CONFIDENTIAL

A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE IIA STUDY EVALUATING THE EFFICACY AND TOLERABILITY OF IRL790 IN PARKINSON'S DISEASE DYSKINESIA

PROTOCOL

Version:	6
Version date:	14 January 2019
Superseded version:	Version 5, 24th July 2018
Sponsor:	Integrative Research Laboratories AB (IRLAB)
Product:	IRL790 (2.5mg hard HPMC capsules)
Study Number(s):	IRL790C003
	EudraCT number: 2017-003458-18

NCT number: NCT03368170

Integrative Research Laboratories AB (IRLAB)

Arvid Wallgrens Backe 20

413 46 Göteborg

SWEDEN

Phone: +46 (0) 707 60 16 91

PROTOCOL APPROVAL PAGE

This protocol has been read and approved by:

Sponsor representative: **Signature:** **Date:**	

Chief Investigator: **Signature:** **Date:**	

The Clinical Trial Company: **Signature:** **Date:**	

Statistician: **Signature:** **Date:**	

INVESTIGATOR PROTOCOL APPROVAL PAGE

A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE IIA STUDY EVALUATING THE EFFICACY AND TOLERABILITY OF IRL790 IN PARKINSON'S DISEASE DYSKINESIA

I, the undersigned, have read and understood the protocol and am aware of my responsibilities as an Investigator. I agree to conduct the study in accordance with this protocol and any subsequent amendments, the Declaration of Helsinki, ICH GCP guidelines, and the laws and regulations of the country in which the study is being conducted.

Investigator Name: **Investigator Title:** **Investigator Address:**	

Investigator Signature: **Date:**	

AMENDMENT HISTORY

Protocol Version	Change	Justification
V6 14 January 2019	Excl crit 9: Added definition of renal impairment 7.3. Update of list of contraception methods regarded as highly effective according to CTFG recommendations Incl crit 4: Clarification that patients need >25% dyskinesia to score 2 or more 4.1. Clarification the re-screening is allowed Added to contact list that CTC Clinical Trial Consultants are also functioning as Swedish CRO	Response to Swedish MPA Response to Swedish MPA Clarification Clarification New info
V5 24 July 2018	7.8. Follow Up (5-8 days after End of Treatment) The following procedures and assessments are to be carried out at Follow Up (4-5 days after Visit 4) Changed to the following: The following procedures and assessments are to be carried out at Follow Up (5-8 days after Visit 4): 5.2 Non-permitted concomitant medications Table updated with the following: bupropion, paroxetine, quinidine, terbinafine	Correction of typographical error

	Updated wording The list will be provided to the Investigator sites and maintained/updated throughout the study to provide information on clinical inhibitors for P450-mediated metabolisms and clinical inhibitors for transporters. The list will be updated as new information becomes available and circulated to all sites. Wording amended to the following: The list will be provided to the Investigator sites and maintained/updated throughout the study to provide information on clinical inhibitors for P450-mediated metabolisms and clinical inhibitors for transporters. . Please note this is not an exhaustive the list will be updated as new information becomes available and circulated to all sites.	Table updated to list correct CYP2D6 Strong Inhibitors
V4 11 June 2018	Section 8.1.1 ethnic origin changed to ethnicity and race 8.1.5 resting 12 lead ECG-PQ changed to PR 11.4 – ethnic origin changed to ethnicity and race Amendment history changed 9. clarification that exclusion on hypotension and/or hepatic disease must be clinically significant	

	Corrected spelling of disease as below: 9. clarification that exclusion on hypotension and/or hepatic disease must be clinically significant Change of Statistician from Dave Fleet to Fredrik Hansson	
V3, 14 NOV 2017	Addition of contact details for Statistics and Interactive Randomisation System	Self-Evident
V3, 14 NOV 2017	Update to Abbreviations	Self-Evident
V3, 14 NOV 2017	Section 1.1.Investigational agent Clarification that the study assesses IRL790 in treatment of Dyskinesia and not Psychosis	Clarification
V3, 14 NOV 2017	Section 1.1.2. Efficacy Clarification of preclinical animal model	Clarification
V3, 14 NOV 2017	Sections 1.3.1. Summary of risk management, 2.2. Secondary objectives, 3.1. Overall study design and plan description, 7.2. Screening (-28 to -7 days prior to randomisation), 7.6. Phone Call (Day 21 ± 2 days), 8.2.2.6. (formerly Parkinson's KinetiGraph™ (PKG)) 24-hour patient diary, 11.7. Efficacy Endpoints, Replacement of actigraphic watch with 24 hour patient diaries	The consistency across study sites cannot be guaranteed in the use of the actigraphic watch. Replaced with a standardised patient diary.

V3, 14 NOV 2017	4.2. Inclusion criteria 5. Clarification that rescue medication is allowed Addition of 9. Able to complete 24-hour patient diaries	 Clarification Addition of diary
V3, 14 NOV 2017	4.3. Exclusion criteria 6. Mini-Mental Status Examination score for exclusion reduced from 26 to 24 7. Hoehn & Yahr - Reference to MDS-UPDRS deleted 7. Hoehn & Yahr – measurement in “off” phase deleted 8. Timeframe for history of heart conditions added – within 5 years 9. clarification that exclusion on hypotension and/or hepatic disease must be clinically significant 10. clarification that patients with illusions or hallucinations with no loss of insight will be eligible 11. Clarification that patients also enrolled in non-interventional clinical trials will be eligible. Removal of Current participation in another clinical trial	 The original level of 26 was considered too high and that patients with MMSE scores of 24 and above should be considered for inclusion Clarification Cannot measure when patient is “off” Clarification Clarification Clarification Clarification Removed in conjunction to update of criteria 11
V3, 14 NOV 2017	Section 6.4. Blinding and randomisation,	

	8.2.2.5.1.Rush filming protocol Clarification that the investigator must ensure that Rush filming is performed with the patient in the "on" phase, during peak dose dyskinesia.	Clarification
V3, 14 NOV 2017	Section 8.2.2.4.Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Definition of "ON" state added	Clarification
V3, 14 NOV 2017	Synopsis & Schedule of assessments Updated to reflect amendments to main protocol text	Self-Evident
V2, 23 OCT 2017	Section 6.4 Blinding and Randomisation Patient unblinding is also contained within the IRS system to allow the unblinding of patients for both Safety and Statistical purposes within the protocol via web or phone (per Sponsor outlined request). Amended to: Patient unblinding is also contained within the IRS system to allow the unblinding of patients for both Safety and Statistical purposes within the protocol via web or phone. If emergency unblinding is required this responsibility lies solely with the investigator, unblinding for other Safety and Statistical purposes will be managed	Response to GNA dated 18Oct17. Response to GNA dated 18Oct17.

	per Sponsor outlined request. Inclusion Criteria 8 Section 7.3 Visit 1 (Day 1) Addition: - Additional Requirements Subjects will be required to avoid exposure to direct sunlight from Visit 1 (day 1) until the follow-up visit (day 28).	
V1, 20 SEPT 2017	Initial	N/A

PROTOCOL SYNOPSIS

TITLE:

A randomised, double-blind, placebo-controlled, Phase IIa study evaluating the efficacy and tolerability of IRL790 in Parkinson's disease dyskinesia.

PROTOCOL NO:

IRL790C003

INVESTIGATOR STUDY SITES:

This study will be conducted at approximately 15 study sites located in the United Kingdom.

OBJECTIVES:

Primary objective:

To evaluate the efficacy of IRL790 in Parkinson's disease dyskinesia.

Secondary objectives:

To evaluate the effects of IRL790 on core symptoms of Parkinson's disease.

To evaluate the pharmacokinetics, safety and tolerability of IRL790 in patients with Parkinson's disease dyskinesia.

METHODOLOGY:

This is a multicentre study where 74 patients with Parkinson's disease exhibiting levodopa induced dyskinesia will be randomised to receive study drug or placebo. Thirty seven patients will be randomised to IRL790 and 37 patients to placebo (1:1 randomisation).
Patients will be screened for eligibility according to inclusion/exclusion criteria within four weeks of initiation of study treatment (Screening visit).

This is an outpatient study with the patients taking the study drug for four weeks at home. IRL790 will be taken twice daily (b.i.d.) as adjunctive treatment to the patients' regular and stable antiparkinsonian medication.
The first two weeks of treatment will allow for per patient titration of study medication to the highest tolerated predefined dose, after which patients will continue on this highest tolerated dose for an additional two weeks.
Changes in disease state and dyskinesia will be measured using the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and Unified Dyskinesia Rating Scale (UDysRS); furthermore, patients will administer two 24-hour diaries on run-in and on the fourth week of dosing to assess daily movements.
Pharmacokinetic (PK) samples will be collected for the determination of concentrations of IRL790 and its metabolites IRL902 and IRL872 in plasma. They will be collected before and after IMP administration at two visits.
A Follow-up Visit will be performed for all patients five to eight days after last administration of IMP.

NUMBER OF PATIENTS:

Approximately 74 patients will be enrolled. Patients who are enrolled but not treated will be classed as Screen Failures and will be replaced.

In the event that a patient withdraws from the study for any reason other than an adverse event or other safety concern, or is lost to follow-up within 30 days of treatment, a new patient will

be enrolled to replace the withdrawn patient. The replacement will be managed through a centrally administered study wide randomisation list. The reason for the patient's withdrawal from the study must be recorded.

INCLUSION/EXCLUSION CRITERIA:

Inclusion criteria

1. Male or female ≥18 and ≤79 years of age.
2. Signed a current Ethics Committee approved informed consent form.
3. Parkinson's disease, per UK Parkinson's Disease Society (UKPDS) Brain Bank Clinical Diagnostic Criteria.
4. Waking day dyskinesia of >25% determined as a score of ≥2 as per Question 4.1 of the MDS-UPDRS.
5. On a stable regimen of antiparkinson medications for at least 30 days prior to screening, including a levodopa preparation administered not less than three times daily and willing to continue the same doses and regimens during study participation. Rescue medication such as Madopar dispersable and Apomorphine injections are allowed.
6. Taking a maximum of eight regular levodopa intakes per day, excluding bedtime and night time levodopa.
7. Any other current and allowed prescription/non-prescription medications and/or nutritional supplements taken regularly must have been at a stable dose and regimen for at least 30 days prior to screening and the patient must be willing to continue the same doses and regimens during study participation (this criterion does not apply to medications that are being taken pre-study only on an as-needed basis).
8. Patient must be willing and able to avoid direct exposure to sunlight from day 1 to day 28.
9. Able to complete at least one valid 24-hour patient diary at Visit 1.

Exclusion criteria

1. History of neurosurgical intervention related to Parkinson's disease (e.g. deep brain stimulation).
2. Treatment with pump delivered antiparkinsonian therapy (i.e. subcutaneous apomorphine or levodopa/carbidopa intestinal infusion).
3. History of seizures within two years prior to screening.
4. History of stroke or transient ischemic attack (TIA) within two years prior to screening.
5. History of cancer within five years prior to screening, with the following exceptions: adequately treated non-melanomatous skin cancers, localised bladder cancer, non-metastatic prostate cancer or in situ cervical cancer.
6. Presence of cognitive impairment, as evidenced by a Mini-Mental Status Examination (MMSE) score of less than 24 during screening.
7. A Hoehn and Yahr stage of five.

8. Any history of a significant heart condition or cardiac arrhythmias within the past 5 years, any repolarisation deficits or any other clinically significant abnormal ECG as judged by the Investigator
9. Severe or ongoing unstable medical condition including a history of poorly controlled diabetes; obesity associated with metabolic syndrome; uncontrolled hypertension; cerebrovascular disease, or any form of clinically significant cardiac disease, clinically significant symptomatic orthostatic hypotension; clinically significant hepatic disease, renal failure or abnormal renal function (definition of abnormal renal function is creatinine clearance <45 ml/min (calculated according to the Cockcroft-Gault formula).
10. Any history of a neurological other than Parkinson's disease or a psychiatric disorder, including history of DSM IV diagnosed major depression or psychosis. Patients with illusions or hallucinations with no loss of insight will be eligible. Patients with mild depression who are well controlled on a stable dose of an antidepressant medication for at least 4 weeks before screening will be eligible.
11. Enrolment in any other clinical study involving medication, medical devices or surgical procedures, current or within three months prior to screening visit, or previous participation in the present study. Patients enrolled in non-interventional clinical trials will be eligible.
12. Drug and/or alcohol abuse.
13. History of severe drug allergy or hypersensitivity.
14. If female, is pregnant or lactating, or has a positive pregnancy test result pre-dose.
15. Patients unwilling to use two forms of contraception (one of which being a barrier method see Section 7.3) 90 days for men and 30 days for women after last IMP dose
16. Any planned major surgery within the duration of the study.
17. Any other condition or symptoms preventing the patient from entering the study, according to the Investigator's judgement.

DOSE/ROUTE/REGIMEN:

IRL790 will be given twice daily (b.i.d.) and given as adjunct treatment to the patients' regular and stable antiparkinsonian medication. IMP treatment duration will be four weeks.

IRL790 capsules, 2.5mg free base equivalent: White hard HPMC capsule, coni snap size 3, colour white containing IRL790 x ½ L-tartrate.

Dosage: The starting dose will be three capsules (7.5mg) b.i.d. The dose will be titrated in intervals between two (5mg) to four capsules (10mg) b.i.d.

REFERENCE TREATMENT:

Placebo capsules: Placebo capsules: White hard HPMC capsule, coni snap size 3, colour white containing starch. Capsules are identical in appearance to active IMP.

CRITERIA FOR EVALUATION:

Efficacy assessments

- **Primary Outcome Measure**

The primary evaluation endpoint is:

- Change in the Unified Dyskinesia Rating Scale (UDysRS) total score from Baseline (Day 1) to Visit 4.

- **Secondary Outcome Measures**

The secondary evaluation endpoints are:

- Change in Total Objective Score (III, IV) of the UDysRS from Baseline (Day 1) to Visit 4.
- Change in daily "OFF"-time as assessed with patient diaries from run-in to Visit 4.
- Change in Unified Parkinson's Disease Rating Scale (MDS-UPDRS) total score of part III (motor), and sum score of Questions 4.1 and 4.2 (dyskinesia) in part IV from Baseline (Day 1) to Visit 4.

- **Exploratory outcome measures**

Additionally a number of exploratory end points will be assessed. The following items will be assessed:

- Unified Parkinson's Disease Rating Scale (MDS-UPDRS), part I (total score), part II (total score) and part IV (total score) from Baseline (Day 1) to Visit 4.
- Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Question 1.2 (Hallucinations and Psychosis) from Baseline (Day 1) to Visit 4.
- Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Question 1.6 (Features of dopamine dysregulation syndrome) from Baseline (Day 1) to Visit 4.
- Clinician's Global Impression of Change in overall PD symptoms from Baseline (Day 1) to Visit 4.
- Daily "ON"-time with troublesome dyskinesia as assessed with patient diaries from run-in to Visit 4.
- Daily "ON"-time as assessed with patient diaries from run-in to Visit 4.

Safety assessments

- Frequency, seriousness and intensity of Adverse Events (AEs).
- Physical examination.
- Electrocardiogram (ECG) recordings.
- Vital signs (blood pressure, heart rate).
- Safety laboratory measurements.

Pharmacokinetic (PK) assessments

- After multiple doses: morning trough and C_{max}
- Dose proportionality after multiple doses based on morning trough and C_{max}
- P-Prolactin Pharmacokinetics

STATISTICAL METHODS:

A single analysis at the conclusion of the investigation is planned and there will be no interim analyses.

All the efficacy safety (including laboratory safety) and pharmacokinetic data collected will be amalgamated into a single database with datasets constructed according to these categories.

All data will be described and analysed according to Treatment group (IRL790, Placebo), day of assessment (Screening, Day 1 (Baseline), 7, 14, 21, 28, End of Treatment (Day 28 or last observation in the event of withdrawal), plus Follow-up (if appropriate)). However as this is a maximum tolerated dose (MTD) investigation where appropriate summaries according to Dose group may also be described (7.5mg b.i.d. upwards). Each data summary will be supported by individual patient listings.

Power and Sample Size:

Seventy Four (74) evaluable patients (37 per group) are sufficient to demonstrate an effect size of 0.67 between the active treatment and control (IRL790 vs Placebo) for the UDysRS primary endpoint with 80% power and type 1 error rate 0.05 (two tailed).

Recruitment will continue until sufficient evaluable patients are available.

Demographics and Baseline Characteristics:

All basic information regarding the sample of patients recruited to represent the PD population with dyskinesia will be summarised.

Analysis Sets

Three analysis sets (or patient populations) will be evaluated: The Full Analysis Set (FAS), Per Protocol Set (PPS) and the Safety Set (SS). The FAS is considered of primary importance.

Efficacy assessments

The primary efficacy variable is the UDysRS total score.

The secondary efficacy variables involve a subset of the UDysRS, the MDS-UPDRS rating scales and the daily “off” time as assessed with patient diaries. Similarly, the exploratory efficacy variables comprise a number of other subsections from the MDS-UPDRS and patient diaries.

The Change from baseline (Screening) at Day 28 (Visit 4, Week 4) and End of Treatment (Day 28 (Visit 4, Week 4 or earlier in the event of withdrawal) will be derived, summarised and analysed. The End of Treatment last assessment available is considered the primary time-point of interest and will be analysed as interval type data.

Each endpoint will be analysed using an Analysis Of Covariance (ANCOVA) model to compare the two treatment groups (IRL790 vs Placebo). The model will include Change from baseline as the dependent variable, Treatment group as a fixed factor and Baseline as the covariate term. Actual p-values and 95% confidence intervals for least square mean estimates of the treatment effects and differences from placebo will be presented.

The CGI (an exploratory efficacy variable) however is categorical data which is ordinal in nature and will be analysed using the Van Elteren hypothesis test.

Pharmacokinetic (PK) assessments

PK variables measured in plasma are: IRL790 parent drug and two of its metabolites (IRL902 (n-dealkylated) and IRL872 (acetylated)). In addition, the biomarker P-Prolactin is also measured.

Samples are obtained pre-dose and 2h post dose (C_{max}) on Day 1 and Day 28 and will be summarised as interval data. If appropriate, these will be presented overall for the IRL790 treated group but also according to IRL dose.

To assess the relationship between the treatment doses (7.5mg b.i.d. upwards) and drug plasma concentration a polynomial regression model to fit dose or log(dose) vs plasma concentration for each variable and sampling time will be used. However, this is dependent on the number of patients in each of the dose groups of this maximum tolerated dose (MTD) investigation.

Safety assessments

Safety evaluations include: Adverse events and Concomitant medications reporting, Complete physical examination, Vital signs, ECG (12 lead) and Clinical safety laboratory tests (clinical chemistry, haematology and coagulation). All will be presented as data summaries. No formal statistical analyses will be performed.

Adverse events (Overall, By seriousness, By severity, By relationship) and Concomitant medications (Overall) recorded throughout the investigation will be reported following classification according to MedDRA (SOC/PT) and WHODD (ATC Level 2.4) dictionaries respectively.

All other safety evaluations are performed at Screening, Day 28 (Visit 4 or at Withdrawal) and Follow-up (5-8 days after Visit 4) and will be summarised accordingly.

Safety laboratory samples assayed at the local hospital will be presented as interval summaries according to Site.

SAFETY

Recruitment:
The DSMB will convene after 20 and 40 patients have completed the Follow-Up visit (with adequate safety assessment data) for a formal safety review.

Note that recruitment will continue throughout the 20 and 40 patient DSMB

Data Safety Monitoring Board

The DSMB will convene under the following circumstances:

- The DSMB must meet once the 20th and 40th patient has completed the Follow-Up visit
- The DSMB must meet as soon as there has been a SUSAR

The DSMB has the right to recommend to the Sponsor that the study be suspended, terminated or lower doses be given, if considered appropriate.

STUDY SCHEDULE

	Screening	Visit 1 (Baseline)	Visit 2	Visit 3	Phone call	Visit 4 (EOT)[1]	FU
		Treatment Period					Follow-up
Day	**-28- to -7**	**1**	**7**	**14**	**21**	**28**	**5-8 days after EOT**
Time window	**-**	**-**	± 2 days	± 2	± 2 days	-2 to 0 days	
Informed Consent	X						
Demographics/Medical History	X						
Inclusion/Exclusion Criteria	X						
Concomitant Medication	X	X	X	X	X	X	X
Height	X						
Weight	X						X
Physical Examination	X					X	X
Vital Signs	X					X	X
12-lead ECG	X[2]					X	X
Haematology / Clinical Chemistry	X					X	X
Dipstick Urinalysis	X					X	X
Pregnancy Test	X					X	
PK sample[3]		X				X	
MMSE	X						
Hoehn and Yahn scale	X						
MDS-UPDRS	X[4]	X				X	
UDysRS		X				X	
24-hour patient diary	X				X		
CGI-C						X	
Treatment Emergent Adverse Events			X	X	X	X	X
Randomisation		X					
Dispense Trial Medication		X		X			
Compliance			X	X	X	X	
Dose adjustment[5]			X	X			
Baseline events[6]	X	X					

[1] All withdrawals have a final re-assessment if possible
[2] Triplicates separated by at least one minute
[3] Taken before and 2 hours after IMP administration
[4] Question 4.1 only
[5] Dose Adjustment if required
[6]Medical events that occur between signing the ICF and first dose

CONTACT NAMES AND ADDRESSES

Sponsor:	Integrative Research Laboratories AB (IRLAB)
Address:	Integrative Research Laboratories AB (IRLAB) Arvid Wallgreen backe 20, 413 46 Göteborg, Sweden
Contact details:	[redacted] joakim.tedroff@irlab.se
Personnel:	Joakim Tedroff, MD, PhD, CMO
CRO:	[redacted]
Address:	[redacted]
Contact details:	[redacted]
Personnel:	[redacted]
Pharmacovigilance Address:	[redacted]
Telephone	[redacted]
Fax	[redacted]

Statistics and Swedish CRO	[redacted]
Address:	[redacted]
Telephone	[redacted]
Personnel:	[redacted]
Interactive Randomisation System:	[redacted]
Address:	[redacted]
Telephone	[redacted]

ABBREVIATIONS

ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
AE	Adverse Event
AIM	Abnormal Involuntary Movements
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical classification system
AUC	Area under the concentration time curve
b.i.d.	Twice daily
BMI	Body Mass Index
CA	Competent Authority
CGI-C	Clinical Global Impression of Change
CI	Chief Investigator
C_{max}	Maximum concentration
CMH	Cochran Mantel-Haenszel
CNS	Central Nervous System
CRF	Case Report Form
CRO	Clinical Research Organisation
CSA	Clinical Study Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ED50	Median Effective Dose
EOT	End Of Treatment
EU	European Union
FAS	Full Analysis Set
FSH	Follicle Stimulation Hormone

GCP	Good Clinical Practice
GP	General Practitioner
Hb	Haemoglobin
hERG	Human Ether-à-go-go-Related Gene
HPMC	Hydroxypropyl Methylcellulose
ICH	International Council on Harmonisation
ICF	Informed Consent Form
ID	Identification/Identifier
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
IRL	Integrative Research Laboratories
IRS	Interactive Randomisation System
LDH	Lactate dehydrogenase
L-Dopa	Levodopa
LID	L-Dopa Induced Dyskinesia
MAD	Multiple Ascending Dose
MDS- UPDRS	Movement Disorder Society – Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MMSE	Mini–Mental State Examination
MTD	Maximum Tolerated Dose
NMDA	N-methyl-D-aspartate
NOAEL	No Observed Adverse Effect Levels
6-OHDA	6-hydroxydopamine
PD	Parkinson's Disease
PDP	Parkinson's Disease Psychosis
PK	Pharmacokinetic
PPS	Per Protocol Set
PT	Preferred Term
PT	Prothrombin time
RBC	Red Blood Cells
REC	Research Ethics Committee

SAE	Serious Adverse Event
SAD	Single Ascending Dose
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDV	Source Data Verification
SOC	System Organ Class
SOP	Standard Operating Procedure
SS	Safety Set
SUSAR	Suspected Unexpected Serious Adverse Reaction
$T_{1/2}$	Apparent terminal half-life
T_{max}	Time to maximum concentration
T3	Triiodothyronine
T4	Thyroxine
[redacted]	[redacted]
TEAE	Treatment Emergent AE
TIA	Transient ischaemic attack
TMF	Trial Master File
TSH	Thyroid-stimulating hormone
UAE	Unexpected Adverse Event
UKPDS	UK Parkinson's Disease Society
UDysRS	Unified Dyskinesia Rating Scale
WBC	White Blood Cells
WHO	World Health Organization
WHODD	World Health Organisation Drug dictionary
Enrolled patient	Patient who has signed the informed consent
Screen failure	Enrolled patient not included
Included patient	Patient randomised
Withdrawn patient	Patient randomised but not completed
Completed patient	Patient completed the study period, including follow-up

TABLE OF CONTENTS

1. BACKGROUND INFORMATION AND STUDY RATIONALE

Parkinson's disease is a relatively common neurodegenerative disorder characterised by motor symptoms such as poorness and slowness of movement, tremors and loss of balance. Psychiatric symptoms such as anxiety and depression as well as other non-motor symptoms are also common. The disorder is associated with a markedly increased risk of developing dementia [1]. Treatments that restore dopamine deficits in the brain such as levodopa and dopamine agonists have been used since the 1970s to treat the motor symptoms in Parkinson's disease. However, it has long been known that after a few years of initial motor normalisation, such drugs frequently cause adverse effects [2, 3]. Adverse effects on motor symptoms such as wearing-off, on-off and dyskinesias limit the usefulness of current approved drug treatments, prompting the use of device treatments such as deep brain stimulation and infusion pumps for patients in more advanced stages of disease.

It is estimated that within five years of initiation of standard dopamine replacement therapy in Parkinson's disease (PD), about 50% of patients (and after 10 years almost all patients) develop involuntary movements:- so called Levodopa Induced Dyskinesias (LIDs), in response to their medical treatment [4]. LIDs are often the key complication that limits further dose increases in dopaminergic therapy.

There is increasing recognition that non-motor symptoms, such as Parkinson's disease Psychosis (PDP) are burdensome to PD patients. Paranoid delusions result in patient distress and behavioural disturbance; visual or auditory hallucinations are more frequent. PD patients with cognitive impairment are prone to develop hallucinations, i.e. psychotic symptoms, in response to dopaminergic treatments [5]. In a systematic review of clinical populations the prevalence of hallucinations alone was between 21% and 46% [6].

The key pathophysiology of PD involves loss of dopaminergic and noradrenergic innervation. Other cortical, subcortical and autonomic pathologies contribute to the non-motor symptoms of the disorder [7]. It has been suggested that cortico-striatal dys-connectivity and plasticity are key drivers for both the core symptoms of PD as well as for the adverse effects emerging with long standing dopaminergic treatment [8]

Because of the prevalence of dyskinesia and psychosis, and the limited options for effective treatment, developing new safe and effective therapies that treat LIDs, and/or PDP, without aggravating Parkinsonism addresses an unmet medical need in Parkinson's disease.

1.1. Investigational agent

IRL790 was discovered in an *in vivo* systems pharmacology project and has been selected for development aimed as a treatment to reduce levodopa induced dyskinesia and psychosis in PD.

Some specific desired properties of this compound are:

- Efficacy in preclinical PD models of L-dopa induced motor dysfunction, such as reducing dyskinesia, while leaving locomotor activity intact.
- Efficacy in preclinical models of disrupted cortical and striatal dopaminergic or glutamatergic transmission, such as counteracting N-methyl-D-aspartate (NMDA)-antagonist induced hyperactivity demonstrating antipsychotic activity.

- Indications of strengthened cortico-striatal connectivity through neurochemical and transcriptional biomarkers of neurotransmission, related to monoaminergic, cholinergic and glutamatergic neurotransmitter pathways.
- In normal animals, IRL790 has no effect on locomotor activity across a wide dose range.

Two clinical indications, both of which are associated with dysfunctional cortico-striato-thalamic connectivity, are considered for IRL790. The specific anti-dyskinetic and antipsychotic effects of IRL790 suggest its use in the treatment of L-Dopa Induced Dyskinesia (LID) and Parkinson's Disease Psychosis (PDP) in PD. This trial is aimed at assessing IRL790 as a treatment for LID. Its role as a treatment for PDP will be assessed in future trials.

1.1.1. Mechanism of action

IRL790, IRL790 x ½ L-tartrate, belongs to a new class of central nervous system (CNS) active agents called psychomotor stabilisers. These are compounds exerting antidyskinetic and antipsychotic effects via the brain monoaminergic systems without suppressing locomotor activity in normal un-pretreated rats. *In vitro* IRL790 acts as an antagonist of brain neuroreceptors belonging to the dopamine D2-type (D3 and D2) and the Sig-1 receptor (σ1) at sub-micromolar concentrations and serotonin family receptors (5-HT1a, 5-HT2) at micromolar concentrations.

IRL790 at the same doses behaves as an antidyskinetic and antipsychotic leaving normal behaviour largely unaffected, combined with its neurochemical mode of action indicates a novel compound profile in PD with potential to alleviate LID and psychosis while sparing normal motor functions.

1.1.2. Efficacy

Behaviourally, IRL790 has the ability to normalise overt motor abnormalities induced by disruptions in both dopaminergic and glutamatergic neurotransmission in a dose dependent manner, hence directly addressing symptoms arising from aberrations in cortico-striatal communication.

In an animal model of PD, the unilateral 6-hydroxy-dopamine lesioned rat model, IRL790 significantly reduced L-Dopa induced dyskinesia but left the L-Dopa dependent motor activation intact.

Furthermore, in a phase 1b study, patients with advanced PD experiencing levodopa induced dyskinesia were randomised to receive IRL790 or placebo as adjunct treatment for 28 days. Five patients treated with IRL790 reported transient mild worsening of parkinsonism during dose titration. Thirteen patients completed the study, nine patients on IRL790 and four patients on placebo.

Patients with advanced Parkinson's disease consistently tolerated IRL790. The adverse events reported in patients with advanced Parkinson's disease were mitigated by dose adjustments and following dose titration, IRL790 seemed to reduce dyskinesia (assessed by UDysRS) without compromising motility.

1.2. Preclinical data

IRL790 has been shown to be negative in *in vitro* genotoxicity tests. Single and repeated oral administrations of IRL790 resulted in dose-related locomotor reductions and behavioural signs in rats and dogs. Following repeated administration for up to one month, microscopic changes were observed in the mammary gland, female reproductive organs, liver, adrenal glands, glandular stomach, pancreas and parotid glands in rats. In dogs, microscopic changes were noted in the small sized arteries of the alimentary tract, urinary bladder, gall bladder and lung.

The CNS-related clinical signs in rats and dogs (tremor, decreased activity, abnormal gait and convulsion) and most of the histopathological findings in rats, such as changes in mammary gland and female reproductive organs, are considered to be a consequence of exaggerated pharmacology and/or compound-related perturbations of prolactin levels. Apart from findings related to exaggerated pharmacology (i.e. mild and transient clinical signs and slight histopathological changes in female mammary gland and vaginal epithelium), no treatment-related findings were observed at 25 mg/kg/day in rats and 18 mg/kg/day in dogs. These doses were considered to be the No Observed Adverse Effect Levels (NOAELs) for the 1-month studies resulting in a mean C_{max} of 10.8 µM and a mean $AUC_{0\text{-}24h}$ of 47.2 µM/h in rats and a mean C_{max} of 8.9 µM and a mean $AUC_{0\text{-}24h}$ of 84 µM/h in dogs. IRL790 has low affinity for Human Ether-à-go-go-Related Gene (hERG) (IC50; 223.9 µM) and is therefore predicted to have low liability for QT prolongation. IRL790 was tested for excitability, automaticity, cardiac wavelength, TRIaD and proarrhythmia in the Hondeghem model using rabbit isolated hearts [9]. IRL790 was concluded to be safe in the dose range tested (0.5 to 45 µM).

IRL790 was also evaluated for cardiovascular variables in a conscious beagle dog model following single twice daily (b.i.d) oral administrations. In this study, no physiologically relevant or statistically significant changes were observed in any of the variables investigated at any of the doses tested [10].

1.3. Risks / benefits

Collectively, the data from nonclinical and clinical studies indicate that IRL790 is likely to have an acceptable safety profile. Possible adverse effects associated with IRL790 include mild and transient CNS associated adverse events (headache/loss of concentration/tremor/light headedness) and potential increases in plasma prolactin at higher dose levels.

The doses to be used in this study have been selected based on the previous clinical study (see Section 1.7). A flexible dose titration using 2.5mg capsules with a starting dose of 7.5mg b.i.d. with a subsequent dose range from 5mg to 10mg b.i.d. will allow the physician to titrate an optimal dose for each individual patient, while retaining a pronounced margin of safety.

Studies in humans have not identified any safety issues for the doses studied and the highest obtained plasma concentration of IRL790 in healthy volunteers was below the highest recommended level. To mitigate the risk for intolerability and AEs, the protocol allows for flexible dose titration and involves careful monitoring of the patients well-being.

1.3.1. Summary of risk management

The Principal Investigator at each research site will ascertain that adequate facilities and procedures are available to handle emergency situations should they occur during the study.

During the treatment period the study patients will visit the clinic on Days 1, 7, 14 and 28 for monitoring of safety variables; PK sampling will occur on Days 1 & 28. A phone call will be

made on Day 21 to collect information on any AEs or changes in concomitant medication (as well as instructing the user to complete two 24-hour diaries assessing daily motor function). Each study patient will be provided with a Patient Information Card with information about the study, the IMP, 24-hour diaries, patient study ID, name of the Investigator and an emergency number.

Besides the risks related to the IMP as described above, study specific evaluations and sampling procedures like blood-pressure measurements using a blood pressure cuff and frequent blood-sampling, can cause transient discomfort but the risk is deemed to be low and ethically justifiable.

1.4. Dose rationale

The pharmacological effects of IRL790 have been evaluated in a range of preclinical animal models. As to the suggested indication, levodopa induced dyskinesias in PD; the 6-OHDA AIM scoring rat model is most commonly suggested for use in pharmacological validation of anti-dyskinetic efficacy of new therapies and is thus regarded to have predictive validity. Using this rodent lesion model, IRL790 has been studied in two independent tests, both in-house and by an external laboratory. IRL790 showed significant efficacy in reducing AIMs (active doses <10 mg/kg s.c. with an ED50 of 3.7 mg/kg s.c.), without compromising beneficial effects of L-DOPA. Taken together, a dose range of around 1-4 mg/kg in the rat ($C_{max} \approx 0.5$-2 µM, AUC ≈ 0.,6 – 3 µM x h) covers effective doses up to and above the ED50s in the main preclinical *in vivo* pharmacological efficacy models.

Integrating this data with *in vitro* affinity and functional assessments for the main molecular targets in the dopamine receptor family (dopamine D3 and D2 receptors) indicates that efficacy in patients with PD could be expected at C_{max} levels below 0.5 µM in plasma. In such patients, the dosing of IRL790 is also likely to be personalised and hence flexible dosing will be explored in the initial clinical studies. A flexible dose titration ranging from 5mg b.i.d. up to a maximum 10mg b.i.d. will allow the physician to titrate an optimal dose for each individual patient, while retaining a sufficient margin of safety. Given the plasma half-life of about 7 hours, sufficient coverage during the waking hours of the day is expected.

To mitigate the risk for intolerability and AEs, the protocol allows for flexible dose titration and involves careful monitoring of the patients' well-being.

1.5. Trial conduct

This study will be conducted in compliance with the protocol and according to Good Clinical Practice and applicable regulatory standards. No deviation from the protocol will be implemented without the prior review and approval of the ethics committee and regulatory authorities except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the ethics committee and regulatory authorities as soon as possible.

1.6. Population

Parkinson's disease (PD) is the second most common neurodegenerative disorder affecting more than one million people in the European Union (EU) and North America. It is estimated that within five years after initiation of standard dopamine replacement therapy, about 50% of patients with PD develop involuntary movements, so called levodopa (L-Dopa) induced

dyskinesia (LID) in response to their medical treatment. LID is often the key complication that limits further dose increases in dopaminergic therapy. Moreover, treatment induced psychotic symptoms (Parkinson's disease psychosis [PDP]) may also develop over time in a substantial proportion of patients. There are no approved treatments for such long term complications.

IRL790 was discovered and developed in a project aimed at finding a treatment for LIDs and PDP in patients with PD treated with antiparkinsonian medications. Results from preclinical studies in experimental animals suggest that the compound could help to ameliorate such untoward effects without appreciably affecting the basic efficacy of antiparkinsonian medications.

1.7. Previous Clinical Studies

IRL790 has been investigated in two clinical studies, IRL790C001, a phase I randomised, double-blind, placebo-controlled, cross-over, single ascending dose (SAD) and multiple ascending dose (MAD) study in male healthy volunteers and IRL790C002, a phase 1b study of patients with advanced PD experiencing levodopa induced dyskinesia.

In the SAD part of IRL790C001, subjects were divided into two cohorts. Within each cohort the subjects were randomised to one of four treatment sequences, which included three dose levels of IMP. One of the dose levels was repeated once, taken with a standardised meal, all other doses were taken without food. In each of the six administered dose levels (5, 15, 40, 80, 120mg IRL790), six subjects received active drug and two subjects received matching placebo.

In the MAD part of this study, twenty-three subjects were treated with IMP. In the first cohort, nine subjects received IRL790, 40 mg/day for 10 consecutive days and three subjects received matching placebo. In the second cohort, nine subjects received IRL790, 80 mg/day for 10 consecutive days and three subjects received matching placebo.

Overall, IRL790 was well tolerated when given to healthy male subjects at single doses up to 120 mg and at multiple doses of 80mg per day for 10 days. The maximum tolerated dose was set to 120mg as a single dose and the maximal dose for multiple dosing was set to 80mg per day. Most of the treatment emergent (74%) AEs were of grade 1 intensity while 26% were of grade 2 intensity. The majority of AEs (48%) reported were considered as not related to study treatment while 11% were possibly related and 41% probably related. Overall treatment emergent AEs were mild, transient and possibly CNS related.

In agreement with preclinical findings, the pharmacokinetic evaluation in humans showed dose-linear kinetics with rapid absorption (average T_{max} ≈1 h) and log-linear decline with a plasma half-life around 7h. Urine recovery data confirmed elimination from plasma occurred by a combination of renal excretion (fractional excretion around 35%) and metabolic degradation.

In the phase 1b study, patients with advanced PD experiencing levodopa induced dyskinesia were randomised to receive IRL790 or placebo (3:1 randomisation) as adjunct treatment for 28 days. During the first two weeks of treatment, dosing was gradually increased until signs of intolerability occurred after which dose adjustments were made. Following this titration period the dosing was kept stable for the remaining two weeks. Fifteen patients were randomised to treatment, 11 to IRL790 and four to placebo. Generally, adverse events were of mild intensity and transient after dose adjustments. Ten patients in the IRL790 treated group and four patients in the placebo group reported at least one related adverse event. Nervous system disorder was

the most common adverse event (31% of all reported adverse events). Five patients treated with IRL790 reported transient worsening of parkinsonism during dose titration, an adverse effect which was mitigated by dose reduction. Thirteen patients completed the study, nine patients on IRL790 and four patients on placebo. Two patients treated with IRL790 discontinued treatment due to adverse events.

Patients with advanced Parkinson's disease consistently tolerated IRL790. The adverse events reported in patients with advanced Parkinson's disease were mitigated by dose adjustments and following dose titration, IRL790 seemed to reduce dyskinesia (assessed by Unified Dyskinesia Rating Scale UDysRS) without compromising motility.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary objective

The primary objective of the study is to evaluate the effects of IRL790 on levodopa induced dyskinesia in patients with Parkinson's disease.

The primary evaluation endpoint is:

- Change in the Unified Dyskinesia Rating Scale (UDysRS) total score from Baseline (Day 1) to Visit 4 (Day 28 End of Treatment or earlier in the event of withdrawal).

2.2. Secondary objectives

The secondary objectives of the study are:

- To evaluate the effects of adjunctive treatment with IRL790 on levodopa induced dyskinesia assessed with the total objective score (part III + IV) in the Unified Dyskinesia Rating Scale (UDysRS), as compared to placebo.
- To evaluate the effects of adjunctive treatment with IRL790 on symptoms of PD assessed with Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III (motor)), and sum of Questions 4.1 and 4.2 (dyskinesia) in part IV as compared to placebo.
- To evaluate the effects of adjunctive treatment with IRL790 on the daily motor "OFF" time as assessed by patient completed 24-hour diaries, as compared to placebo.

Secondary endpoints

The secondary evaluation endpoints are:

- Change in Total Objective Score (III, IV) of the UDysRS from Baseline (Day 1) to Visit 4 (Day 28).
- Change in total daily "OFF" time as assessed by patient completed 24-hour diaries, from run-in to Visit 4 (Day 28).
- Change in Unified Parkinson's Disease Rating Scale (MDS-UPDRS) total score of part III (motor), and sum score of Questions 4.1 and 4.2 (dyskinesia) in part IV to Visit 4 (Day 28).

Exploratory endpoints

Additionally a number of exploratory end points will be assessed. The following items will be assessed:

- Unified Parkinson's Disease Rating Scale (MDS-UPDRS), part I (total score), part II (total score) and part IV (total score) from Baseline (Day 1) to Visit 4 (Day 28).
- Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Question 1.2 (Hallucinations and Psychosis) from Baseline (Day 1) to Visit 4 (Day 28).
- Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Question 1.6 (Features of dopamine dysregulation syndrome) from Baseline (Day 1) to Visit 4 (Day 28).
- Clinician's Global Impression of Change in overall PD symptoms from Baseline (Day 1) to Visit 4 (Day 28).
- Change in ”ON” time with troublesome dyskinesia as assessed by patient completed 24-hour diaries, from run-in to Visit 4 (Day 28).
- Change in ”ON” time as assessed by patient completed 24-hour diaries, from run-in to Visit 4 (Day 28).

3. STUDY DESIGN

3.1. Overall study design and plan description

This is a multi-centre, randomised, double-blind, placebo-controlled trial with the primary objective to evaluate the efficacy of 28 days treatment with IRL790 in patients with PD experiencing LID.

Consenting patients will be screened for eligibility according to study-specific inclusion/exclusion criteria (see Sections 4.2 and 4.3) within 7-28 days before start of IMP administration (Screening Visit).

At the Screening visit patients will be instructed and trained to complete two 24-hour diaries for assessment of daily motor function and to bring the completed diaries to the clinic at Visit 1. Patients completing at least one valid diary will be eligible for inclusion.

Following baseline assessments at Visit 1 (Day 1) patients will be randomised to receive IRL790 or placebo (1:1 randomisation). The treatment allocation will be double-blinded, i.e. it will not be disclosed to the patients, the site staff or the Sponsor (see Section 6.4). Study medication will be dispensed and the first capsules of IMP will be administered in the clinic. The patient will be instructed to take the second daily dose in the afternoon of the same day as the study visit.

During the treatment period, Visits 2-4 will be performed on Days 7, 14 and 28 and a follow-up phone call on Day 21. Dose adjustments of IRL790 will be made as described in Section 6.2.

During the telephone follow-up call on Day 21, the patient will be asked to complete two 24-hour diaries for assessment of daily motor function and bring the completed diaries to the clinic at Visit 4 on Day 28.

On Day 28 (Visit 4) the morning IMP dose will be administered at the clinic. ECG will be assessed two hours after IMP administration. Blood samples for PK analysis will be collected pre-dose and two hours post dose.

The MDS-UPDRS part 3 will be assessed with the patient in the "on state"[7] on Day 1 (Visit 1) and Day 28 (Visit 4 End of Treatment or earlier in the event of withdrawal).

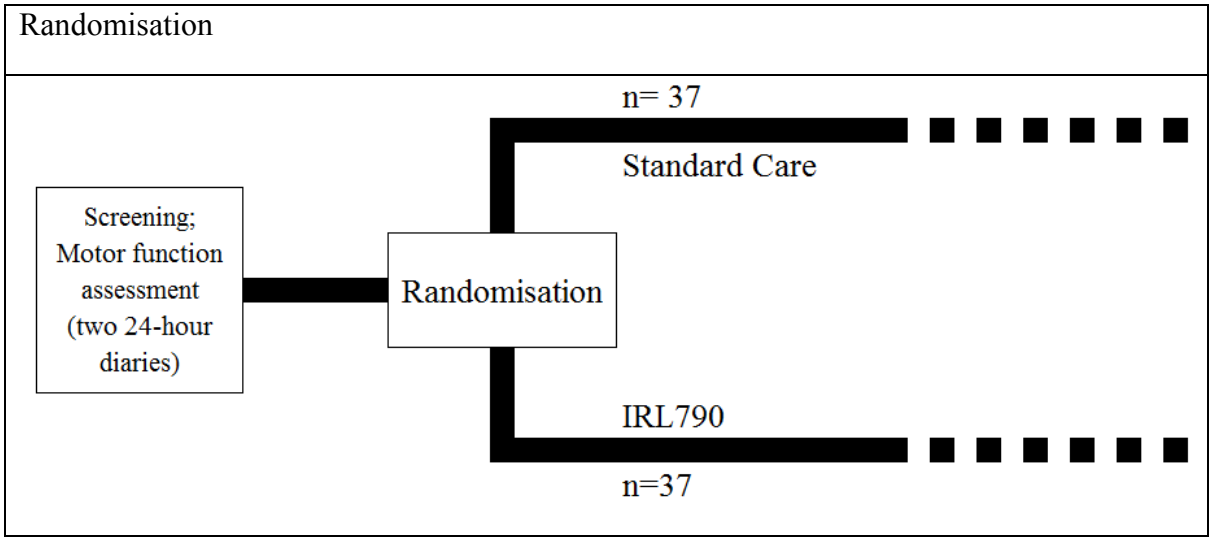
To assess dyskinesia, the UDysRS will be administered on Day 1 (Visit 1) and Day 28 (Visit 4 End of Treatment or earlier in the event of withdrawal). The physician rated part III will be assessed with the patients in the "on" state. Patients will be filmed using the "Rush filming protocol" (see Appendix 25.3) in the "on" state. The film sequences will be transferred to a blinded Central Rater for assessment and the results from this rating will subsequently be included in the CRF.

A follow-up visit will take place 5-8 days after the last IMP dose.

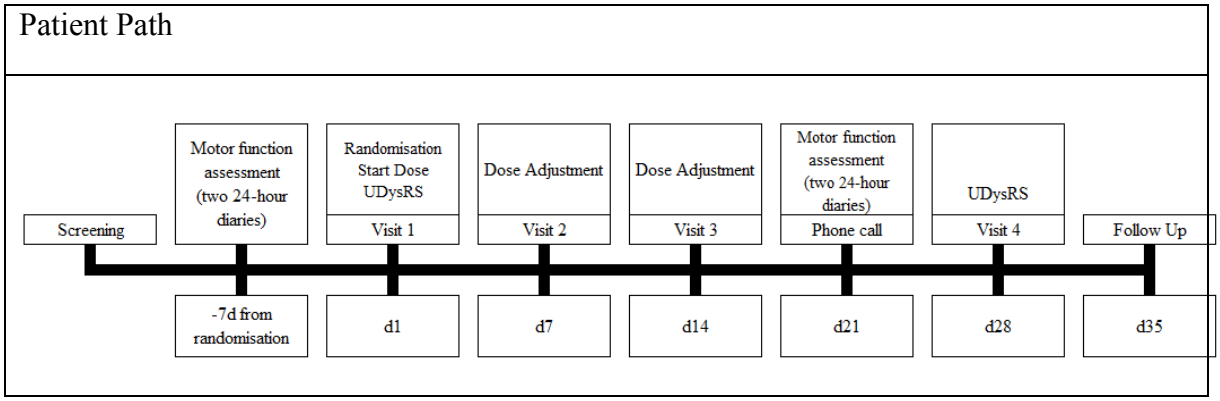
Unscheduled visits will be performed as needed during the study and should be documented in the appropriate section of the CRF.

Each assessment is further described in Section 7.

3.1.1. Study Schematic



[7] "On-Dyskinesia" refers to the choreic and dystonic movements described to the patient as "jerking or twisting movements that occur when your medicine is working."
"Off-Dystonia" should be described to the patient as "spasms or cramps that can be painful and occur when your Parkinson's disease medications are not taken or are not working.



3.2. Rationale for study design and dose selection

The pharmacological effects of IRL790 have been evaluated in a range of preclinical animal models. Integrating the preclinical *in vivo* data and *in vitro* assessments for the main molecular target, the dopamine D3 receptor, indicates that efficacy in patients with PD could be expected at doses below 500 nM in plasma.
The Phase 1b study of IRL790 in advanced Parkinson's disease indicated that efficacy could be achieved at such plasma concentrations with retained tolerability and safety and where the biomarker prolactin, indicating target engagement, was moderately elevated.
Given the variability in tolerability of IRL790 in PD patients, the dosing of IRL790 will continue to be personalised and hence flexible dosing will be explored in this study. A flexible dose titration range of 5-10 mg b.i.d. will allow the physician to titrate an optimal dose for each individual patient, while retaining a large margin of safety. Given the plasma half-life of about 7 hours, sufficient coverage during the waking hours of the day is expected.

To mitigate the risk for intolerability and AEs, the protocol allows for flexible dose titration and involves careful monitoring of the patients' well-being.

3.3. Discussion of study design, including the choice of control groups

The study has a parallel group design, which is deemed more appropriate than a cross-over considering the aetiology of the illness. Patients will be randomised, in equal proportions, to placebo or the active dose regimen.

Bias is controlled through a placebo group.

4. PATIENT SELECTION CRITERIA

4.1. Patient recruitment

Patients will be recruited from the population of outpatients at the study sites. Patients may also be recruited by other methods such as clinic lists, research registers, and patients learning about the study from websites or other sources or from a local research event. Potentially eligible patients interested in taking part of the study may therefore be referred from other sites.

The Investigator will keep records of all patients screened and included. The reason for screen failure should be stated for all patients screened but not included. The reason for withdrawal should be stated for all patients included but not completed.

Seventy Four (74) evaluable patients are required.

Patients who screen fail can be re-screened once depending on the reason for screen fail and as judged by the Investigator. The patient will then receive a new screening number.

4.2. Inclusion criteria

For inclusion in the study, patients must fulfil all the following criteria:

1. Male or female ≥18 and ≤79 years of age.
2. Signed a current Ethics Committee approved informed consent form.
3. Parkinson's disease, per UK Parkinson's Disease Society (UKPDS) Brain Bank Clinical Diagnostic Criteria.
4. Waking day dyskinesia of >25% determined as a score of ≥2 as per Question 4.1 of the MDS-UPDRS.
5. On a stable regimen of antiparkinson medications for at least 30 days prior to screening, including a levodopa preparation administered not less than three times daily and willing to continue the same doses and regimens during study participation. Rescue medication such as Madopar dispersable and Apomorphine injections are allowed.
6. Taking a maximum of eight regular levodopa intakes per day, excluding bedtime and night time levodopa.
7. Any other current and allowed prescription/non-prescription medications and/or nutritional supplements taken regularly must have been at a stable dose and regimen for at least 30 days prior to screening and the patient must be willing to continue the same doses and regimens during study participation (this criterion does not apply to medications that are being taken pre-study only on an as-needed basis).
8. Patient must be willing and able to avoid direct exposure to sunlight from day 1 to day 28.
9. Able to complete at least one valid 24-hour patient diary at Visit 1.

4.3. Exclusion criteria

Patients must not enter the study if any of the following exclusion criteria are fulfilled:

1. History of neurosurgical intervention related to Parkinson's disease (e.g. deep brain stimulation).
2. Treatment with pump delivered antiparkinsonian therapy (i.e. subcutaneous apomorphine or levodopa/carbidopa intestinal infusion).
3. History of seizures within two years prior to screening.
4. History of stroke or transient ischemic attack (TIA) within two years prior to screening.
5. History of cancer within five years prior to screening, with the following exceptions: adequately treated non-melanomatous skin cancers, localised bladder cancer, non-metastatic prostate cancer or in situ cervical cancer.

6. Presence of cognitive impairment, as evidenced by a Mini-Mental Status Examination (MMSE) score of less than 24 during screening.
7. A Hoehn and Yahr stage of five.
8. Any history of a significant heart condition or cardiac arrhythmias within the past 5 years, any repolarisation deficits or any other clinically significant abnormal ECG as judged by the Investigator
9. Severe or ongoing unstable medical condition including a history of poorly controlled diabetes; obesity associated with metabolic syndrome; uncontrolled hypertension; cerebrovascular disease, or any form of clinically significant cardiac disease, clinically significant symptomatic orthostatic hypotension; clinically significant hepatic disease, renal failure or abnormal renal function (definition of abnormal renal function is creatinine clearance <45 ml/min (calculated according to the Cockcroft-Gault formula).
10. Any history of a neurological other than Parkinson's disease or a psychiatric disorder, including history of DSM IV diagnosed major depression or psychosis. Patients with illusions or hallucinations with no loss of insight will be eligible. Patients with mild depression who are well controlled on a stable dose of an antidepressant medication for at least 4 weeks before screening will be eligible.
11. Enrolment in any other clinical study involving medication, medical devices or surgical procedures, current or within three months prior to screening visit, or previous participation in the present study. Patients enrolled in non-interventional clinical trials will be eligible.
12. Drug and/or alcohol abuse.
13. History of severe drug allergy or hypersensitivity.
14. If female, is pregnant or lactating, or has a positive pregnancy test result pre-dose.
15. Patients unwilling to use two forms of contraception (one of which being a barrier method see Section 7.3) 90 days for men and 30 days for women after last IMP dose
16. Any planned major surgery within the duration of the study.
17. Any other condition or symptoms preventing the patient from entering the study, according to the Investigator's judgement.

4.4. Patient withdrawals

In all circumstances, patients will be made aware of the rights to refuse participation in a clinical trial and are entitled to freely withdraw their consent, without giving reasons. Patients will be assured that the withdrawal from the trial will not cause prejudice, will not result in any determinant and will not affect treatment. In addition, refusal to give consent or withdrawal of consent to participate in research will not lead to any liability or discrimination against the person concerned.

The Investigator has the right to withdraw patients from the study in the event of:

- Use of any non-permitted concomitant medication
- Non-compliance with the protocol and/or lack of willingness or commitment to co-operate in all phases of the study

- Protocol deviation
- Pregnancy after entry into study
- An adverse event which is considered intolerable by the patient
- Intercurrent illness that necessitates pharmacological treatment with a drug which interacts in any way with the test treatment
- Development of an exclusion criterion
- Treatment failure

Should a patient decide to withdraw for other reason, all effort will be made to complete and report observations as thoroughly as possible. A complete final evaluation at the time of withdrawal will be performed with an explanation of the exact reason why the patient is withdrawing from the study.

The Investigator is responsible for the optimal individual treatment of the patient.

The Investigator must fill in the "Study termination" section of the CRF explaining all reasons for withdrawal.

After a patient withdraws from a trial, the Investigator remains responsible for reporting SAEs considered causally related to the study drug. In addition, the Investigator must ensure appropriate treatment and follow-up of each adverse event ongoing at the time of the patient's discontinuation.

In the event that a patient withdraws from the study for any reason other than an adverse event or other safety concern or is lost to follow-up within 30 days of treatment, the Principal Investigator may enrol a new patient to replace the withdrawn patient. The reason for the patient's withdrawal from the study must be recorded.

4.4.1. Replacements

In the event that a patient withdraws from the study for any reason other than an adverse event or other safety concern, or is lost to follow-up within 30 days of treatment, a new patient will be enrolled to replace the withdrawn patient. The replacement will be managed through a centrally administered study wide randomisation list. The reason for the patient's withdrawal from the study must be recorded.

5. CONCOMITANT MEDICATIONS

5.1. Permitted concomitant medications

Patients included in the study will be on stable anti-Parkinson treatment for at least 30 days prior to inclusion and during the study.

Other medications considered necessary for the patient's safety and well-being may be given at the discretion of the Investigator.

5.2. Non-permitted concomitant medications

All concomitant therapy used during and within four weeks prior to the study period must be recorded in the CRF. No other drug under investigation may be used concomitantly with the study medication.

Concomitant medications that are strong inhibitors of CYP2D6 should be avoided. As the elimination pathways of IRL790 regarding other CYP enzymes are unknown (except for CYP2A6, CYP2D6 and CYP3A4), there may be a risk of significant exposure increase when medications that are strong enzyme and transporter inhibitors are used together with IRL790. Strong inhibitors of these enzymes and transporters, including grapefruit juice, should be avoided throughout the study.

Examples of clinical inhibitors for P450-mediated metabolisms and clinical inhibitors for transporters[8]		
Isoenzyme (cytochrome P450)	**Strong Inhibitors**	**Moderate Inhibitors**
CYP1A2	ciprofloxacin, enoxacin, fluvoxamine, zafirlukast	methoxsalen, mexiletine, oral contraceptives
CYP2B6	-	-
CYP2C8	clopidogrel, gemfibrozil	deferasirox, teriflunomide
CYP2C9	-	amiodarone, felbamate, fluconazole, miconazole, piperine
CYP2C19	fluconazole, fluoxetine, fluvoxamine, ticlopidine	-
CYP2D6	bupropion, fluoxetine, paroxetine, quinidine, terbinafine	cimetidine, cinacalcet, duloxetine, fluvoxamine, mirabegron
Transporter	**Inhibitor**	
P-gp	amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil	
BCRP	curcumin, cyclosporine A, eltrombopag	

[8] The list will be provided to the Investigator sites and maintained/updated throughout the study to provide information on clinical inhibitors for P450-mediated metabolisms and clinical inhibitors for transporters. Please note this is not an exhaustive and will be updated as new information becomes available and circulated to all sites.

OAT1B1, OATP1B3	atazanavir and ritonavir, clarithromycin, cyclosporine, erythromycin, gemfibrozil, lopinavir and ritonavir, rifampin (single dose), simeprevir
OAT1, OAT3	p-aminohippuric acid (PAH), probenecid, teriflunomide
MATE1, MATE2-K	cimetidine, dolutegravir, isavuconazole, ranolazine, trimethoprim, vandetanib

6. TREATMENT(S)

6.1. Appearance and content

IRL790 capsules, 2.5mg free base equivalent: White hard HPMC capsule, coni snap size 3, colour white containing IRL790 x ½ L-tartrate.

Placebo capsules: White hard HPMC capsule, coni snap size 3, colour white containing starch.

6.2. Dosage and administration

The IMP (2-4 capsules) will be swallowed together with 200 mL of tap water in the morning and in the afternoon approximately 8 hours apart of each administration day, except for Day 28 when the last dose will be taken in the morning at the clinic visit after trough PK sampling.

Titration Phase

The starting dose of IRL790 will be 7.5 mg (three capsules) b.i.d (Visit 1, Day 1).

Formal dose adjustments can be made at the discretion of the treating physician according to the following:

Visit	Adjustment
Visit 2 (Day 7)	The dose can be increased to 10mg b.i.d., maintained at 7.5mg b.i.d. or decreased to 5mg b.i.d
Visit 3 (Day 14)	The dose can be adjusted to 5 mg, 7.5mg or 10mg b.i.d. (2-4 capsules b.i.d.) Note: Dose de-escalation/re-escalation is permitted at Visit 3 but is only in a 2.5mg (1 capsule) step.[9]

The reasoning for dose adjustment must be recorded in the CRF.

[9] i.e. Dose re-escalation from 5mg to 10mg b.i.d. or de-escalation from 10mg to 5mg b.i.d. is ***not*** permitted

Unscheduled dose de-escalation can be made between Visit 1 and Visit 3 only in the case of intolerance; unscheduled dose escalation is not permitted.

Fixed Dose Phase

The fixed IRL790 dose for the remaining 14 days of treatment will be determined on Day 14 (Visit 3) for each patient.

Unscheduled dose de-escalation can be made between Visit 3 and Visit 4 only in the case of intolerance.

There will be no treatment with IRL790 available after end of study participation.

6.3. Packaging and labelling

Finished product of IMP (active drug and placebo) will be packed and labelled by PCI, United Kingdom.

Labels will comply with applicable Good Manufacturing Practice (GMP) requirements (EudraLex Volume 4, Good manufacturing practices, ANNEX 13, Manufacture of Investigational Medicinal Products).

Containers will be packed with sufficient IMP for the study treatment period and labelled with the appropriate information required, before release and shipment.

6.4. Blinding and randomisation

This is a double-blind study, thus, the study patients and the site personnel who are making the study assessments will be blinded to the study treatments of IRL790 and Placebo (capsules of IRL790 and placebo will be of identical appearance.).

Treatment allocation (1:1 randomisation) will be performed via a web-based IVRS and based on the randomisation list generated by Endpoint Clinical.

Interactive Randomisation System (IRS):

The Interactive Response System (IRS) will manage the randomisation and IMP inventory supply chain. IRS will deliver the IMP at the correct time for both new and existing patients. IRS will also support the dosing schedules and is used to track patient activities in real time throughout study visits. Real-time web reports and alerts platform (email, fax, SMS) give access to compliance feedback for continuous transparency of the study's progress. Patient unblinding is also contained within the IRS system to allow the unblinding of patients for both Safety and Statistical purposes within the protocol via web or phone. If emergency unblinding is required this responsibility lies solely with the investigator, unblinding for other Safety and Statistical purposes will be managed per Sponsor outlined request. Unblinding access can be controlled within the IRS by role type allowing only the appropriate role to unblind the appropriate patient.

Prolactin Results

It is expected that Prolactin levels will be raised in participants randomised to IRL790. It should be noted that this elevation in Prolactin is not expected to be clinically significant (i.e. will not exceed the upper limit of normal) but is potentially detectable when comparing Visit 4 results to screening.

There is no risk to the analysis of endpoints by unblinding as the Visit 4 safety test results (including Prolactin level) will only be available several hours after performing the UDysRS and other rating tests.

No ratings can be performed after safety test results are received.

Rush Filming Protocol

To control variance, Parts III & IV of the UDysRS will be recorded using the Rush Filming Protocol and assessed by a Central Rater. The films will be recorded digitally with the patient in "on" state and each assigned a randomisation number ensuring that the Central Rater is blinded as to which films were recorded at Visit 1 (Pretreatment) and Visit 4 (End of Treatment). The investigator must ensure that the filming is performed with the patient in the "on" phase, during peak dose dyskinesia.

Pharmacokinetic Samples

The laboratory analysing the PK samples will have access to the randomisation list; only samples taken from patients in the active arm of the study will be analysed. Results of PK analysis will not be linked to patient number until the database is locked.

Breaking the Blind

IRL790 and Placebo (capsules of identical appearance.) will be dispensed in identical containers according to a blinded randomisation scheme. Study patients, Investigators, study staff and the Sponsor will remain blinded to the randomisation scheme until the blind is formally broken for all patients. For this to occur all patients must have completed the study and the study database must be locked.

Prior to database lock, a treatment assignment may be unblinded only when knowledge of the treatment received is necessary for interpreting a serious adverse event, or essential for the medical management of the patient, or to provide critical safety information about a drug that could have implications for the ongoing conduct of the trial. Blinding codes must only be broken in emergency situations for reasons of patient safety.

Investigators will receive a confidential code to access the IRS system that will enable them to selectively break the code for an individual patient. When the blinding code is broken, the reason must be fully documented and entered on the case report form (CRF).

If a patient's treatment assignment is unblinded, the Medical Monitor will be notified of the unblinding incident and the following information will be provided by the PI: date, time, patient's trial identification (number and initials), and the reason for unblinding. The patient will be withdrawn.

The identity and responsibility of those individuals at the study site who gain access to the unblinded treatment assignment must be documented. It is mandatory that all personnel who

are involved in the unblinding, and who have access to the unblinded treatment assignment, maintain the confidentiality of the information and do not divulge the treatment assignment.

6.5. Treatment compliance and accountability

Treatment compliance will be recorded at each visit during the treatment period. Unused medication and empty containers will be returned to the study site at Visit 4 (Day 28 End of Treatment or earlier in the event of withdrawal).

6.6. Drug storage

The IMP should be stored at room temperature (not to exceed 30^{o}C).

Any unused study medication will be returned to the Sponsor or the Hospital Pharmacy for destruction. Empty containers will be destroyed at the study site. The Monitor will perform final IMP accountability reconciliation at the study end to verify that all unused IMP is adequately destroyed/returned and documented.

7. STUDY PLAN

7.1. Continuous Assessments

The following assessments will be carried out on a continuous basis and as events arise:

- Adverse Events
- Concomitant Medication
- Medication Compliance

7.2. Screening (-28 to -7 days prior to randomisation)

The following assessments will be performed and documented in all patients consented to the study to assess whether a patient meets eligibility criteria:

- Informed Consent (prior to any non-standard of care screening procedures being initiated)
- Demographics/Medical History
- Inclusion/Exclusion Criteria (screen failures to be recorded)
- Pregnancy Test
- Concomitant Medications
- Height
- Weight
- Physical Examination
- Vital Signs
- 12-lead ECG
- Haematology/Clinical Chemistry
- Dipstick Urinalysis
- MDS-UPDRS question 4.1
- MMSE
- Hoehn and Yahr score

- Baseline events
- 24-hour patient diaries – Patients, after receiving training on diary completion, will be instructed to complete 24-hour diaries for assessment of daily motor function on two days in the weeks before Visit 1 and bring the completed diaries to the clinic. (see section 8.2.2.6)

- **GP Letter**

The patient's GP will be informed of the patient's entry in to the clinical trial.

7.3. Visit 1 (Day 1)

Eligible patients will be randomised to either trial drug (IRL790) or placebo.

The following procedures and assessments are to be carried out at Visit 1 (Day 1):

- Concomitant Medications
- PK sample
- MDS-UPDRS
- UDysRS
- Baseline Events
- Randomisation
- Dispense and Administer Trial Medication – starting dose 7.5mg (3 capsules b.i.d)

- **Patient Information Card**

All study patients enrolled will be provided with a Patient Information Card to be carried throughout the study. The card will include the following information:

- That the carrier is participating in a clinical study
- Patient study ID
- That the carrier is potentially treated with IMP
- The name and telephone number of the Investigator
- Name and address of the Sponsor

- **Contraceptive Requirements:**

The patient must be reminded to use two forms of contraception (one of which being a barrier method) for three months (90 days) for men and four weeks (30 days) for women.

Male patients

Male patients must use acceptable methods of contraception if the male patient's partner could become pregnant from the time of the first administration study medication until three months following administration of the last dose of study medication. The acceptable methods of contraception are as follows:

- Surgical sterilisation (vasectomy with documentation of azoospermia) *and* a barrier method (condom or occlusive cap (diaphragm or cervical/vault caps) used with spermicidal foam/gel/film/cream/suppository)

- The female partner uses oral contraceptives (combination oestrogen/ progesterone pills), injectable progesterone or subdermal implants *and* a barrier method (condom or occlusive cap (diaphragm or cervical/vault caps) used with spermicidal foam/gel/film/cream/suppository)
- The female partner has undergone documented tubal ligation (female sterilisation). *In addition*, a barrier method (condom or occlusive cap (diaphragm or cervical/vault caps) used with spermicidal foam/gel/film/cream/suppository) must be used
- The female partner has undergone documented placement of an intrauterine device (IUD) or intrauterine system (IUS) *and* the use of a barrier method (condom or occlusive cap (diaphragm or cervical/vault caps) used with spermicidal foam/gel/film/cream/suppository)
- True abstinence when this is in line with the preferred and usual lifestyle of the patient. *Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are **not** acceptable methods of contraception*

Male patients are expected to use a condom and contraceptive methods with a failure rate of < 1% to prevent pregnancy and drug exposure to a partner and refrain from donating sperm from the date of dosing until three months after last dosing of IMP.

Note:
Male patients whose female partner(s) is (are) pregnant must use a condom from the time of the first administration of treatment or study medication until three months (90 days) following administration of the last treatment or dose of study medication.

Female patients

Female patients of childbearing potential must use medically acceptable methods of contraception from the time of the first administration of treatment or study medication until four weeks following administration of the last treatment or dose of study medication. Acceptable methods include:

- A documented placement of an IUD or IUS *and* the use of a barrier method (condom or occlusive cap (diaphragm or cervical/vault caps) used with spermicidal foam/gel/film/cream/suppository).
- Documented tubal ligation (female sterilisation). *In addition*, a barrier method (condom or occlusive cap (diaphragm or cervical/vault caps) used with spermicidal foam/gel/film/cream/suppository) should also be used;
- Oral contraceptives (combination oestrogen/progesterone containing pills), injectable progesterone or subdermal implants *and* the use of a barrier method (condom or occlusive cap (diaphragm or cervical/vault caps) used with spermicidal foam/gel/film/cream/suppository).
- True abstinence when this is in line with the preferred and usual lifestyle of the patient. *Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are **not** acceptable methods of contraception.*

- **Additional Requirements**

Subjects will be required to avoid exposure to direct sunlight from Visit 1 (day 1) until the follow-up visit (day 28).

7.4. Visit 2 (Day 7 ± 2 days)

The following procedures and assessments are to be carried out at Visit 2 (Day 7 ± 2 days):

- Concomitant Medications
- Treatment Emergent Adverse Events
- Compliance
- Dose Adjustment (See Section 6.2)

7.5. Visit 3 (Day 14 ± 2 days)

The following procedures and assessments are to be carried out at Visit 3 (Day 14 ± 2 days):

- Concomitant Medications
- Treatment Emergent Adverse Events
- Dispense Trial Medication
- Compliance
- Dose Adjustment (See Section 6.2)

7.6. Phone Call (Day 21 ± 2 days)

The following assessments are to be carried out at via phone call on Day 21 ± 2 days:

- Concomitant Medications
- Treatment Emergent Adverse Events
- Compliance
- 24-hour patient diaries - Patients will be instructed to complete 24-hour diaries for assessment of daily motor function on two days in the week before Visit 4 and bring the completed diaries to the clinic.

7.7. Visit 4 (End of Treatment, Day 28 -2 to 0 days)

The following procedures and assessments are to be carried out at Visit 4 (Day 28 -2 to 0 days):

- Concomitant Medications
- Physical Examination
- Vital Signs
- 12-lead ECG
- Haematology/Clinical Chemistry
- Dipstick Urinalysis
- Pregnancy Test
- PK sample
- MDS-UPDRS
- UDysRS
- CGI-C
- Treatment Emergent Adverse Events
- Compliance

NOTE: Withdrawn patients will undergo Visit 4 assessments

7.8. Follow Up (5-8 days after End of Treatment)

The following procedures and assessments are to be carried out at Follow Up (5-8 days after Visit 4):

- Concomitant Medication
- Weight
- Physical Examination
- Vital Signs
- 12-lead ECG
- Haematology/Clinical Chemistry
- Dipstick Urinalysis
- Treatment Emergent Adverse Events

7.9. Early Termination Visit

Patients have the right to withdraw from the trial at any time and for any reason. If a patient refuses to be seen for further visits the assessments at Visit 4 (End of Treatment) should be performed at the time they have indicated that they will not attend for further visits, assuming they are available and consent to this.

8. STUDY PROCEDURES / EVALUATIONS

Signed informed consent must be obtained before any screening procedures are initiated. The informed consent procedure is further described in Section 14.

8.1. Clinical evaluations

8.1.1. Demographics/Medical History

The following demographic data will be recorded: gender, age, ethnicity and race.

Medical/surgical history will be obtained by interview in order to verify that the eligibility criteria are met.

Diagnosis of Parkinson's disease must have been made as per the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria

The duration of the patients' Parkinson's disease will be assessed by the following endpoints:

- Years from diagnosis
- Years from symptom onset

8.1.2. Height/Weight

Weight and height will be measured without shoes. Body mass index will be calculated from the height and weight recorded and rounded to the nearest whole number.

8.1.3. Physical Examination

A complete physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities.

8.1.4. Vital Signs

Heart rate, systolic and diastolic blood pressure will be measured in the supine position after five minutes of rest.

8.1.5. Resting 12-lead ECG

Single 12-lead ECGs will be recorded in a supine position after five minutes of rest. PR, QRS, QT, and QTcF intervals will be recorded. The time of the ECG recordings must be noted in the CRF.

8.2. Evaluations & Assessments

8.2.1. Clinical laboratory evaluations

The anticipated volume of blood samples collected during the study from each patient will not exceed 250 mL per patient.

Any remains from the safety laboratory samples will be disposed of after analyses.

Blood samples for analysis of clinical chemistry, haematology and coagulation variables will be collected at Screening, Visit 4 (Day 28 End of Treatment or earlier in the event of withdrawal) and Follow-Up and sent to the certified laboratory at each local hospital and analysed by routine analytical methods. Urine analysis will be performed at clinic using dip sticks.

The following safety laboratory variables will be assessed:

Clinical Chemistry

Alanine aminotransferase (ALT)
Alkaline phosphatase (ALP)
Amylase
Aspartate aminotransferase (AST)
Calcium
Albumin
Total bilirubin
Creatinine
Creatinine kinase
Lactate dehydrogenase (LDH)
Random Glucose
Total cholesterol
Magnesium
Phosphate

Haematology

Basophils
Eosinophils
Haematocrit
Haemoglobin (Hb)
Lymphocytes
Monocytes
Neutrophils
Platelet count
Red blood cell (RBC) count
White blood cell (WBC) count with differential count

Coagulation

Prothrombin time (PT) or International Normalised Ratio (INR)

Potassium	**Urinalysis (dip stick)**
Prolactin	Glucose
Sodium	Hb/erythrocytes
Thyroid-stimulating hormone (TSH)	Nitrite
Triiodothyronine (Free T3)	Protein
Thyroxine (T4)	
Triglycerides	
Urea nitrogen	
Follicle Stimulating Hormone (FSH)	
Estradiol	

NOTE: Sample collection to be carried out prior to dosing at Visit 4
Estradiol is only required for Post-menopausal participants only.

8.2.2. Non-standard assays or procedures

8.2.2.1. Pharmacokinetic samples

Venous blood samples (approximately 5mL) for the determination of concentrations of IRL790 and its metabolites IRL902 (n-dealkylated) and IRL872 (acetylated) in plasma will be collected before and two hours (for trough and C_{max}) after IMP administration at the specified time-points (Visits 1 & 4). The date and time of collection of each sample will be recorded in the CRF.

Samples will be collected, handled, labelled stored and shipped as detailed in the laboratory manual.

Samples for determination of concentrations of IRL790 and its metabolites in plasma will be analysed by the Swedish National Veterinary Institute, by means of a validated LC-MS/MS method. The details of the analytical method used will be described in a separate bioanalytical report.

8.2.2.2. Mini-Mental State Examination (MMSE)

The MMSE will be administered at screening. (See Appendix 1 Mini-Mental State Examination (MMSE))

8.2.2.3. Hoehn and Yahr scale

The Hoehn and Yahr scale is a five point scale for describing how the symptoms of Parkinson's disease progress:

Stage	Hoehn and Yahr Scale
0	Asymptomatic
1	Unilateral involvement only
2	Bilateral involvement with impairment of balance
3	Mild 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

8.2.2.4. Unified Parkinson's Disease Rating Scale (MDS-UPDRS)

The MDS-UPDRS part 1-4 will be administered at Visit 1(Baseline, Day 1) and Visit 4 (Day 28 End of Treatment or earlier in the event of withdrawal). The MDS-UPDRS part III should be administered with the patient in "on" state. (See Appendix 2 Unified Parkinson's Disease Rating Scale (MDS-UPDRS)). The "on" state is defined when the patient is at his/her best mobility, usually 1-2 hours post levodopa. The rater should make sure that the defined "on" state is in agreement with the patient's perception of best mobility. Preferably, the same rater should complete MDS-UPDRS III at baseline and end of treatment visits.

8.2.2.5. Unified Dyskinesia Rating Scale (UDysRS)

The UDysRS will be administered at Visit 1(Baseline, Day 1) and Visit 4 (Day 28 End of Treatment or earlier in the event of withdrawal). The physician rated part (part III and IV) will be assessed by filming the patient 1-2 hours after levodopa in the "on" state. The Rush filming protocol will be employed and the films will be sent for subsequent rating performed by a blinded Centralised Rater. (See Appendix 3 Unified Dyskinesia Rating Scale (UDysRS))

8.2.2.5.1. Rush filming protocol

The Rush filming protocol will be used to assess severity, distribution and functional impairment of dyskinesia. The investigator must ensure that the filming is performed with the patient in best "on", usually 1-2 hours post levodopa, during peak dose dyskinesia. The following situations will be captured while filming the patient:

1. Communication: Instruct patient to look at evaluator (or camera) and describe a picture (the Cookie Thief Drawing).
2. Drinking from a cup: Instruct the patient to pick up a 4 oz cup filled to within 1 cm of brim with water with the dominant hand and bringing it to lips, drink contents and replace cup on table.

3. Dressing: Instruct the patient to put on a lab coat and do up three buttons, undo the buttons and take the coat off. [Allow up to 60 seconds].
4. Ambulation: Instruct the patient to rise from a chair, walk 15 feet, return and sit back down in the chair.

8.2.2.6. 24-hour patient diary

Patient diaries have gained wide acceptance as endpoints for clinical development of therapeutics aiming to reduce treatment-related motor complications [18]. Motor fluctuations are associated with compromise in activities of daily living and health-related quality of life. For this clinical trial patients will record their 24-hours motor function in 30-minute intervals, beginning at midnight. For each 30-minute interval the patient will rate the state he or she has been in for the past 30 minutes; Off, On or On with troublesome dyskinesia. The patient will also denote the time when he or she has been asleep.

- For this trial, patient training to improve accuracy and compliance is essential. Patients will be instructed and trained on how to complete the diary at the Screening visit (training detailed in the Study Operations Manual). The investigator must ensure that each patient understands how and when to fill in the diaries before leaving the clinic. Patients that have not been able to complete at least one valid diary at Visit 1 will not be included. Patients not completing at least one valid diary on Visit 1 may be rescheduled for Visit 1 following additional diary completion training. The 24-hour diaries will be captured on two days at run-in at the patient's choosing and at two days of Week 4 of treatment at the patients choosing.

- For each of the two periods (run-in and week 4 of treatment) the Investigator will register the following data in the appropriate sections of the CRF:

    - The total daily time for the two diaries the patients spent in "OFF", "ON" and "ON with troublesome dyskinesia".

- A patient diary will be regarded as valid if less than four of the 30-minute intervals have missing data for the waking part of the day (missing sleep assessments will be ignored).

- If one of the two diaries is regarded invalid due to missing data or for any other reason the time spent in OFF", "ON" and "ON with troublesome dyskinesia" derived from the valid diary should be registered in the CRF. If none of the two diaries are valid at Visit 4, missing data should be recorded in the CRF.

8.2.2.7. Clinical Global Impression of Change (CGI-C)

The CGI-C will be administered at the Visit 4 (Day 28 End of Treatment or earlier in the event of withdrawal). The Investigator will rate on a 7-grade scale how, in their judgment, the patients´ global clinical condition has changed from baseline. (See Appendix 4 Clinical Global Impression of Change (CGI-C))

8.2.3. Specimen preparation, handling and shipping

8.2.3.1. Instructions for specimen preparation, handling and storage

The samples for analysis of PK variables will be stored at -20°C or below until analysed. The samples will be disposed of after the clinical study report has been finalised.

If a patient withdraws consent to the use of biological samples donated, the samples will be disposed of/destroyed, if not already analysed and documented.

The Principal Investigator will ensure that:

- Patient withdrawal of informed consent is notified immediately to Sponsor.
- Biological samples from the patient, if stored at the research clinic prior to shipment, are immediately identified, disposed of/destroyed and the action is documented.

The Sponsor must ensure that laboratories holding samples are informed about the withdrawn consent immediately and that samples are disposed of/destroyed or returned to the research clinic and the action is documented.

Specimen preparation, handling, storage and shipment will be detailed in the study operations manual.

9. ADVERSE EVENT REPORTING

9.1. Definitions

Adverse Event (AE)

Untoward medical occurrence in a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign (including laboratory abnormal finding), system or disease temporally associated with the use of the medicinal product, whether or not considered as related to the investigational medicinal product.

A *baseline event* is any AE in a clinical study patient that occurs after the participant has signed the Informed Consent Form (ICF) up until the first administration of IMP.

A *treatment emergent* AE (TEAE) is any AE not present prior to the initiation of IMP administration or any event already present that worsens in either intensity or frequency following exposure to the IMP.

Adverse Drug Reaction (ADR)

Untoward and unintended responses to an investigational medicinal product related to any dose administered.

All adverse events judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression “reasonable causal relationship” means to convey in general that there are facts or evidence meant to suggest a causal relationship.

Serious Adverse Event (SAE)

Untoward medical occurrence or effect that at any dose falls in one or more of the following categories:

- Results in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing inpatients' hospitalisation. Hospitalisation refers to a situation whereby an AE is associated with unplanned overnight admission into hospital.
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Is a medically significant adverse event

Planned hospitalisations or surgical interventions for a condition that existed before the patient signed the ICF and that did not change in intensity are not SAEs.

Unexpected Adverse Event (UAE)

When the nature or severity of an AE or SAE is not expected based on the information provided in the IB, it is considered to be an unexpected AE or SAE. The Sponsor or designee is responsible for determining the expectedness of an AE.

Suspected Unexpected Serious Adverse Reactions (SUSARs)

SUSARs are AEs that are suspected to be related to the IMP (i.e. AEs assessed as possibly, probably or definitely related according to Section 9.4) and are both unexpected and serious. The Sponsor or designee is responsible for determining whether a reported SAE meets the definition of a SUSAR.

9.2. Expectedness

An expected adverse reaction is an adverse reaction, the nature or severity of which is consistent with the applicable product information (see Investigator's Brochure), otherwise it is considered unexpected.

Based on non-clinical safety data in experimental animals as well as on Phase 1 data in healthy male volunteers and in patients with advanced Parkinson's disease, adverse events are likely to predominantly be CNS related. Adverse reactions in patients with advanced Parkinson's disease are listed below:

Potential AEs associated with IRL790 treatment

Nervous system	Cardiac	General disorders and administration site condition	Musculoskeletal and connective tissue disorders
Parkinsonism	Postural dizziness	Lethargy	Muscular weakness
Tremor	Dyspnoea	Fatigue	
Muscular rigidity		Oedema	
Insomnia			
Somnolence			
Headache			
Slurred thinking			

Dissociation			
Balance disorder			
Dizziness			
Concentration difficulties			

9.3. Intensity of adverse event

The grading of the severity of AEs will follow the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 [14]. Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline.

The Investigator must assess the *severity* of an AE using the following definitions, and record it on the *Adverse Event Form* in the CRF:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation 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.*

9.4. Causality assessment

The Investigator must assess the *causal relationship* between a treatment emergent adverse event and the IMP using the definitions below and record it on the *Adverse Event Form* in the CRF as well as on the *Serious Adverse Event Report Form*, if applicable:

- *Probable* – the AE has a strong temporal relationship to the IMP or recurs on re-challenge, and another aetiology is unlikely or significantly less likely
- *Possible* – the AE has a suggestive temporal relationship to the IMP, and an alternative aetiology is equally or less likely

- *Not related* – the AE has no temporal relationship to the IMP or is due to underlying/concurrent illness or effect of another drug (that is, there is no causal relationship between the IMP and the AE)

An AE is considered causally related to the use of the IMP when the causality assessment is *probable* or *possible*.

For *baseline events*, a causality assessment is not relevant.

9.5. Action taken regarding the study drug

The action taken regarding study drug must be described by selecting one of the following:

- Permanently discontinued
- Stopped temporarily
- Dose reduced
- Dose increased
- No action taken
- Unknown/not applicable

9.6. Outcome

The Investigator must assess the *outcome* of an AE using the definitions below and record it on the *Adverse Event Form* in the CRF:

- *Recovered* – the patient has recovered completely, and no symptoms remain
- *Recovering* – the patient's condition is improving, but symptoms still remain
- *Recovered with sequelae* – the patient has recovered, but some symptoms remain (for example, the patient had a stroke and is functioning normally, but has some motor impairment)
- *Not recovered* – the patient's condition has not improved and the symptoms are unchanged (for example, an atrial fibrillation has become chronic)
- *Death*

9.7. Recording adverse events

AEs (including *baseline events*) identified using any of the following methods will be recorded:

AEs spontaneously reported by the patient

AEs observed by the Investigator or medical personnel

AEs elicited based on non-leading questions from the Investigator or medical personnel

Collection of *baseline events* starts after the patient signs the ICF and continues until the first administration of IMP.

TEAE collection starts with administration of the IMP and continues until the last follow-up assessment. Any AE with start date on the day of first IMP administration must be recorded with start time.

At the Follow-up Visit, information on new AEs or SAEs, if any, and stop dates for AEs recorded and on-going during the dosing period must be recorded.

AEs (including *baseline events*) must be recorded on an *Adverse Event Form* in the CRF. The Investigator must provide information on the AE, preferably with a diagnosis or at least with signs and symptoms; start and stop dates, start and stop time; intensity; causal relationship to IMP; action taken, and outcome.

If the AE is serious, this must be indicated on the *Adverse Event Form* in the CRF. Furthermore, the Investigator must fill out the *Serious Adverse Event Report Form* and report the SAE to Diamond Pharma Services as described in Section 9.8.

AEs, including out-of-range clinically significant safety laboratory values, must be recorded individually, except when considered manifestations of the same medical condition or disease state; in such cases, they must be recorded under a single diagnosis.

If the severity/intensity of an AE increases a new *Adverse Event Form* must be completed in the CRF.

Patients with AEs occurring during the study must be treated according to clinical practice at the discretion of the Investigator.

AEs must be followed up until resolution or the follow-up assessment, whichever comes first. At the Follow-up Visit, information on new AEs, if any, and stop dates for previously reported AEs must be recorded.

It is the responsibility of the Investigator to follow up on all SAEs until the patient has recovered, stabilised, or recovered with sequelae and to report to the Sponsor all relevant new information using the same procedures and timelines as those for the initial report. Relevant information includes discharge summaries, autopsy reports, and medical consultation.

SAEs spontaneously reported by a patient to the Investigator within 30 days after the last follow-up assessment must be handled in the same manner as SAEs occurring during the study. These SAEs will be reported to the Sponsor.

9.8. Serious Adverse Events

All SAEs must be reported to the CI, CRO and Sponsor immediately and within 24 hours of awareness, regardless of causal relationship. An SAE form must be filled in by a member of the research team and kept in the TMF.

All SAEs occurring until the end of the trial must be reported by fax and/or email immediately by the Investigator or designated assistant is made aware of the event and by full report as soon as possible thereafter.

All SAEs must be emailed or faxed to Diamond Pharma Services:
Email: PVServices@diamondpharmaservices.com
Fax number: +44 (0)1279 418 964

Where the Investigator requires advice regarding the handling of Serious Adverse Events, the contact in case of emergency is:

Diamond Pharma Services Emergency 24 hour phone number: +44 (0)1279 441 616

Pregnancies occurring during the study must be reported immediately by fax using the SAE Form.

IRL and Diamond Pharma Services will keep the Investigator and DSMB (Section 23) informed of all SAEs reported to them for the product under investigation, from anywhere in the world, for the duration of the trial at a frequency appropriate to the trial.

In addition, any new safety information that would adversely affect the safety of patients or the conduct of the trial will be reported by IRL to the CAs, RECs, DSMB and Investigators. If the trial is to be suspended as a result of a SUSAR, or due to any urgent safety measure taken, the CA and REC will be notified as soon as possible and within three days of the decision.

IRL will submit Safety Reports to the CAs and RECs annually or more frequently if so requested.

9.9. Reporting of SUSARs

Diamond Pharma Services will report SUSARs occurring in the trial to the CA and to the relevant Research Ethics Committees (REC(s)) in line with the applicable regulatory requirements and to the DSMB as outlined in Section 23.

10.DATA MANAGEMENT

Data will be recorded on a CRF by the Investigator (or designee). The database, data entry and electronic checks will be developed using a Clinical Database Management System. Computerised data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency and completeness of the data. An electronic audit trail system will be used to track all data changes in the database.

Data clarification queries will be generated electronically in order to clarify any issues which arise regarding the data entered into the CRF and database.

A 100% quality control check of the data entry will be performed on a randomly selected sample of the CRFs.

Medical history findings and adverse events will be coded using the MedDRA dictionary; medications will be coded using the World Health Organisation Drug dictionary.

10.1.Trial Documentation and Trial Confidentiality

10.1.1. Trial Documentation, CRFs and Document Keeping

The Investigator must generate and maintain adequate records (patient medical records, Case Report Forms, source documents) to enable the conduct of this trial to be fully documented. Each patient enrolled into the trial must have a CRF completed and the CRF must be reviewed and signed off by the Investigator. This applies to those patients who failed to complete the

trial (even during the pre-randomisation period). CRFs are to be completed either at the time of the patient's visit or as soon as possible after the visit so that they always reflect the latest observations on the patients participating in the study. The Investigator must verify that all data entries in the CRFs are accurate and correct. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the investigational staff and are accessible for verification by the clinical monitor. If electronic records are maintained, the method of verification must be discussed with the investigational staff. A source data verification log will be prepared by the CRO. This will describe the proportion of CRF data that will be verified by the monitor against the patients' medical records and source data.

The Sponsor recommends that the author of an entry in the source documents be identifiable. Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded on the CRF are consistent with the original source data.

If data are recorded directly into the CRF, there should be, at a minimum, an entry in the medical record that each of the assessments was performed; who performed it and the date it was done.

The CRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections, and alterations are to be made by the responsible Investigator or an authorised member of the investigational staff.

Data clarification and query resolution will be conducted on an ongoing basis by the monitor and the contract data management company. The Sponsor will have overall responsibility for the data.

The Principal Investigator must be aware of their responsibility to retain patient identification codes in line with regulatory requirements after completion or discontinuation of the trial. If a patient ceases treatment prematurely, then the reason must be noted in the CRF. If a patient ceases treatment because of an adverse event, reasonable efforts must be made to clearly document the outcome.

The Principal Investigator will allow authorised Sponsor personnel, auditors and regulatory authorities direct access to the patients' medical records.

Copies of protocols, CRF page/printouts, originals of test results, reports, drug dispensing logs, correspondence, records of informed consent or other documents pertaining to the conduct of the trial must be kept on file by the Investigator in line with regulatory requirements or for the period of time specified by local law for the preservation of hospital patient documents, whichever is the longer. No trial documents should be destroyed without prior written agreement between Sponsor and the Investigator. Where storage at the centre is limited, the Sponsor may make arrangement for documents to be stored at an independent data archiving facility on behalf of the Principal Investigator. Should the Investigator wish to assign the trial records to another party, or move them to another location, the clinical trial monitor must be consulted.

10.1.2. Confidentiality of Trial Documents and Patient Records

The Investigator must ensure the patients' anonymity is maintained. On CRFs or other documents submitted to [redacted]/the Sponsor/third party contractor, patients must NOT be identified by their names but by an identification code (usually their trial number). The

Investigator will be responsible for maintaining a separate log of patients' codes, names and unique identifiers. This log will be maintained as required by applicable regulatory requirements. Documents not for submission to [redacted]/the Sponsor/third party contractor, e.g. patients' written consent forms, must be maintained by the Investigator in strict confidence.

11. STATISTICAL METHODS

Statistical methods are outlined, however a Statistical Analysis Plan (SAP) will be produced between finalisation of the CRF and database lock. This will include detailed descriptions of all statistical methodology utilised, planned analyses (with any 'sensitivity' analyses), together with master table and listing shells and outline figures for reporting.

11.1.General Considerations

A single analysis at the conclusion of the investigation is planned and there will be no interim analyses (other than data safety reviews) that may impact on the experiment wide type 1 error rate.

All data will be described and analysed according to Treatment group (IRL790, Placebo), Day of assessment (Screening, Day 1 (Baseline), 7, 14, 21, 28, End of Treatment (Day 28 or last observation in the event of withdrawal), plus Follow-up (if appropriate)). However as this is a maximum tolerated dose (MTD) investigation where appropriate summaries according to dose group may also be described.

All interval (quantitative continuous) data will be presented as means, standard deviation, minimum, maximum, median, lower quartile and upper quartile as well as number of observations for both Actual values and Change from baseline data. All Categorical (qualitative binary, ordinal) data will be presented in contingency tables as frequencies and percentages with the denominator the total number of patients available from the relevant analysis set.

Statistical methods applied will be appropriate to the nature and distribution of the data. A (two-sided[10]) significance level of 5% (<0.05) will be implemented throughout and in view to the stage of development of the drug no statistical adjustment for 'multiplicity' of analysis testing performed is planned. Graphical displays will be used to support the findings wherever possible. All will use two-sided 95% confidence intervals to allow estimation of the minimum likely effect size, which will be useful when moving the development programme forward to Phase III.

The null hypothesis assumed throughout is that there is no difference between the Active treatment and the Control for any comparison performed (IRL790 vs Placebo). The alternative hypothesis is that there is in fact a difference and this may be in either direction in favour of active or the control.

All data derivations, manipulations and reporting procedures will use SAS v9.4 in a Windows 10 operating system environment. All data summaries will be supported by data listings with individual patient details.

[10] A two tailed type 1 error rate allows satisfaction of a routinely accepted bilateral alternative hypothesis. Strong evidence would be required to justify that the treatment could not adversely affect outcome.

11.2.Sample Size/Power Calculation

Seventy Four (74) evaluable patients (37 per group) are sufficient to demonstrate an effect size of 0.67 between the active treatment and control (IRL790 vs Placebo) for the UDysRS primary endpoint with 80% power and type 1 error rate 0.05 (two tailed).

As the drop-out rate is unknown at the outset recruitment will continue across the 15 sites until the total evaluable number of patients required is obtained.

The effect size used is derived from the mean difference between the active and control groups (at the end of the treatment period) standardised according to the pooled 'between' group standard deviation. Estimates for these were obtained from published literature (Table 1).

Table 1: Sources For Effect Size

Reference	Mean Difference (A-P) (Diff) (n per group) After X Weeks Treatment	Pooled Standard Deviation	Effect Size[11]
Goetz (2013)[15]	31-23 (14) (30 per group) 4wks Actual values	~12	0.58
Pahwa (2017)[16]	16 - 8 (8) (60 per group) 12wks Change from baseline	~12.3 (SE:1.6)	0.65[12]
Pahwa (2015)[17]	16.7 - 6.7 (10) (20 per group) 8wks Change from baseline	~13 (SE: 3)	0.77[13]

11.3.Analysis Sets

Three analysis sets (or patient populations) will be evaluated: The Full Analysis Set (FAS), Per Protocol Set (PPS) and the Safety Set (SS).

The Full Analysis Set (FAS) will consist of all randomised and treated patients who receive one or more doses and who provide post baseline data whether or not they fully comply with the requirements of the protocol. However, given the stage of development patients will be analysed according to the treatment they actually receive in the event of randomisation errors and not according to the scheduled treatment assignment.

The Per Protocol Set (PPS) will consist of patients from the FAS but exclude those with major protocol violations. A list of all relevant situations which constitute major protocol violations and constitute reasons for exclusion from the PPS will be described in the SAP.

Patients who are to be included in and excluded from the PPS will be identified and listed following a Blind Data Review performed prior to the conclusion of the clinical investigation, database lock and unblinding.

[11] NB: Smaller effect size = larger sample size required to detect difference
[12] n per group approx 37 with 80% power
[13] n per group approx 28 with 80% power

Statistical analyses for the primary and secondary endpoints will be performed using both the FAS and PPS. Although the FAS is considered of primary importance, the PPS will enable evaluation of the sensitivity and robustness of the estimates of the magnitude of the treatment effect

All other evaluations will involve the FAS population (i.e.: Demographic and baseline characteristics, Exploratory investigations, Pharmacokinetics).

The Safety Set (SS) will consist of all patients who receive at least one dose of study drug. All safety and tolerability evaluations will be based on this analysis set. Again patients who receive the wrong treatment according to the randomisation schedule will be analysed according to the treatment actually received.

The SS population will be applied to all safety and tolerability assessments and analyses.

11.4.Study Population

All basic information regarding the sample of patients recruited to represent the PD population with dyskinesia will be summarised. This will include all assessments performed prior to the start of treatment (Screening) including Demographics (Gender, Age, Ethnicity and Race), Medical history, Diagnosis of PD, Duration of PD, Height, Weight, BMI, MMSE, Hoehn and Yahn Scale score and Prior medications. Each will be described overall and according to treatment group.

11.5.Baseline Treatment Dose Group Comparability

No formal statistical comparisons of the treatment groups at Screening or Baseline (Visit 1, Day 1) will be performed as this serves only to assess the randomisation process.

11.6.Treatment Compliance

At the conclusion of treatment period an assessment of compliance with the required dosing schedule will be performed and summarised by treatment group (((total tablets taken - total prescribed)/total prescribed)*100%).

11.7.Efficacy Endpoints

The primary efficacy variable is the UDysRS total score.

This rating scale has two primary sections: Historical [Part 1 (On-Dyskinesia) and Part 2 (Off-Dystonia)], Objective [Part 3 (Impairment) and Part 4 (Disability)]. The Historical part has 15 items and the Objective part 11 items with each item having 0-4 ratings, where 0 = normal, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe. The subtotals for both the Historical and Objective parts are summed to give an overall score.

The secondary efficacy variables involve a subset of the UDysRS, the MDS-UPDRS and the 24-hour patient diaries (Table 2).

The MDS-UPDRS has four parts with; (Part 1) nonmotor experiences of daily living (13 items), (Part 2) motor experiences of daily living (13 items), (Part 3) motor examination (18 items), and (Part 4) motor complications (six items). Each subscale has 0-4 ratings, where 0 = normal, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe.

Therefore in all efficacy evaluations the higher scores indicate worse symptoms.

Table 2: Secondary Endpoints:

Scale	Component	Attribute
UDysRS	Total Objective Score (III, IV)	Total score
MDS-UPDRS	Part III (Motor)	Part Score
	Part IV Questions 4.1 and 4.2	Sum score
24-hour patient diaries	OFF time	Total daily hours

The exploratory efficacy variables comprise a number of additional subsections of the MDS-UPDRS and 24-hour patient diaries (Table 3).

Table 3: Exploratory Endpoints:

Scale	Component	Attribute
MDS-UPDRS	Part I	Total score
	Part II	Total score
	Part IV	Total score
	Question 1.2 (Hallucinations and Psychosis)	Score
	Question 1.6 (Features of dopamine dysregulation syndrome)	Score
24-hour patient diaries	ON time	Total daily hours
	ON time with troublesome dyskinesia	Total daily hours

All the endpoints are measured at Screening and at Visit 4 (or earlier in the event of withdrawal) or during the intervening period for the 24-hour patient diaries.

The Change from baseline (Screening) at Day 28 (Visit 4, Day 28) and End of Treatment (Day 28 (Visit 4, Day 28 or earlier in the event of withdrawal)) for each patient will be derived for each endpoint and each endpoint summarised descriptively (according to Treatment group and Day of assessment (Screening, Day 28, End of Treatment). The End of Treatment last assessment available will be analysed as Interval data.

11.8.Pharmacokinetic Endpoints

PK variables measured in plasma include: IRL790 parent drug and two of its metabolites (IRL902 (n-dealkylated) and IRL872 (acetylated)). In addition, biomarker P-Prolactin is also measured.

Samples obtained pre-dose and 2h post dose (C_{max}) on Day 1 and Day 28 will be summarised as interval data (using number (n), arithmetic mean, standard deviation (SD), minimum and maximum value, geometric mean and coefficient of variation (CV%)). If appropriate these will be presented overall for the IRL790 treated group but also according to IRL dose.

In order to potentially assess the pharmacokinetic relationship between the treatment doses (7.5mg b.i.d. upwards) parent drug and metabolite assays obtained pre-dose and 2h post dose (C_{max}) on Day 1 and Day 28 each will be analysed separately.

This analysis will involve application of a polynomial regression model to fit dose or log(dose) vs drug plasma concentration with subsequent evaluation of the significance of the curve fit. However as this is a maximum tolerated dose (MTD) investigation the number of patients in each group is not known in advance. The analysis is therefore dependent on the resulting group sizes.

11.9.Efficacy Analyses

All Primary, Secondary and Exploratory endpoints (except CGI) can be considered quantitative continuous data (Interval in type). As such the Change from baseline at and at End of Treatment (Visit 4, Day 28 or earlier in the event of withdrawal) will be derived for each patient and analysed using an Analysis Of Covariance (ANCOVA) model to compare the two treatment groups (IRL790 vs Placebo).

The ANCOVA analysis will allow estimation of the size of treatment effects as well as magnitude of differences between the active treatment and control (IRL790 - Placebo). The dependent variable will be the Change from baseline value and Treatment group the explanatory (independent) variable and fixed factor. A baseline covariate term will be included to ensure minimum variance unbiased estimation.

In view of the small sample size and relatively large number of sites there are insufficient degrees of freedom to include Site as a factor in the model.

Model assumptions will be investigated and a suitable data transformation or non-parametric equivalent model substituted if appropriate.

Actual p-values and 95% confidence intervals for least square mean estimates of the treatment effects and differences from placebo will be presented for these models.

The CGI exploratory endpoint is the only other type of data collected. This qualitative and ordinal categorical variable will be analysed using the Van Elteren non parametric hypothesis test (equivalent to Cochran Mantel-Haenszel test with modified ridits (CMH-row mean scores differ). Statistical significance (p-values) for differences between the two Treatment groups (IRL790, Placebo) will be reported together with the actual response proportions.

11.10. Safety Analyses

Safety evaluations include: Adverse events and Concomitant medications reporting, Complete physical examination, Vital signs, ECG (12 lead) at rest and Clinical safety laboratory tests (clinical chemistry, haematology and coagulation).

Adverse events and concomitant medications are recorded throughout the investigational period with the rest performed at Screening, Day 28 (Visit 4 or at Withdrawal) and Follow-up (5-8 days after Visit 4).

All safety laboratory samples are assayed at the local hospital.

All safety evaluations will be presented as Interval or Categorical data summaries (as appropriate) according to Treatment group and Day of assessment (if appropriate) for the Safety population. No formal statistical analyses will be performed.

11.10.1. Adverse Events

All AEs will be summarised according to TEAE or Baseline Event following classification of the verbatim terms according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The number and percentage of patients for all classified events will be presented according to System organ class (SOC) and Preferred term (PT) by treatment group and overall.

Separate summaries will be presented for all AEs by event frequency of occurrence and also for all AEs according to Seriousness, Severity and Relationship.

If appropriate separate summaries according to IRL790 maximum tolerated dose received may be used to support the findings.

11.10.2. Concomitant Medications

Concomitant medication will be summarised by Anatomical Therapeutic Chemical (ATC) code levels 2 and 4 using the World Health Organisation Drug dictionary (WHODD) with the number and percentage of patients by treatment group and overall.

11.10.3. Physical Examinations

Physical examination results will be categorically summarised as the number and percentage of patients according to body type, treatment group and assessment day.

In addition, Weight additionally measured at Follow up following Screening will be summarised with descriptive statistics for Actual values and Change from Screening by treatment group.

11.10.4. Vital Signs

For blood pressure and pulse rate, descriptive statistics of Actual values and Change from Screening will be used to summarise by treatment group and assessment day. Categorically classified (Normal/Abnormal) results will also be summarised.

11.10.5. ECG (12-Lead) At Rest

ECG variables will be summarised according to Actual values and Change from Screening using descriptive statistics and will be presented by treatment group and assessment visit. Categorically classified (Normal/Abnormal) results will also be summarised.

11.10.6. Clinical Laboratory Tests

All haematology, clinical chemistry and coagulation laboratory tests will be summarised using descriptive statistics for Actual values and Change from Screening and presented by treatment group and assessment day for each Hospital site separately (due to assays performed locally).

Additionally the local laboratory normal ranges will be used to classify the results as: High, Normal or Low and categorical summaries presented overall according to treatment group and assessment visit. Pooling across all sites is possible here due to the categorical classification.

12. ETHICS COMMITTEE APPROVAL

The study proposal will be submitted to the Ethics Committee in accordance with the national requirements.

The REC shall give its opinion in writing before the clinical trial commences. The Investigator should provide written reports to the REC annually or more frequently if requested on any changes significantly affecting the conduct of the trial and / or increasing risk to the patients.

13. REGULATORY REQUIREMENTS

The study will be authorised by Medicines and Healthcare products Regulatory Agency (MHRA).

Enrolment of patients will not commence until approval has been received from both the Ethics Committee(s) and Competent Authority.

The study will be conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) and all other national requirements.

14. INFORMED CONSENT

It is the responsibility of the Investigator or an authorised associate to give each potential study patient adequate verbal and written information before any study specific assessments are performed.

The information will include the objectives and the procedures of the study as well as any risks or inconvenience involved. It will be emphasised that participation in the study is voluntary and that the patient may withdraw from participation at any time and for any reason, without any prejudice. All patients will be given the opportunity to ask questions about the study and will be given sufficient time to consider participation before signing the ICF.

Before performing any study-related procedures the ICF must be signed and personally dated by the patient and by the Investigator. A copy of the Patient Information including the signed ICF will be provided to the patient.

Documentation of the discussion and the date of informed consent must be recorded in the source documentation and in the CRF. The Patient Information sheet and the signed ICF should be filed by the Investigator for possible future audits and/or inspections.

The final approved version of the Patient Information and ICF must not be changed without approval from the Sponsor and the applicable EC.

15. DIRECT ACCESS TO SOURCE DOCUMENTATION / DATA

The Investigator must permit trial-related monitoring, audits, Ethics Committee review or regulatory inspection, providing direct access to source data/documents.

16. STUDY MONITORING AND MANAGEMENT

16.1.Training of study site personnel

Before enrolment of the first study patient a Sponsor representative or delegate will perform a Study Initiation Visit at the study site. The requirements of the Clinical Study Protocol and related documents will be reviewed and discussed and the investigational staff will be trained in any study specific procedures and system(s) utilised.

It is the responsibility of the Investigator to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study and have a detailed knowledge of and training in the procedures that are to be executed by them. Any new information of relevance to the performance of this study must be forwarded to the staff involved in a timely manner.

The Investigator will keep a list of all personnel involved in the study together with their function and study related duties delegated. A Curriculum Vitae will be available for all staff delegated study-specific duties.

16.2.Clinical Monitoring

The study site will be periodically monitored at times agreed on by the Investigator and the Monitor. At the time of each monitoring visit, the function of the Monitor is to:

- provide information and support to the investigational team.
- confirm that facilities and resources remain acceptable.
- confirm that the investigational team is adhering to the Clinical Study Protocol, applicable SOPs, guidelines, manuals and regulatory requirements.
- verify that data are being accurately and timely recorded in the CRFs and that IMP accountability checks are being performed.
- verify that data in the CRF are consistent with the clinical records (SDV).
- verify that the correct informed consent procedure has been adhered to for participating patients.

- ensure that withdrawal of informed consent to the use of the patient's biological samples will be reported and biological samples are identified and disposed/destroyed accordingly, and that this action is documented and reported to the patient.
- verify that AEs are recorded and reported in a timely manner and according to the Clinical Study Protocol.

When the study has been completed, all queries have been resolved and the database has been locked, the Monitor will perform a close-out visit at the study site.

16.3.Source Data

The primary source documents for this study will be the patient's medical records and all rating scale CRFs and worksheets used to directly record assessment scores for MMSE, MDS-UPDRS, UDysRS and CGI-C throughout the study. If separate research records are maintained by the investigator(s) both the medical record and the research records should be monitored/audited for the purpose of the study.

A separate source data agreement will be generated at the study site before start of enrolment, specifying the location of the source of derived information appearing in the CRF. This document must be signed by the Principal Investigator and the Monitor to confirm agreement before start of recruitment.

The Investigator should guarantee access to source documents to the Monitor, Competent Authorities and the ECs, as required.

16.4.Study agreements

The Principal Investigator must comply with all the terms, conditions, and obligations of the Clinical Study Agreement (CSA) for this study.

Agreements between Sponsor and the study sites must be in place before any study-related procedures can take place, or patients be enrolled.

16.5.Study time table and end of study

The end of the clinical part of the study is defined as the last visit of the last patient participating in the study.

The study is expected to start in Quarter 4, 2017 and to be completed by Quarter 2, 2018.

17. QUALITY ASSURANCE

Authorised representatives of Sponsor, Competent Authority or EC may perform audits or inspections at the study site, including Source Data Verification (SDV). The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted and data were recorded, analysed, and accurately reported according to the Clinical Study Protocol, ICH-GCP guidelines and any applicable regulatory requirements. The Investigator will contact the Sponsor immediately if contacted by a Competent Authority about an inspection at the study site.

18. INSURANCE

Appropriate insurance cover has been secured in favour of patients participating in clinical trials. The cover is provided to the patient on terms and conditions of the clinical trial insurance. Insurance cover exists for health damages as a result of measures carried out in connection with the clinical trial.

19. CONFIDENTIALITY

All study documents are provided by the Sponsor in confidence to the Investigator and appointed staff. No study material may be disclosed to any party not directly involved in the study without written permission from the Sponsor.

The Investigator must assure that patient's anonymity will be provided. The Investigator will keep a separate list with at least the initials, the patient's study number, names, addresses and telephone numbers. The Investigator will maintain this for as long as requested by the Sponsor.

Details of access to the patients' data, conforming to the requirements of EU Directive 95/46/EC, will be fully described within the patient information sheet. The consequence of the patients' withdrawal of consent with regards to the use of data will also be described.

20. PREMATURE TERMINATION OF THE STUDY

The Sponsor reserves the right to discontinue the study at any time, but intends only to exercise this right for valid scientific or administrative reasons.

After such a decision, the Investigator must inform all participating patients and perform relevant assessments, preferably according to the scheme for the final assessments. All delivered and unused IMP and other study materials must be returned and all CRFs completed as far as possible.

21. RECORD RETENTION

After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file.

Essential documents must be retained for at least two years after the final marketing approval in an ICH region or until two years have elapsed since the formal interruption of the clinical development of the product under study.

It is the responsibility of the Sponsor to inform the Investigator of when these documents can be destroyed. The Investigator must contact the Sponsor before destroying any trial-related documentation. In addition, all patients' medical records and other source documentation will be kept for the maximum time permitted by the institution.

22. PUBLICATION OF RESULTS

22.1.Clinical Study Report

A summary report must be submitted to the Competent Authority and EC within 12 months of completion of the study.

A Clinical Study Report, in compliance with ICH E3; *Structure and content of Clinical Study Reports*, describing the conduct of the study, the statistical analysis performed and the results obtained, will be prepared. The report will be reviewed and approved by, as a minimum, the Chief Investigator, Statistician and the Sponsor.

22.2.Annual safety report

If the study duration exceeds one year, the Sponsor must submit an annual safety report to the Competent Authority and to the REC. The report shall summarise all SAEs and contain an update of the risk-benefit evaluation if there has been any change since the approval of the clinical study.

22.3.Confidentiality and ownership of study data

Any confidential information relating to the IMP or the study, including any data and results from the study will be the exclusive property of the Sponsor. The Investigator and any other persons involved in the study will protect the confidentiality of this proprietary information belonging to the Sponsor.

22.4.Publication

The Sponsor is entitled to publish and/or present any results at scientific meetings, and to submit clinical trial data to national and international Regulatory Authorities. The Sponsor reserves the right to use such data for commercial purposes.

The results from this study will be submitted for publication only at the discretion of the Sponsor.

23. DATA SAFETY MONITORING BOARD (DSMB)

A committee will be set-up to monitor safety throughout the trial period. The committee will comprise a group of independent experts and will include a chairperson, a neurologist experienced in Parkinson's disease and a statistician all of whom will be independent of the Sponsor and will not be involved in the conduct of the trial.

A charter describing how the DSMB works and how it communicates with other study participants (e.g. steering committee) will be prepared.

The DSMB will review unblinded study information which will include:

- List of any protocol violations
- Numbers of patient withdrawals/reason for withdrawal
- Adverse/serious adverse events
- Laboratory data

Following review of the safety data, the committee will prepare written reports which will be forwarded to the Sponsor advising of any recommendations regarding modifications, continuation or termination of the study.

Where changes in the study conduct are recommended to the Sponsor, sufficient (blinded) information will be provided to allow the Sponsor to decide whether and how to implement these recommendations.

DSMB Meetings:

The DSMB will convene after 20 and 40 patients have completed the Follow-Up visit (with adequate safety assessment data) for a formal safety review.

The assessment will provide three possible outcomes:

1. Proceed as planned
2. Proceed after substantial modification of the protocol
3. Discontinue the study

Recruitment will continue throughout the 20 and 40 patient DSMB

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25. APPENDICES

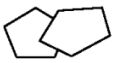
25.1. Appendix 1 Mini-Mental State Examination (MMSE)

Localised Versions of the Rating scales will be used

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

Instructions: Ask the questions in the order listed. Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day of the week? Month?"
5		"Where are we now: State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. Number of trials:_____
5		"I would like you to count backward from 100 by sevens." (93, 86, 79,72, 65, …) Stop after five answers. Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?
2		Show the patient two simple objects, such as a wristwatch and a pencil, and the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything. (This sentence must contain a noun or a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

(Adapted from Rovner & Folstein, 1987)

Page **1** of **4**

Instructions for administration and scoring of the MMSE

Orientation (10 points):
• Ask for the date. Then specifically ask for parts omitted (e.g., "Can you also tell me what season it is?"). One point for each correct answer.
• Ask in turn, "Can you tell me the name of this hospital (town, county, etc.)?" One point for each correct answer.

Registration (3 points):
• Say the names of three unrelated objects clearly and slowly, allowing approximately one second for each. After you have said all three, ask the patient to repeat them. The number of objects the patient names correctly upon the first repetition determines the score (0-3). If the patient does not repeat all three objects the first time, continue saying the names until the patient is able to repeat all three items, up to six trials. Record the number of trials it takes for the patient to learn the words. If the patient does not eventually learn all three, recall cannot be meaningfully tested.
• After completing this task, tell the patient, "Try to remember the words, as I will ask for them in a little while."

Attention and Calculation (5 points):
• Ask the patient to begin with 100 and count backward by sevens. Stop after five subtractions (93, 86, 79, 72, 65). Score the total number of correct answers.
• If the patient cannot or will not perform the subtraction task, ask the patient to spell the word "world" backwards. The score is the number of letters in correct order (e.g., dlrow=5, dlorw=3).

Recall (3 points):
• Ask the patient if he or she can recall the three words you previously asked him or her to remember. Score the total number of correct answers (0-3).

Language and Praxis (9 points):
• Naming: Show the patient a wrist watch and ask the patient what it is. Repeat with a pencil. Score one point for each correct naming (0-2).
• Repetition: Ask the patient to repeat the sentence after you ("No ifs, ands, or buts."). Allow only one trial. Score 0 or 1.

• 3-Stage Command: Give the patient a piece of blank paper and say, "Take this paper in your right hand, fold it in half, and put it on the floor." Score one point for each part of the command correctly executed.
• Reading: On a blank piece of paper print the sentence, "Close your eyes," in letters large enough for the patient to see clearly. Ask the patient to read the sentence and do what it says. Score one point only if the patient actually closes his or her eyes. This is not a test of memory, so you may prompt the patient to "do what it says" after the patient reads the sentence.
• Writing: Give the patient a blank piece of paper and ask him or her to write a sentence for you. Do not dictate a sentence; it should be written spontaneously. The sentence must contain a subject and a verb and make sense. Correct grammar and punctuation are not necessary.
• Copying: Show the patient the picture of two intersecting pentagons and ask the patient to copy the figure exactly as it is. All ten angles must be present and two must intersect to score one point. Ignore tremor and rotation.

(Folstein, Folstein & McHugh, 1975)

Interpretation of the MMSE

Method	Score	Interpretation
Single Cutoff	<24	Abnormal
Range	<21 >25	Increased odds of dementia Decreased odds of dementia
Education	21 <23 <24	Abnormal for 8th grade education Abnormal for high school education Abnormal for college education
Severity	24-30 18-23 0-17	No cognitive impairment Mild cognitive impairment Severe cognitive impairment

Sources:

• Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the mini-mental state examination by age and educational level. *JAMA*. 1993;269(18):2386-2391.
• Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-198.
• Rovner BW, Folstein MF. Mini-mental state exam in clinical practice. *Hosp Pract*. 1987;22(1A):99, 103, 106, 110.
• Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. *J Am Geriatr Soc*. 1992;40(9):922-935.

25.2.Appendix 2 Unified Parkinson's Disease Rating Scale (MDS-UPDRS)

Localised Versions of the Rating scales will be used

MDS-UPDRS

The Movement Disorder Society (MDS)-sponsored new version of the UDPRS 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 UDPRS 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 concerning a number of behaviors that are assessed by the investigator with all pertinent information from patients and caregivers and IB that is completed by the patient with or without the aid of the caregiver, but independently of the investigator. It 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 Part1A, Part1B and Part2 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

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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:

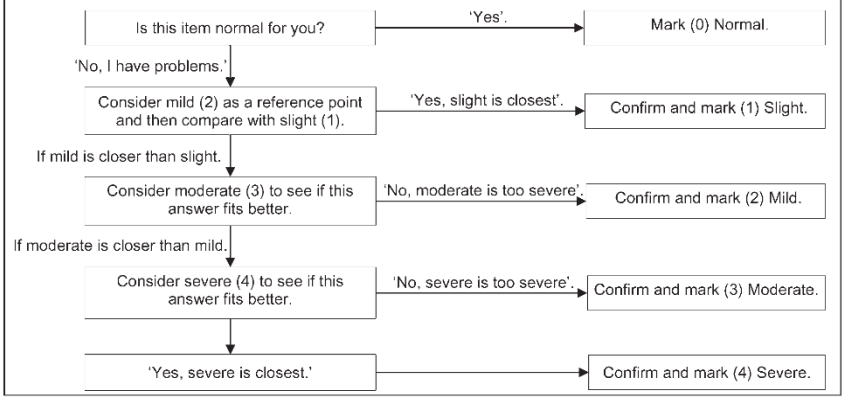
1. Mark at the top of the form the primary data source as patient, caregiver, or patient and caregiver in equal proportion.
2. The response to each item should refer to a period encompassing the prior week including the day on which the information is collected.
3. All items must have an integer rating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



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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.	

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	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.	☐

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	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.	☐

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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].

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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

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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.	☐

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	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.	☐

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	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.	☐

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	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.	☐

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	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.	☐

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	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.	☐

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	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.	☐

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	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.	☐

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	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.	

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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: _____

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	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.	☐

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	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

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	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

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	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

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	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.	☐

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	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.	☐

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	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

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	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

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	SCORE
3.18 CONSTANCY OF REST TREMOR 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.	☐

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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.	1. Total Hours Awake: _____
3: Moderate:	51 - 75% of waking day.	2. Total Hours with Dyskinesia:
4: Severe:	> 75% of waking day.	3. % Dyskinesia = ((2/1)*100): _____

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	SCORE
4.2 FUNCTIONAL IMPACT OF DYSKINESIAS 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): _____	☐

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	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%).	☐

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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.

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_____ 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 presen	☐ 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	

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25.3.Appendix 3 Unified Dyskinesia Rating Scale (UDysRS)

Localised Versions of the Rating scales will be used

Unified Dyskinesia Rating Scale (UDysRS)

Overview: The Unified Dyskinesia Rating Scale (UDysRS) is developed to evaluate involuntary movements often associated with treated Parkinson's disease. There are two primary sections:

- Historical [Part 1 (On-Dyskinesia) and Part 2 (Off-Dystonia)]
- Objective [Part 3 (Impairment) and Part 4 (Disability)]

On-Dyskinesia refers to the **choreic and dystonic movements** described to the patient as **"jerking or twisting movements that occur when your medicine is working."**

Off-Dystonia should be described to the patient as "**spasms or cramps that can be painful and occur when your Parkinson's disease medications are not taken or are not working**.

Throughout the assessment, the focus is on these two forms of movements and a continual emphasis must be placed on excluding from the evaluation the impact of parkinsonism itself and tremor from the ratings.

Part I: On-Dyskinesia Ratings: Instructions for the rater

This portion of the scale assesses the presence and impact of on-dyskinesia on patients' experiences of daily living. There are 11 questions. Part 1A is administered by the rater and is one question that focuses on time spent with on-dyskinesia. Off-dystonia is NOT considered. Part 1B is a component of the Patient Questionnaire that covers ten questions on the impact of on-dyskinesia on experiences of daily living. Part 2 will focus on off-dystonia and will have a similar structure: 2A section for the rater and three questions (2B) formatted as a questionnaire for the patient/caregiver

Part 1A - Instructions for the Rater
In administering Part IA, the examiner should comply with the following guidelines:

1. Mark on 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., amputees), the item is marked **UR** for Unable to Rate.

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

5. For the question that you will administer, there is 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 rater. 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. The first section focuses on the choreic and dystonic forms of on-dyskinesia and does not assess OFF-DYSTONIA (see later). Additionally, the patient must be reminded throughout the assessment that the focus is NOT on parkinsonism itself nor on tremor.

7. If questions 2-11 (Part 1B) have any answers greater than zero, make sure that the item "TIME SPENT WITH ON DYSKINESIA" (Question 1) reflects that dyskinesia occurred over the past week. If questions 13-15 (Part 2B) have any answers greater than zero, make sure that the item "TIME SPENT WITH OFF DYSTONIA" (Question 12) reflects that dystonia occurred over the past week.

Part 1A: On-Dyskinesia

Read this statement to the patient:

I am going to ask you questions about on-dyskinesia, which is a medical term to describe jerking or twisting movements that occur when your medicine is working to control your Parkinsonism. My questions and the questionnaire that you will answer over the next several minutes do not concern tremor, which is a regular back and forth shaking or any part of the slowness or stiffness of Parkinson's disease itself. The topic is the jerking or twisting movements called on-dyskinesia that can be associated with medication treatment of Parkinson's disease. Do not consider spasms occur when your medications are not working or when you do not take your medication for Parkinson's disease. I will ask about those later. Concentrate only on **jerking or twisting movements that occur when your medicine is working to control your Parkinson's disease.**

Primary source of information:

__Patient __Caregiver __Patient and Caregiver in Equal Proportion

Part 1.A . ON-DYSKINESIA [exclusive of OFF-state dystonia]—rater to complete

SCORE

_____

1. TIME SPENT WITH ON-DYSKINESIA

Instructions to examiner: Determine the hours in the usual waking day when the patient is ON, and then the hours of dyskinesia. Calculate the percentage. If the patient has dyskinesia 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 are your medications working to control your Parkinson's disease (hours on ____)? During the hours that your medications are working, do you have jerking or twisting movements? Do not count the times when you have tremor, which is a regular back and forth shaking or times when you have painful cramps or spasms when you have not taken medication or when the medications for Parkinson's disease are not working. I will ask about those later. **Concentrate only on these types of jerking or twisting movements that occur when your Parkinson's medicine is working.**. Add up all the time during the waking day when your medications are working and you have these jerking or twisting movements. How many hours ____ (use this number for your calculation).

0:	Normal:	No dyskinesia
1:	Slight:	≤ 25% of on-time
2:	Mild:	26-50% of on-time
3:	Moderate:	51-75% of on-time
4:	Severe:	> 75% of on-time

1. Total Hours On:	_____
2. Total Hours of on-Dyskinesia	_____
% On-Dyskinesia = ((2/1)*100)	_____

Part 1 B: Patient Dyskinesia Questionnaire:

This questionnaire will ask you about the effect of movements called "on-dyskinesias" on your usual activities. **On-dyskinesias are jerking or twisting movements that occur in patients with Parkinson's disease when their medicines are working.**

Please answer question about how dyskinesia affect your activities.

Do not answer these questions based on how other problem affect your activities.

- Do not base your answers on tremor, which is a regular back and forth shaking and part of the Parkinson's disease itself.
- Do not base your answers on slowness or stiffness that is part of Parkinson's disease itself
- Do not base your answers on spasms or cramps that can be painful and occur when your medicines are not working. You will answer questions about this problem later.
- **Concentrate only on jerking or twisting movements when your Parkinson's medicine is working.**

There are 10 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 the average or usual impact of on-dyskinesia over the past week including today. Only one answer is allowed for each question, so please mark the answer that best describes how on-dyskinesia, if present, affects these activities most of the time.

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

2. SPEECH: Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on-dyskinesias usually cause problems with your speech? Consider only effects of dyskinesias, not problems caused by Parkinson's disease. **SCORE**

0: Normal: Not at all, no problems. ___
1: Slight: Dyskinesias were present, but they did not interfere with my speech.
2: Mild: Dyskinesias caused a few problems with my speech and people asked me to repeat myself occasionally.
3: Moderate: Dyskinesias caused enough problems that I tried to avoid talking when I had on-dyskinesias.
4: Severe: When I had dyskinesias, most or all of my speech could not be understood.

3.CHEWING AND SWALLOWING: Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on-dyskinesias usually cause problems swallowing pills or eating meals? Did you need your pills cut or crushed or your meals to be made soft, chopped or blended to avoid choking? Consider only effects of dyskinesias, not problems caused by Parkinson's disease. **SCORE**

0: Normal: Not at all, no problems. ___
1: Slight: Dyskinesias were present, but they did not interfere with my chewing or swallowing.
2: Mild: Dyskinesias caused a few problems with chewing and swallowing and it took me longer to chew or swallow because of on-dyskinesias.
3: Moderate. Dyskinesias caused enough problems that I tried to avoid chewing and swallowing when I had on-dyskinesias.
4: Severe: When I had dyskinesias, I was unable to chew or swallow at all.

4. EATING TASKS: Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on-dyskinesias usually cause troubles handling your food and using eating utensils? For example, did you have trouble handling finger foods or using forks, knifes, spoons, chopsticks? Consider only effects of dyskinesias, not problems caused by Parkinson's disease. **SCORE**

0: Normal: Not at all, no problems. ___
1: Slight: Dyskinesias were present, but they did not interfere with my eating .
2: Mild: Dyskinesias caused a few problems with eating and it took me longer to eat because of on-dyskinesias.
3: Moderate: Dyskinesias caused enough problems that I tried to avoid eating when I had on-dyskinesias.
4: Severe: When I had dyskinesias, I needed help for most or all eating tasks.

5. DRESSING: Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on-dyskinesias usually cause problems with your dressing? For example, did you need help with buttoning, using zippers, putting on or taking off your clothes or jewelry? Consider only effects of dyskinesias, not problems caused by Parkinson's disease. **SCORE**

0: Normal: Not at all, no problems. ___
1: Slight: Dyskinesias were present but they did not interfere with dressing tasks.
2: Mild: Dyskinesias caused a few problems with dressing and it took me longer to get dressed because of on-dyskinesias.
3: Moderate: Dyskinesias caused enough problems that I tried to avoid getting dressed when I had on-dyskinesias.
4: Severe: When I had dyskinesias, I needed help for most or all dressing tasks.

6. HYGIENE: Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on-dyskinesias usually cause problems with your personal hygiene? For example, did you need help with washing, bathing, shaving, brushing teeth, or combing your hair? Consider only effects of dyskinesias, not problems caused by Parkinson's disease. **SCORE**

0: Normal: Not at all, no problems. ___
1: Slight: Dyskinesias were present but they did not interfere with hygiene tasks.
2: Mild: Dyskinesias caused a few problems with hygiene tasks and it took me longer to do these activities because of on-dyskinesias.
3: Moderate: Dyskinesias caused enough problems that I tried to avoid doing hygiene tasks when I had on-dyskinesias.
4: Severe: When I had dyskinesias, I needed help for most or all of my hygiene tasks.

7. HANDWRITING: Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on-dyskinesias usually cause trouble with your handwriting. Consider only effects of dyskinesias, not problems caused by Parkinson's disease. **SCORE**

0: Normal: Not at all, no problems. ___
1: Slight: Dyskinesias were present, but they did not interfere with my handwriting.
2: Mild: Dyskinesias caused a few problems with writing and it took me longer to write because of on-dyskinesias.
3: Moderate: Dyskinesias caused enough problems that I tried to avoid writing when I had on-dyskinesias.
4: Severe: When I had dyskinesias, most or all words could not be read.

8. DOING HOBBIES AND OTHER ACTIVITIES: Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on-dyskinesias usually cause trouble doing your hobbies or other things that you like to do? Consider only effects of dyskinesias, not problems caused by Parkinson's disease. **SCORE**

0: Normal: Not at all, no problems. ___
1: Slight: Dyskinesias were present but they did not interfere with these activities.
2: Mild: Dyskinesias caused a few problems with these activities and it took me longer to do them because of on-dyskinesias.
3: Moderate: Dyskinesias caused enough problems that I tried to avoid doing hobbies or other activities when I had on-dyskinesias.
4: Severe: When I had dyskinesias, I was unable to do most or all of these activities.

9. WALKING AND BALANCE: Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on-dyskinesias usually cause problems with balance and walking. Consider only effects of dyskinesias, not problems caused by Parkinson's disease. **SCORE**

0: Normal: Not at all, no problems. ___
1: Slight: Dyskinesias were present but they did not interfere with walking or balance.
2: Mild: Dyskinesias caused a few problems with walking. It took me longer to walk because of on-dyskinesias and I occasionally bumped into things.
3: Moderate: Dyskinesias caused enough problems that I usually used a walking aid (cane, walker) to walk safely without falling. However, I did not usually need the support of another person. I tried to avoid walking when I had on-dyskinesias.
4: Severe: When I had dyskinesias, I could not walk safely without falling.

10. PUBLIC AND SOCIAL SETTINGS: Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on-dyskinesias usually cause problems when you were dealing with other people or in public? Consider only effects of dyskinesias, not problems caused by Parkinson's disease. **Score**

0: Normal: Not at all, no problem. ____
1: Slight: Dyskinesias were present but they did not interfere with these activities.
2: Mild: Dyskinesias caused a few problems and I was self-conscious in public but I did not avoid social situations.
3: Moderate: Dyskinesias caused enough problems that I tried to avoid some social situations when I had on-dyskinesias.
4: Severe: When I had dyskinesias, I could not be with people, even friends or family.

11. EXCITING OR EMOTIONAL SETTINGS: Over the past week, when your Parkinson's disease medications were working, did jerking or twisting movements called on-dyskinesias usually cause problems during emotional conversations, exciting movies, or other highly stimulating situations. Consider only effects of dyskinesias, not problems caused by Parkinson's disease.

Score ____

0: Normal: Not at all, no problem.
1: Slight: Dyskinesias were present, but they did not interfere with these activities.
2: Mild: Dyskinesias caused few problems.
3: Moderate: Dyskinesias caused enough problems that I tried to avoid some exciting situations when I had on-dyskinesias.
4: Severe: When I had dyskinesias, I could not stay in exciting situations.

If questions 2-11 (Part 1B) have any answers greater than zero, make sure that the item "TIME SPENT WITH ON DYSKINESIA" (Question 1) reflects that dyskinesia occurred over the past week.

Part 2: Off-Dystonia Ratings:

Overview: This portion of the scale assesses the presence and impact of off-dystonia on patients' experiences of daily living. There are four questions. Part 2A is administered by the rater (one question) and focuses on time spent with off-dystonia. Part 2B is a component of the Patient Questionnaire that covers three questions on the impact of painful off-dystonia on experiences of daily living.

In administering Part 2A, the examiner should comply with the following guidelines:

1. The responses should refer to a period encompassing the prior week including the day on which the information is collected.

2. The response must be an integer rating (no half points, no missing scores). In the event that the question does not apply or cannot be rated (e.g., amputees), the item is marked UR for Unable to Rate.

3. The answers should reflect the usual level of off-dystonia when present and words such as "usually", "generally", "most of the time" can be used with patients.

4. For the single question that you will administer, there is 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 rater. 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.

5. This section focuses on dystonia during the off-period and this covers dystonia in the early morning or nighttime when patients often have not taken medication or during the day at the end of a dose cycle when they are parkinsonian. The patient must be reminded throughout the assessment that the focus is on off-dystonia and not on parkinsonism itself, tremor, or the on-dyskinesia already covered.

Part 2 A: OFF-Dystonia completed by rater.

Read this statement to the patient:

I am going to ask you questions about another type of movement, called **off-dystonia**. I am interested in spasms or cramps that occur when the Parkinson's disease medications are not taken or are not working well. We call that time period OFF. Off-dystonia is sometimes painful and often occurs in the early morning or nighttime, but occasionally at other times as well when your Parkinson's disease medications are not working. The feet and toes can be affected or other body areas My question and the questionnaire that you will answer over the next few minutes do not concern **tremor**, which is a regular back and forth shaking. Also, the questions are not about the slowness or stiffness of Parkinson's disease itself. Finally, they also do not concern the jerking or twisting movements called dyskinesia already covered. For these questions, please concentrate only on **the spasms or cramps that we call OFF-Dystonia**

(completed by rater) **SCORE**

12. TIME SPENT WITH OFF-DYSTONIA _____

Over the past week, on a typical day, think about the number of hours of the day when you are stiff and slow, whether this is before you take morning medications, perhaps late in the evening, or during the day when the good effects of medication have worn out. Within these "OFF" times, how many hours or minutes do you have spasms or cramps that we call OFF-dystonia?

0 = Never

1 = Less than 30 minutes a day

2 = Less than 60 minutes a day.

3 = Less than 2 hours a day.

4 = Greater than 2 hours a day.

Questionnaire for Patient

Part 2 B : Patient Questionnaire:

Instructions:

This questionnaire asks you questions about spasms or cramps that occur when Parkinson's disease medications are not taken or when they are not working well. We call that time OFF. Off-dystonia movements are sometimes painful and often occur in the early morning or nighttime, but occasionally at other times when your Parkinson's disease medications are not working.

Do not answer these questions based on how other problem affect your activities.

- Do not base your answers on tremor, which is a regular back and forth shaking and part of the Parkinson's disease itself.
- Do not base your answers on slowness or stiffness that is part of Parkinson's disease itself.
- Do not base your answers on jerking, twisting movements that you have already rated.
- **Concentrate only on spasms or cramps, called off-dystonia. In general, these movements develop in the early morning, nighttime or when the good effects of medicines have worn off. Sometimes, there is pain along with the spasms.**

There are 3 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 the average or usual impact of off-dystonia over the past week including today. Only one answer is allowed for each question, so please mark the answer that best describes what you can do most of the time.

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

13. EFFECTS OF SPASMS OR CRAMPS CALLED OFF-DYSTONIA SEPARATE FROM PAIN ON ACTIVITIES. During the past week, separate from pain, have spasms or cramps called off-dystonia occurred? **SCORE**

0: Normal:	Not at all.
1: Slight:	Off-dystonia occurred but it did not interfere with my daily activities.
2: Mild:	Off-dystonia caused a few problems and it took me longer to do activities because of off-dystonia.
3: Moderate:	Off-dystonia caused enough problems that I avoided doing these activities when I had off-dystonia.
4: Severe:	When off-dystonia occurred, I could not do many activities.

___

14. EFFECTS OF PAIN FROM OFF-DYSTONIA ON DAILY ACTIVITIES: On average during this past week, if spasms or cramps called off-dystonia occurred, did pain limit your activities? **SCORE**

0: Normal:	Not at all, no pain from off-dystonia.
1: Slight:	I had pain from off-dystonia, but it did not limit my activities
2: Mild:	Pain from off-dystonia caused a few problems and it took me longer to do activities because of pain from off-dystonia.
3: Moderate:	Pain from off-dystonia caused enough problems that I avoided doing these activities when I had pain from off-dystonia.
4: Severe:	Because of pain from dystonia, I could not do many activities.

___

15. DYSTONIA PAIN: On average during the past week, how severe was the pain from the spasms or cramps of off-dystonia? **SCORE**

0: Normal:	Not painful
1: Slight:	Mild ache or discomfort.
2: Mild:	Moderate ache and discomfort.
3: Moderate:	Severe discomfort.
4: Severe:	Excruciating pain.

___

If questions 13-15 (Part 2B) have any answers greater than zero, make sure that the Item "TIME SPENT WITH OFF DYSTONIA" (Question 12) reflects that dystonia occurred over the past week.

Part 3. OBJECTIVE EVALUATION OF DYSKINESIA DYSABILITY
Instructions for the rater: In this section, you will observe the patient or observe a videotape of the patient during four activities of daily living.

- **You will rate IMPAIRMENT by scoring the global intensity of the dyskinesia (giving an overall rating by body part that includes both choreic dyskinesia and dystonia) during each task.**
- **You will rate DISABILITY by scoring the functional impact of dyskinesia on each of the tasks.**
- **You will then account for the different types of dyskinesia you observed and judge the most prominent form of dyskinesia.**
- **The final IMPAIRMENT score for each body part will be HIGHEST score seen in that body part during the four tasks. Use the data sheet to enter the highest score.**
- **The DISABILITY score is entered for each of the four tasks.**
- **During the evaluations, ignore deficits caused by parkinsonism.**

Instructions on conducting the examination or videotape.

Communication: Instruct subject to look at evaluator (or camera) and describe a picture (recommended Cookie Thief Drawing, but others can be used). Evaluate interference with communication as judged by ability to maintain eye contact, cadence and pronunciation of words and distraction of subject and listener caused by movements. Ignore dysarthria caused by parkinsonism.

Drinking from a cup: Instruct the subject to pick up a 4 oz cup filled to within 1 cm of brim with water with the dominant hand and bringing it to lips, drink contents and replace cup on table. Ignore bradykinesia or tremor from parkinsonism.

Dressing: Instruct the subject to put on a lab coat and do up three buttons, undo the buttons and take the coat off. [Allow up to 60 seconds]. Ignore bradykinesia or tremor from parkinsonism.

Ambulation: Instruct the patient to rise from a chair, walk 15 feet, return and sit back down in the chair. Ignore tremor or bradykinesia from parkinsonism.

Rush filming protocol

INTENSITY SCALE: IMPAIRMENT (PART 3)

0=No dyskinesia
1=Questionable or mild dyskinesia
2=Moderate dyskinesia with movements which are not intrusive nor distort voluntary movements
3=Severe dyskinesia which disturbs but does not prohibit posture or voluntary movements
4=Incapacitating dyskinesia which prohibits some postures and voluntary movements

IMPAIRMENT SCORE	Communication	Drinking	Dressing	Ambulation	Highest score
FACE					(16)
NECK					(17)
R ARM/SHOULDER					(18)
L ARM/SHOULDER					(19)
TRUNK					(20)
R LEG/HIP					(21)
L LEG/HIP					(22)

DISABILITY SCALE (PART 4)

Communication

0=No dyskinesia
1=Dyskinesia present but does not impair communication
2=Dyskinesia impairs communication but patient is fully understandable
3=Dyskinesia interferes with communication such that parts of communication cannot be understood but overall content is understandable
4=Dyskinesia interferes with comprehension of overall communication _____(23)

Drinking from a cup

0=No dyskinesia observed
1=Dyskinesia present but it does not affect performance of the task
2=Dyskinesia affect the smooth performance but causes no splashing or spilling
3=Dyskinesia affects performance such that patient spills a few drops of water
4=Dyskinesia affects performance such that patient spills more than a few drops or dyskinesia causes coughing or choaking. _____(24)

Dressing

0=No dyskinesia observed
1=Dyskinesia present but does not interfere with or slow dressing
2=Dyskinesia affects smooth performance of task but the performance is at most minimally slowed
3=Dyskinesia interferes and slows performance but it is completed within 60 seconds
4=Dyskinesia precludes completing the task within 60 seconds _____(25)

Ambulation

0=No dyskinesia observed
1=Mild dyskinesia present but does not alter normal synchrony or cadence
2=Dyskinesia is present which alters the normal cadence of rising, sitting or walking but does not slow overall performance.
3=Dyskinesia is present which disrupts or distorts arising, sitting or walking. Performance is slowed. Patient is able to rise and walk without imminent danger of falling.
4=Dyskinesia prohibits walking safely without assistance _____(26)

Considering all of the activities above:

Patient exhibits: (check all applicable answers) ____On dyskinesia ____Off dystonia _____Transition state (neither clearly On or Off ____No dyskinesia or dystonia
What movements were seen? (check all types) _____chorea _____dystonia _____Other
The predominant dyskinesia was (check one) _____chorea _____dystonia _____Other

Score summary

Historical	Score	Objective	Score
1. Time dyskinesia		16. Face	
2. Speech		17. Neck	
3. Chewing/Swallowing		18. Right Hand/arm/shoulder	
4. Eating tasks		19. Left Hand/arm/shoulder	
5. Dressing		20. Trunk	
6. Hygiene		21. Right foot/leg/hip	
7. Handwriting		22. Left foot/leg/hip	
8. Doing hobbies/activities		23. Communication	
9. Walking/balance		24. Drinking	
10. Public/social		25. Dressing	
11 Exciting situations		26. Ambulation	
12 Time Off dystonia			
13. Dystonia effects on activities (not pain)			
14. Effect of Pain from dystonia			
15. Dystonia pain severity			
Historical sub-score (sum)		Objective sub-score (sum)	
Total UDysRS score (Historical + Objective):			

25.4.Appendix 4 Clinical Global Impression of Change *(*CGI-C)

Localised Versions of the Rating scales will be used

Clinical Global Impression of Change Rating

Clinical Impression of Change from Baseline:

☐ Marked improvement
☐ Moderate improvement
☐ Minimal improvement
☐ No change
☐ Minimal worsening
☐ Moderate worsening
☐ Marked worsening

25.5.Appendix 5 Declaration of Helsinki

Recommendations Guiding Medical Physicians in Biomedical Research Involving Human Volunteers

Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964 amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975 and the 35th World Medical Assembly, Venice, Italy, October 1983 and revised 41st World Medical Assembly Hong Kong, 1989 and by the 48th World Medical Assembly, South Africa, October 1996

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient".

The purpose of biomedical research involving human volunteers must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human volunteers.

In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person volunteered to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human volunteers. They should be kept under review in the future.

It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I Basic Principles

Biomedical research involving human volunteers must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

The design and performance of each experimental procedure involving human volunteers should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the Investigator and the Sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

Biomedical research on human volunteers should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human volunteer must always rest with a medically qualified person and never rest on the volunteer of the research, even though the volunteer has given his or her consent.

Biomedical research involving human volunteers cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the volunteer.

Every biomedical research project involving human volunteers should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the volunteer or to others. Concern for the interest of the volunteer must always prevail over the interests of science and society.

The right of the research volunteer to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the volunteer and to minimise the impact of the study on the volunteer's physical and mental integrity and on the personality of the volunteer.

Physicians should abstain from engaging in research projects involving human volunteers unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports on experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

In any research on human beings, each potential volunteer must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the volunteer's freely-given informed consent, preferably in writing.

When obtaining informed consent for the research project the physician should be particularly cautious if the volunteer is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

In the case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it

impossible to obtain informed consent, or when the volunteer is a minor, permission from the responsible relative replaces that of the volunteer in accordance with national legislation.

Whenever the minor child is in fact able to give consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II Medical Research Combined With Professional Care (CLINICAL RESEARCH)

In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee.

The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient

III Non-Therapeutic Biomedical Research Involving Human Volunteers (NON-CLINICAL BIOMEDICAL RESEARCH)

In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

The volunteer should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

The Investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the volunteer.