCOVA analysis on rank-transformed data or other non-parametric methods, if the Normality assumption is not met.

Categorical data summaries will include:

- Frequency counts and percentages.
- Logit model for inferential statistics.
- If the Normality assumption is met, t-test or ANCOVA using the baseline value as a covariate will be used.
- If the Normality assumption is not met, a rank –ANCOVA analysis i.e., an ANCOVA analysis on rank-transformed data or other non-parametric methods will be used.

10 ADVERSE EVENTS (DEFINITIONS AND REPORTING)

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study when there is a safety evaluation, the Investigator or site staff will be responsible for detecting, documenting, and reporting AEs and SAEs as detailed in this section of the protocol.

10.1 ADVERSE EVENT

An adverse event (AE) is defined as any unfavorable or unintended sign, symptom, or disease that occurs or is reported by the subject to have occurred, or a worsening of a pre-existing condition. An AE may or may not be related to the study treatment.

AEs will be elicited through direct questioning and subject reports. Any abnormalities in visit evaluations, physical examination findings or laboratory results that the Investigator believes are clinically significant to the research subject and that occurred after initiation of the first study treatment will be reported as AEs. Abnormal findings that are NOT clinically significant should not be recorded as an AE.

10.2 REPORTING OF ADVERSE EVENTS

Report initiation for all AEs and SAEs will begin at the time of the first randomized treatment and continue up until the final study visit. All events will be followed to resolution or until 30 days after the subject completes the study. A final assessment of outcome will be made at that time.

All AEs must be recorded in the subject's medical records and on the CRF. AEs will be reported using customary medical terminology along with the following information: the onset and end dates, whether the event is considered to be an SAE (see Section 10.4), the impact the event had on study treatment (see Section 10.2.1), the CTCAE grade (intensity) of the event (see Section 10.2.2), the causality of the event (see Section 10.2.3), whether treatment was given as a result of the event (see Section 10.2.4), and the outcome of the event (see Section 10.2.5).

10.2.1 IMPACT ON STUDY TREATMENT

The impact the event had on the study treatment will be assessed as either: none, study treatment interrupted, study treatment discontinued, or not applicable. The "not applicable" assessment will be used only when the subject is no longer in the treatment phase of the protocol, or if the outcome of the event was "death".

10.2.2 CTCAE GRADE (INTENSITY) ASSESSMENT

The guidelines outlined in CTCAE v4.03 will be used for assessing the intensity of the event. The general guidelines for assessing the AE grade appear below. Full guidelines may be obtained at http://evs.nci.nih.gov/ftp1/CTCAE.

Table 10-1: CTCAE v4.03 General Guidelines

Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL†.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
†Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

-Common Terminology Criteria for Adverse Events (CTCAE), v4.03: June 14, 2010

10.2.3 CAUSALITY ASSESSMENT

Adverse events will be assigned a relationship (causality) to the study treatment. The Principal Investigator must review each AE and make the determination of relationship of the event to the study treatment. Relationship of AEs to study treatment will be classified as follows:

1. **Definitely related**: This category applies to those AEs that the Investigator feels are incontrovertibly related to the study treatment. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the study treatment; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it follows a known response pattern to treatment with the study treatment.
2. **Probably related:** This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the study treatment. An AE may be considered probable if or when (must have three): (1) it follows a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It follows a known response pattern to treatment with the study treatment.
3. **Possibly related**: This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are judged unlikely but cannot be ruled out with certainty to the study treatment. An AE may be considered possible if or when (must have two): (1) it follows a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It follows a known response pattern to treatment with the study treatment.
4. **Remotely related**: In general this category can be considered applicable to those AEs which, after careful medical consideration at the time they are evaluated, are judged likely to be unrelated to the study treatment. An AE may be considered unlikely if or when (must have two): (1) it does not follow a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It does not follow a known response pattern to treatment with the study treatment.
5. **Unrelated**: This category applies to those AEs which, after careful consideration at the time they are evaluated, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.) and determined with certainty to have no relationship to the study treatment.

10.2.4 TREATMENT GIVEN AS A RESULT OF THE EVENT

The event impact in terms of treatment provided will be as either: none, medication administered, non-medication therapy administered, surgery, or other (with a specification).

10.2.5 OUTCOME ASSESSMENT

The outcome of the event will be assessed as either: resolved, resolved with sequelae, ongoing, or death. Only one AE per subject is allowed to have an outcome assessment as "death." If there are

multiple causes of death for a given subject, only the primary cause of death will have an outcome of death.

10.3 EXPECTED / ANTICIPATED ADVERSE EVENTS

There are no expected AEs associated with participation in this study.

10.4 SERIOUS ADVERSE EVENTS

A SAE is defined as any AE that:

- Results in death
- Is life threatening (the subject is at immediate risk of dying from the AE)
- Requires subject hospitalization or prolongs existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.5 REPORTING OF SERIOUS ADVERSE EVENTS (SAE)

The Investigator is required to report all SAEs that occur during the time period specified in Section 10.2. Once the Investigator becomes aware of an SAE, he/she must report the SAE to Amarex Safety Department within 24 hours:

CRO Medical Monitor	Attn: Shide Badri, MD Amarex LLC 20201 Century Boulevard, Suite 450 Germantown, MD 20874 Email: saereporting@amarexcro.com Phone: +1 (240) 454-6844 Fax: +1 (240) 454-6602

A written report, including a full description of the event as described in Section 10.2, must follow within 24 hours from the time the Investigator first learned of the event. The Amarex Medical Monitor may request additional supporting documentation as it becomes available, such as lab reports, ECG reports, discharge summary, hospital notes, etc.
The Investigator is also responsible for reporting all SAEs to the appropriate Institutional Review Board (IRB) in accordance with local laws and regulations. The Investigator is responsible for maintaining documentation in the study file that indicates the IRB has been properly notified.

10.6 SAE FOLLOW-UP

All subjects experiencing an SAE, including the discontinued subjects, must be closely followed until sufficient information is obtained to indicate a return to normal status or until the event stabilizes at a level acceptable to the investigator (i.e., recovery, return to baseline status, no further improvement expected, or death).

For each SAE indicated as an unresolved event on the initial report, regardless of whether the subject completed the study or withdrew, the site should submit a follow-up report with updated information.

11 DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

Subjects will be identified on CRFs by a unique subject identification number and on source documents by name and date of birth. No personal identifier will be used in any publication or communication used to support this research study. The subject identification number will be used if it becomes necessary to identify data specific to a single subject.

The monitors, auditors, personnel authorized by the Sponsor, the local IRB, and the FDA are eligible to review medical and research records related to this study as a part of their responsibility to protect human subjects in clinical research and will be given direct access to source data and documentation (e.g., medical charts/records, printouts etc.) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements. Access to electronic medical records may be governed by institution policy and each site will be required to ensure access while remaining compliant with institutional requirements.

12 DATA SAFETY MONITORING COMMITTEE (DSMC)

A Data Safety and Monitoring Committee (DSMC), independent of the study operations will be established to consider safety data generated during the study. The details of the DSMC responsibilities will be included in the DSMC charter. The DSMC charter will be developed and operated in adherence to the current FDA guidance on DSMC (Establishment and Operation of Clinical Trial Data Safety Monitoring Committees [March 2006]). The DSMC meetings will take place at least once and at other time-points as determined by the DSMC charter. In addition to the pre-specified time-points, the DSMC may also decide to schedule a meeting whenever they decide a review of emergent safety data is warranted. The charter will detail the roles and responsibilities of the DSMC members once they have been appointed. The study data will be provided to the Committee members in the form of a data report. Meetings to discuss the data will be held in person or by teleconference, based on the DSMC Chair's decision. The meetings will be in two stages: an "open stage" which will involve discussion on general aspects of the trial, and a "closed stage" between the DSMC members only. The remit of the DSMC will be primarily to assess the safety aspects of the trial.

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 MONITORING REQUIREMENTS

In an effort to fulfill the obligations outlined in 21 CFR Part 312 and ICH guidelines which require the Sponsor to maintain current personal knowledge of the progress of a study, the Sponsor's designated monitor will visit the center(s) during the study as well as maintain frequent telephone and written communication. The Investigator will permit the Sponsor to monitor the study as frequently as is deemed necessary and provide access to medical records to ensure that data are being recorded adequately, that data are verifiable and that protocol adherence is satisfactory.

The Investigator will permit representatives of the Sponsor and/or designated CRO to inspect all CRFs and corresponding study subject original medical records (source documents) at regular intervals throughout the study. Subject original medical records and other relevant data must be available to support all data recorded in the CRF. In addition to the original medical records, these data may include but are not limited to, study, laboratory and diagnostic reports, wound images and tracings, etc.

Site inspections serve to verify strict adherence to the protocol and the accuracy of the data being entered on the CRFs, in accordance with federal regulations. A Monitoring Log will be maintained at each study site that the monitor will sign, date, and state the type of visit.

The Investigator should be aware that the study site and subject records may be inspected by the Sponsor and or representatives of the designated CRO, FDA, or other regional regulatory authority.

The final statistical analysis of data will be performed after all clinical monitoring has been completed, all data queries have been resolved, and all data have been verified (Quality Control checked) prior to formal database lock. The Sponsor will authorize the final database lock.

13.2 ACCEPTABILITY OF CASE REPORT FORMS

All CRFs will be completed as soon as possible after the subject's visit. Corrections to data on the CRFs will be made according to standard data correction procedures. The Investigator will review CRFs to indicate that, to his/her knowledge, they are complete and accurate. CRFs will be reviewed by the Sponsor’s or designated CRO’s monitor, who will make a decision as to their acceptability.

13.3 MODIFICATION OF PROTOCOL

The Investigator will not modify or alter this protocol without first obtaining the concurrence of the Sponsor. Approval by the Investigator’s IRB must also be obtained prior to implementation of the change, with two exceptions:

1. When necessary to eliminate apparent immediate hazard to the subject; or
2. When the modification does not involve the subject’s participation in the trial.

An amendment may also require modification of the ICF. The Investigator will provide an approval letter for the amendment and revised ICF, if applicable, to the Sponsor. An amendment must be in

writing and it must be dated by both the Sponsor and the Investigator. If necessary, the Sponsor will submit protocol amendments to FDA and other appropriate regulatory authorities and notify other Investigators using this protocol.

13.4 REPORTING PROTOCOL DEVIATIONS

The Investigator is obligated to follow the protocol without departure from the requirements written in the protocol. If the Investigator deviates from the protocol requirements, the Sponsor will make the determination as to whether the subject will continue in the study. The Sponsor also has the right to discontinue the subject for protocol violations. The IRB may also have to be contacted if safety to the subject or if the scientific soundness of the study is involved. All protocol deviations must be documented in the CRFs.

14 ETHICS AND REGULATORY REQUIREMENTS

This study is to be conducted in accordance with the specifications of this protocol and in accordance with principles consistent with the Declaration of Helsinki, GCP, 21 CFR 312, ICH E6, HIPAA regulations in 45 CFR Part 164, and the Belmont Principles of respect for persons, beneficence, and justice. No protocol changes will be implemented without the prior review and approval of the IRB, except where it may be necessary to eliminate an immediate hazard to a research subject. In such a case, the change will be reported to the IRB as soon as possible, according to IRB regulations. Additionally, all study products used in this study are manufactured, handled and stored in accordance with applicable Good Manufacturing Practices (GMP) and the products provided for this study will be used only in accordance with this protocol.

14.1 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

The Principal Investigator will provide the Institutional Review Board/Independent Ethics Committee (IRB/IEC) with all appropriate materials as required by their IRB/IEC, including but not limited to the clinical study protocol, ICFs, and any advertising materials. The study will not be initiated until the IRB/IEC provides written approval of the aforementioned documents and until approval documents have been obtained by the Principal Investigator and Sponsor or Sponsor designee. The Investigator will not participate in the decision. If the Investigator is an IRB or IEC member, documentation must be provided indicating recusal from the approval process. Appropriate reports on the progress of this study by the Principal Investigator will be made to the IRB/IEC as required by local and applicable government regulations and in agreement with policy established by the Sponsor. The Investigator is required to maintain an accurate and complete record of all written correspondence to and received from the IRB/IEC, and must agree to share all such documents and reports with the Sponsor.

No changes from the final approved protocol will be initiated without the IRB/IEC's prior written approval or favorable opinion of a written amendment, except when necessary to eliminate immediate hazards to the subjects or when the change involves only logistics or administration.

14.2 INVESTIGATOR'S RESPONSIBILITIES

The Investigators are responsible for performing the study in full accordance with the protocol and the current revision of the Declaration of Helsinki, the Good Clinical Practice: Consolidated Guideline, approved by the ICH, and any applicable national and local laws and regulations. Information regarding any study centers participating in this study that cannot comply with these standards will be documented.

14.3 SUBJECT INFORMED CONSENT REQUIREMENTS

Written and oral information about the study in a language understandable by the subject will be given to all subjects by the Principal Investigator and/or designee. Written informed consent will be obtained from each subject accordingly before any procedures or assessments that would not otherwise be required for the care of the subject are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained and the subject has been given sufficient time to ask questions and consider participation in the study. It will also be explained to the subjects

that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. The written ICF is to be in compliance with CFR 21 Part 50.27, 45 Part 46 and GCP guidelines. The Sponsor and/or designated CRO will approve the ICF and all amendments to the ICF prior to submission to the IRB/IEC. A copy of the ICF to be used will be submitted by the Investigator to the IRB/IEC for review and approval prior to the start of the study. Each study site must provide the Sponsor with an unsigned copy of IRB/IEC-approved ICF along with applicable documentation to support this approval. The original signed ICF is retained in the subject's study records, and a copy is provided to the subject. A second copy may be filed in the subject's medical record, if allowed by institutional policy.

15 DATA HANDLING AND RECORD KEEPING

15.1 RECORDING AND COLLECTION OF DATA

The primary source document for this study will be the subject's medical records. If separate research records are maintained by the Investigator(s), the medical records and the research records will be considered the source documents for the purposes of auditing the study.

Applicable source data will be manually transcribed to the approved CRFs. The Investigator is ultimately responsible for the accuracy of the data transcribed on the forms. All source documents and CRFs will be completed as soon as possible after the subject's visit.

The Investigator will review CRFs to indicate that, to his/her knowledge, they are complete and accurate. If further changes are made after this, the Investigator will need to again sign the Investigator signature page. Designated source documents will be signed and dated by the appropriate study personnel. The Investigator must agree to complete and maintain source documents and CRFs for each subject participating in the study. The Investigator will maintain a confidential list of study subjects that will include each subject's study number, name, date of birth and unique hospital identification number if applicable. This list will be kept by the Investigator and will not be collected by the Sponsor. A notation will be made in the subject's case history/medical chart that he/she is participating in a clinical study and that the subject has provided a signed and dated ICF accordingly as well as the required site HIPAA authorization (if separate from the ICF). The Investigator must also maintain a separate screening log of all the subjects screened for participation in the study; it should include gender; age; eligibility status; reason for ineligibility, if applicable; and study allocated subject number, if applicable.

15.2 CLINICAL DATA MANAGEMENT

The Sponsor and/or designated CRO will be responsible for the processing and quality control of the data. Data management will be carried out as described in the Sponsor's or CRO's standard operating procedures (SOPs) for clinical studies.

The handling of data, including data quality control, will comply with regulatory guidelines (e.g., ICH E6 GCP, and local regulations where applicable) and the Sponsor's or the CRO's SOPs as well as provisions of the study-specific Data Management Plan. All research data will be entered, either electronically or manually, into a computerized database, designed in accordance with 21 CFR Part 11 and based on protocol requirements defined by the Sponsor in association with clinical data manager, including double-data entry, where applicable. The data will be reviewed, manually and/or electronically, and queries will be prepared for any data discrepancies.

15.3 ARCHIVING

All study documentation at the Investigator site and Sponsor site will be archived in accordance with ICH GCP E6 and the Sponsor's quality standards and SOPs.

In accordance with CFR 21 Part 312, study records must be retained by the Investigator for at least two years (or longer per the state/local regulations) after all investigational use of the product is discontinued and the FDA is notified or until two years after the last approval of a marketing application. Study records should not be destroyed without prior written agreement between the Sponsor and the study Investigator. At the completion of the study, details of the archival process must be provided to the Sponsor. Study records are subject to inspection by applicable health and regulatory agencies at any time.

Records to be retained by the Investigator include, but are not restricted to:

- Case Report Forms and the source data and the primary records upon which they are based (e.g., subject's progress notes, AE data, test results, and any other diagnostic procedures required to evaluate the progress of the study).
- Signed protocols and protocol amendments
- Laboratory ranges and certifications
- Product accountability records
- Study personnel signature log
- Monitoring logs
- Correspondence to and from the Sponsor, designee and IRB
- Investigator and sub-Investigator CVs
- Signed informed consent and HIPAA forms
- Subject screening and randomization log
- Serious adverse event reports
- Institutional Review Board approval and re-approval letters
- Other documents pertaining to the conduct of the study

These documents must be maintained and kept on file by the Investigator so that the conduct of the study can be fully documented and monitored.

16 PUBLICATION PLAN

The Investigator will refer to the Investigator agreement and clinical trial agreement for the publication and disclosure policy.

17 REFERENCES

1. Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Goetz, C. G., Tilley, B. C., Shaftman, S. R., Stebbins, G. T., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stern, M. B., Dodel, R., Dubois, B., Holloway, R., Jankovic, J., Kulisevsky, J., Lang, A. E., Lees, A., Leurgans, S., LeWitt, P. A., Nyenhuis, D., Olanow, C. W., Rascol, O., Schrag, A., Teresi, J. A., van Hilten, J. J. and LaPelle, N. (2008), Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. Mov. Disord., 23: 2129-2170.
2. Fahn S, Elton RL, and members of the UPDRS committee. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Goldstein M, Calne DB, eds. Recent developments in Parkinson's Disease. New Jersey: McMillan Health Care, 1987:153-163.
3. Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. Neurology 1967;17:427-442.
4. Peto V, Jenkinson C, Fitzpatrick R, Greenhall R. The development and validation of a short measure of functioning and well-being for individuals with Parkinson' disease. Qual Life Res 1995; 4: 241-248
5. Fearnley, J. M. & Lees, A. J. Ageing and Parkinson's disease: substantia nigra regional selectivity. Brain 114 (Pt 5), 2283-2301 (1991).
6. Halliday, G., Lees, A. & Stern, M. Milestones in Parkinson's disease--clinical and pathologic features. Movement disorders : official journal of the Movement Disorder Society 26, 1015-1021, doi:10.1002/mds.23669 (2011).
7. Przuntek, H., Muller, T. & Riederer, P. Diagnostic staging of Parkinson's disease: conceptual aspects. J Neural Transm 111, 201-216, doi:10.1007/s00702-003-0102-y (2004).
8. Halliday, G., Lees, A. & Stern, M. Milestones in Parkinson's disease--clinical and pathologic features. Movement disorders : official journal of the Movement Disorder Society 26, 1015-1021, doi:10.1002/mds.23669 (2011).
9. Emre, M. et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society 22, 1689-1707; quiz 1837, doi:10.1002/mds.21507 (2007).
10. Olanow CW. The scientific basis for the current treatment of Parkinson’s disease. Annu Rev Med 2004;55:41-60.
11. Schapira AHV, Olanow CW. Neuroprotection in Parkinson’s disease: myths, mysteries, and misconceptions. JAMA 2004;291:358-64.
12. Olanow CW, Kieburtz K, Schapira AH. Why have we failed to achieve neuroprotection in Parkinson’s disease? Ann Neurol 2008; 64 (suppl 2): S101–10.
13. Hart RG, Pearce LA, Ravina BM, Yaltho TC, Marler JR. Neuroprotection trials in Parkinson’s disease: systematic review. Mov Disord 2009; 24: 647–54.
14. Fox SH, Katzenschlager R, Lim SY, et al. The Movement Disorder Society evidence-based medicine review update: treatments for the motor symptoms of Parkinson’s disease. Mov Disord 2011; 26 (suppl 3): S2–41.
15. National Institute of Mental Health (NIMH). Early clinical drug evaluation unit (ECDEU). Clinical global impressions. In: Guy W, ed. ECDEU assessment manual for psychopharmacology, revised edition. Rockville, MD: NIMH USA; 1976: 216–22.

16. Schapira AH, Obeso J. Timing of treatment initiation in Parkinson's disease: a need for reappraisal? Ann Neurol 2006; 59: 559–62.
17. Fahn S, Oakes D, Shoulson I, et al. Levodopa and the progression of Parkinson's disease. N Engl J Med 2004; 351: 2498–508.
18. McRae C, Diem G, Vo A, et al. Schwab & England: standardization of administration. Mov Disord 2000; 15:335–6.
19. Schwab RS, England Jr AC. Projection technique for evaluating surgery in Parkinson's disease. In: Gilingham FJ, Donaldson IML, eds. Third symposium on Parkinson's disease. Edinburgh: E & S Livingstone, 1969:152–7.
20. http://www.fda.gov/downloads/Drugs/.../Guidances/UCM225130.pdf
21. Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, Currier GW, Melvin GA, Greenhill L, Shen S, Mann JJ. The Columbia–Suicide Severity Rating Scale: Initial Validity and Internal Consistency Findings From Three Multisite Studies With Adolescents and Adults. Am J Psychiatry. 2011 Dec;168(12):1266-77
22. Forkmann T, Scherer A, Boecker M, Pawelzik M, Jostes R, Gauggel S. The clinical global impression scale and the influence of patient or staff perspective on outcome. BMC Psychiatry 2011; 11:83.
23. Martinez-Martin P, Forjaz MJ, Cubo E, Frades B, de Pedro Cuesta J, The ELEP project members. Global versus factor-related impression of severity in Parkinson's disease: a new clinimetric index (CISI-PD). Mov Disord 2006; 21:208-14.
24. Kim HG, Park G, Piao Y, Kang MS, Pak YK, Hong SP, Oh MS. Effects of the root bark of Paeonia suffruticosa on mitochondria-mediated neuroprotection in an MPTP-induced model of Parkinson's disease. Food Chem Toxicol. 2014;65:293-300.
25. Park WH, Kang S, Piao Y, Pak CJ, Oh MS, Kim J, Kang MS, Pak YK. Ethanol extract of Bupleurum falcatum and saikosaponins inhibit neuroinflammation via inhibition of NF-κB. J Ethnopharmacol. 2015;174:37-44.
26. Moon YJ, Lee JY, Oh MS, Pak YK, Park KS, Oh TH, Yune TY. Inhibition of inflammation and oxidative stress by Angelica dahuricae radix extract decreases apoptotic cell death and improves functional recovery after spinal cord injury. J Neurosci Res. 2012; 90(1):243-56.
27. The Korean Pharmacopoeia 10th edition. (The KFDA Notification No. 2012–129. 2012. Dec 27th. Korea Food & Drug Administration.)
28. The Japanese Pharmacopoeia 16th Edition (English edition). (March 24, 2011 The MHLW Ministerial Notification No. 65).
29. Chinese Pharmacopoeia 2010. (June 17, 2010 The CFDA Notification No. 2010-43).

18 APPENDICES

18.1 APPENDIX 1: MDS-UPDRS, HOEHN & YAHR SCALE

MDS-UPDRS Permissions

Permission is required to use the MDS-developed Rating Scales (with the exception of personal/individual use). Reproduction, translation, modification, sale, or distribution of any portion of the MDS Rating Scales is strictly prohibited. MDS Rating Scales may not be incorporated into clinical trials, training or certification programs or materials, software programs, or otherwise except through use of the Permissions Request Form and payment of applicable fees.

Continue to p. 2 to view the 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
Rush University Medical Center
1725 W. Harrison Street, Suite 755
Chicago, IL USA 60612

Telephone 312-942-8016
Email: cgoetz@rush.edu

July 1, 2008

July 1, 2008 *Copyright © 2008 Movement Disorder Society. All rights reserved* Page 1
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

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:

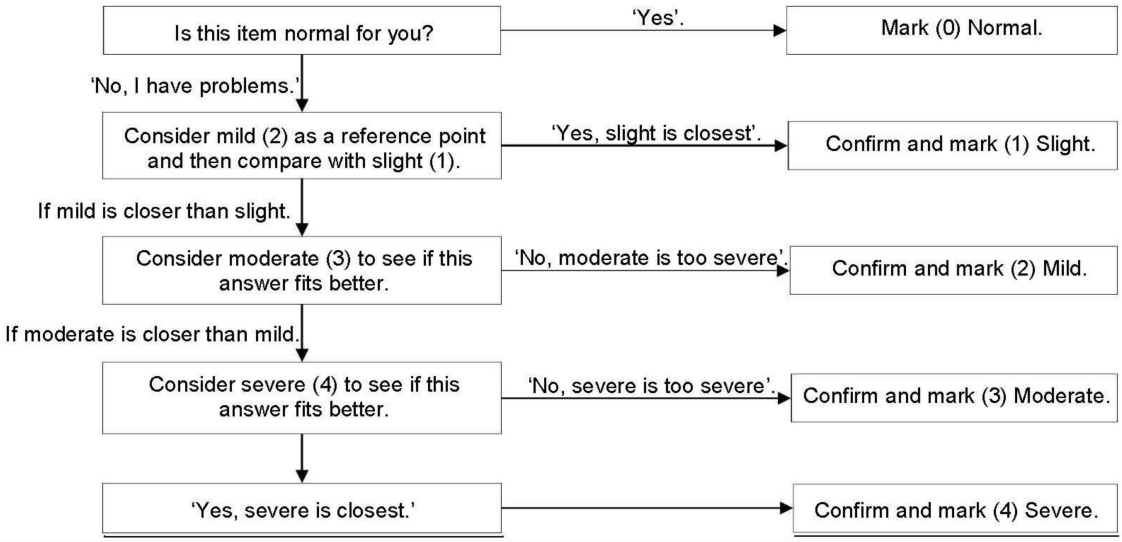
1. Mark at the top of the form the primary data source as patient, caregiver, or patient and caregiver in equal proportion.
2. The response to each item should refer to a period encompassing the prior week including the day on which the information is collected.
3. All items must have an integer rating (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. 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.

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.



July 1, 2008 Copyright © 2008 Movement Disorder Society. All rights reserved Page 2
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

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

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

Part 1A: 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.	☐

July 1, 2008 *Copyright © 2008 Movement Disorder Society. All rights reserved* Page 3
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

	SCORE
1.2 HALLUCINATIONS AND PSYCHOSIS 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 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.	☐

July 1, 2008 *Copyright © 2008 Movement Disorder Society. All rights reserved* Page 4
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

	SCORE
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: 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 interactions. 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 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.	☐

July 1, 2008 *Copyright © 2008 Movement Disorder Society. All rights reserved* Page 5
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

1.6 FEATURES OF DOPAMINE DYSREGULATION SYNDROME	SCORE
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].

July 1, 2008 *Copyright © 2008 Movement Disorder Society. All rights reserved* Page 6
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

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

July 1, 2008 *Copyright © 2008 Movement Disorder Society. All rights reserved* Page 7
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

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 how 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. 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.	☐

July 1, 2008 *Copyright © 2008 Movement Disorder Society. All rights reserved* Page 8
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

	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. 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.	☐

July 1, 2008 *Copyright © 2008 Movement Disorder Society. All rights reserved* Page 9
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

	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.	☐

July 1, 2008 *Copyright © 2008 Movement Disorder Society. All rights reserved* Page 10
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

	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)	
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 everyday. 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.	☐

July 1, 2008 *Copyright © 2008 Movement Disorder Society. All rights reserved* Page 11
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

	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.	☐

July 1, 2008 *Copyright © 2008 Movement Disorder Society. All rights reserved* Page 12
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

	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.	☐

July 1, 2008 *Copyright © 2008 Movement Disorder Society. All rights reserved* Page 13
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

	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.	☐

July 1, 2008 *Copyright © 2008 Movement Disorder Society. All rights reserved* Page 14
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

	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.	☐

July 1, 2008 Copyright © 2008 Movement Disorder Society. All rights reserved Page 15
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

	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.	

July 1, 2008 *Copyright © 2008 Movement Disorder Society. All rights reserved* Page 16
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

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: _____

July 1, 2008 *Copyright © 2008 Movement Disorder Society. All rights reserved* Page 17
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

	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.	☐

July 1, 2008 *Copyright © 2008 Movement Disorder Society. All rights reserved* Page 18
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

	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: 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.	☐ R ☐ L

July 1, 2008 *Copyright © 2008 Movement Disorder Society. All rights reserved* Page 19
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

	SCORE
3.5 HAND MOVEMENTS 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. 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. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L
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. 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.	☐ R ☐ L

July 1, 2008 *Copyright © 2008 Movement Disorder Society. All rights reserved* Page 20
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

	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. 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.	☐ R ☐ 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. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L

July 1, 2008 *Copyright © 2008 Movement Disorder Society. All rights reserved* Page 21
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

	SCORE
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 problems. 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.	☐
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.	☐

July 1, 2008 *Copyright © 2008 Movement Disorder Society. All rights reserved* Page 22
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

	SCORE
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. 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.	☐

July 1, 2008 *Copyright © 2008 Movement Disorder Society. All rights reserved* Page 23
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

	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. 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.	☐ R ☐ L

July 1, 2008 Copyright © 2008 Movement Disorder Society. All rights reserved Page 24
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

	SCORE
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.	☐ R ☐ L
3.17 REST TREMOR AMPLITUDE Instructions to examiner: This and the next item have been placed purposefully at the end of the examination to allow 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 this 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. 4: Severe: > 10 cm in maximal amplitude. Lip/Jaw ratings 0: Normal: No tremor. 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. 4: Severe: > 3 cm in maximal amplitude.	☐ RUE ☐ LUE ☐ RLE ☐ LLE ☐ Lip/Jaw

July 1, 2008 *Copyright © 2008 Movement Disorder Society. All rights reserved* Page 25
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

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.

☐

July 1, 2008 *Copyright © 2008 Movement Disorder Society. All rights reserved* Page 26
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

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.
4: Severe:	> 75% of waking day.

1. Total Hours Awake: _____
2. Total Hours with Dyskinesia: _____
3. % Dyskinesia = ((2/1)*100): _____

Copyright © 2008 Movement Disorder Society. All rights reserved
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

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.	
2: Mild:	26 - 50% of waking day.	☐
3: Moderate:	51 - 75% of waking day.	
4: Severe:	> 75% of waking day.	

1. Total Hours Awake: _____
2. Total Hours OFF: _____
3. % OFF = ((2/1)*100): _____

July 1, 2008 *Copyright © 2008 Movement Disorder Society. All rights reserved* Page 28
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

	SCORE
4.4 FUNCTIONAL IMPACT OF FLUCTUATIONS 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%).	☐

July 1, 2008 Copyright © 2008 Movement Disorder Society. All rights reserved Page 29
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

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.

July 1, 2008 *Copyright © 2008 Movement Disorder Society. All rights reserved* Page 30
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

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– Right hand	
1.5	Apathy		3.5b	Hand movements– Left hand	
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	

July 1, 2008

Copyright © 2008 Movement Disorder Society. All rights reserved.
This chart may not be copied, distributed or otherwise used in whole or in part without prior written consent of the Movement Disorder Society

18.2 APPENDIX 2: SCHWAB & ENGLAND ACTIVITIES OF DAILY LIVING SCALE

100%	Completely independent. Able to do all chores w/o slowness, difficulty, or impairment. Essentially normal. Unaware of any difficulty.
90%	Completely independent. Able to do all chores with some degree of slowness, difficulty and impairment. May take twice as long. Beginning to be aware of difficulty.
80%	Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowing.
70%	Not completely independent. More difficulty with some chores. X 3-4 as long in some. May spend a large part of the day with chores.
60%	Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors, some impossible.
50%	More dependent. Help with 1/2 of chores. Difficulty with everything.
40%	Very dependant. Can assist with all chores but few alone.
30%	With effort, now and then does a few chores alone or begins alone. Much help needed.
20%	Nothing alone. Can do some slight help with some chores. Severe invalid.
10%	Totally dependent, helpless. Complete invalid.
0%	Vegetative functions such as swallowing, bladder and bowel function are not functioning. Bedridden.

18.3 APPENDIX 3: PARKINSON'S DISEASE QUESTIONNAIRE (PDQ-39)

PDQ-39 Questionnaire

Please complete the following

S. No	Due to having Parkinson's disease, how often **during the last month** have you……	Please tick **one box** of each question				
		Never	Occasionally	Sometimes	Often	Always
1.	How difficult 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?	☐	☐	☐	☐	☐
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 closed friends?	☐	☐	☐	☐	☐
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 communication with people properly?	☐	☐	☐	☐	☐
36.	Felt ignored by people?	☐	☐	☐	☐	☐
37.	Had painful muscle cramps or spasms?	☐	☐	☐	☐	☐
38.	Had aches or pains in your joints or body?	☐	☐	☐	☐	☐
39.	Felt unpleasantly hot or cold?	☐	☐	☐	☐	☐

Thank you for completing the PDQ-39 Questionnaire!

18.4 APPENDIX 4: CLINICAL GLOBAL IMPRESSION

Severity of Illness (CGI-S)

Rating should account for severity of the patient's illness.

0 = Not assessed
1 = Normal, not at all ill
2 = Borderline ill
3 = Mildly ill
4 = Moderately ill
5 = Markedly ill
6 = Severely ill
7 = Extremely ill

Global Improvement (CGI-I)

Compared to the patient's condition at the baseline of this study, how much has the patient's illness improved or worsened? (Circle one)

Rating should account for severity of the patient's illness.

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

18.5 APPENDIX 5: COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Figure 18-1: C-SSRS (Lifetime/Recent)

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" 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 "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past 1 month**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or 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 than 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***) Recent - ***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	____	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past 3 months**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior 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 behavior 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/story). 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 Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	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 toward self, gun is taken away by someone else, or 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 or Self-Interrupted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. 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 or self-interrupted _____	Yes ☐ No ☐ Total # of aborted or self-interrupted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization 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 Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

	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* hospitalization 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* hospitalization 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 fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

Figure 18-2: C-SSRS (Since Last Visit)

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" 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 "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 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 than 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 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** ☐
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 Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	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	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check 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.* Behavior 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 behavior 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/story). 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 Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**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 toward self, gun is taken away by someone else, or 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 or Self-Interrupted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. 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 or self-interrupted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization 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 Behavior: Suicidal behavior 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* hospitalization 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* hospitalization 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 fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____