CONFIDENTIAL

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE IIB STUDY EVALUATING THE EFFICACY OF MESDOPETAM ON DAILY ON-TIME WITHOUT TROUBLESOME DYSKINESIA IN PATIENTS WITH PARKINSON'S DISEASE

PROTOCOL

Version:	5.0
Version date:	5 March 2021
Superseded version:	1.1 (29 May 2020)
Sponsor:	Integrative Research Laboratories Sweden AB (IRLAB)
Product:	Mesdopetam (IRL790) (2.5 mg, 5 mg and 7.5 mg hard HPMC capsules)
Study Number(s):	IRL790C005
	EudraCT number: 2020-002010-41

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PROTOCOL APPROVAL PAGE

This protocol has been read and approved by:

Sponsor representative, Joakim Tedroff (Chief Medical Officer, CMO): **Signature:** **Date:**	

Sponsor representative, Maria Jalmelid (Chief of Clinical Operations): **Signature:** **Date:**	

CRO Worldwide Clinical Trials representative, Aimie Nunn (Statistician): **Signature:** **Date:**	

INVESTIGATOR PROTOCOL APPROVAL PAGE

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE IIB STUDY EVALUATING THE EFFICACY OF MESDOPETAM ON DAILY ON-TIME WITHOUT TROUBLESOME DYSKINESIA IN PATIENTS WITH PARKINSON'S DISEASE

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 (ICH E6 (R2)) 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
V 1.1 29 May 2020	Initial version	Not applicable
V 2.0 France 21 Oct 2020 (Local version for France)	Added U-hCG test at visit 3 and visit 4. *Impacted sections: Schedule of study and study procedures, section 10.8, 10.10 and 11.2.1.*	Response to French ANSM comments, dated 12 Oct 2020
	Corrected the Sponsor name by adding "Sweden". *Impacted section: Header, front page and contact name and address page.*	In line with protocol administrative letter change #1, dated 14 Aug 2020
	Changed one of the Sponsor's protocol signees. *Impacted section: Protocol approval page.*	Administrative change
V 2.1 France 24 Nov 2020 (Local version for France)	Clarifying details added to exclusion criterion 11. *Impacted sections: Protocol synopsis and Section 7.3.*	Response to the French Central Ethics Committee - Request for supplementary information issued on 07 Nov 2020
V 3.0 Poland 05 Nov 2020 (Local version for Poland)	Added U-hCG test at visit 3 and visit 4. *Impacted sections: Schedule of study and study procedures, section 10.8, 10.10 and 11.2.1.*	Response to Polish MOH comments, dated 28 Oct 2020
	Corrected the Sponsor name by adding "Sweden". *Impacted section: Header, front page and contact name and address page.*	In line with protocol administrative letter change #1, dated 14 Aug 2020
	Changed one of the Sponsor's protocol signees. *Impacted section: Protocol approval page.*	Administrative change
V 4.0 Italy 24 Nov 2020 (Local version for Italy)	Added definition of woman of childbearing potential and/or postmenopausal woman according to CTFG Guideline Recommendations related to contraception and pregnancy testing in clinical trials, Version 1.1, dated 21/09/2020. *Impacted section: 8.1.*	Response to Italian AIFA comments, dated 12 Nov 2020
	Added U-hCG test at visit 3 and visit 4. *Impacted sections: Schedule of study and study procedures, section 10.8, 10.10 and 11.2.1.*	According to CTFG Guideline Recommendations related to contraception and pregnancy testing in clinical trials, Version 1.1, dated 21/09/2020.
	Corrected the Sponsor name by adding "Sweden". *Impacted section: Header,*	In line with protocol administrative letter change #1, dated 14 Aug 2020

	front page and contact name and address page.	
	Changed one of the Sponsor's protocol signees. *Impacted section: Protocol approval page.*	Administrative change
V 5.0 5 March 2021	Corrected the Sponsor name by adding "Sweden". *Impacted section: Header, front page and contact name and address page.*	In line with protocol administrative letter change #1, dated 14 Aug 2020. Added to local versions (France, Poland, Italy) – now implemented globally.
	Changed one of the Sponsor's protocol signees. *Impacted section: Protocol approval page.*	Administrative change. Added to local versions (France, Poland, Italy) – now implemented globally.
	Added U-hCG test at visit 3 and visit 4. *Impacted sections: Schedule of study and study procedures, section 10.8, 10.10 and 11.2.1.*	Added to local versions (France, Poland, Italy) in response to local requirements – now implemented globally.
	Clarifying details added to exclusion criterion 11. *Impacted sections: Protocol synopsis and Section 7.3.*	Added to local version (France) in response to local requirements – now implemented globally.
	Added definition of woman of childbearing potential and/or postmenopausal woman according to CTFG Guideline Recommendations related to contraception and pregnancy testing in clinical trials, Version 1.1, dated 21/09/2020. *Impacted section: 8.1.*	Added to local version (Italy) in response to local requirements – now implemented globally.
	Addition of safety parameters (vital signs, haematology/clinical chemistry incl prolactin, dipstick urinalysis and ECG) at Visit 1 (Baseline) if 29 days or more between the Screening visit and Visit 1 (Baseline). *Impacted sections: Schedule of study and study procedures, section 10.4 and 11.2.1.*	Added to ensure baseline safety assessments in association to initiation of study treatment.
	Clarification that the three 24-hour home diaries can be completed during three consecutive days or any combination of days during the week prior V1, V3, V4 and V5. *Impacted sections: Schedule of study and study procedures.*	Clarification
	Pregnancy form to be used for reporting of pregnancy, not SAE form. *Impacted section: 12.9.*	Correction

	Correction of Stage 2 Hoehn and Yahr description. *Impacted section: 11.1.2.*	Correction
	Revision of approximate number of sites participating in the study (increased from 28 to 35). *Impacted section: Protocol synopsis.*	Update based on new information
	Minor updates (typos, clarifications) for consistency throughout the document.	Corrections/clarifications

1. PROTOCOL SYNOPSIS

Study title: A randomized, double-blind, placebo-controlled, Phase IIb study evaluating the efficacy of mesdopetam on daily ON-time without troublesome dyskinesia in patients with Parkinson's disease (PD).	
Study Code: IRL790C005	**EudraCT No:** 2020-002010-41
Study period: Estimated date of first patient enrolled: Sep 2020 Estimated date of last patient completed: Jan 2022	**Phase of development:** Phase IIb
Study design: This will be a randomized, double-blind, placebo-controlled multi-centre study.	
Number of patients planned: A total number of 140 patients (35 per group) will be randomized to the study. The Sponsor will evaluate the actual dropout rate after 70 randomized patients have completed Visit 3 (Week 4) and can, if the dropout rate at this point is higher than expected, decide to increase the sample size to a total of maximum 154 randomized patients (+10%).	
Investigator study sites: This study will be conducted at approximately 35 study sites in approximately 6 countries.	
Objectives: <u>Primary objective:</u> • To evaluate the effectiveness of adjunctive treatment with mesdopetam dosed at 2.5 mg, 5 mg or 7.5 mg b.i.d. (permitting a single 2.5 mg dose reduction to a minimum dose of 2.5 mg, up to Day 28) compared to placebo in patients with PD exhibiting troublesome ON-phase dyskinesia. <u>Secondary objectives:</u> • To establish the dose response relationship with 3 dose levels of mesdopetam. • To evaluate the effects of mesdopetam on severity of ON-phase dyskinesia and motor symptoms of PD. • To evaluate the effects of mesdopetam on the daily hours spent in different motor states. • To evaluate the safety and tolerability of mesdopetam given twice daily during 84 consecutive days. • To evaluate trough and 2-hour post dose plasma concentrations of mesdopetam and its two main metabolites, IRL902 (N-dealkylated) and IRL872 (acetylated). <u>Exploratory objectives:</u> • To assess overall PD symptoms. • To assess cognitive function.	

Efficacy Endpoints

Primary efficacy endpoint

Change in average daily hours of ON-time without troublesome dyskinesia with mesdopetam compared to placebo as assessed with 24-hour patient home diaries from baseline to end of treatment (EOT) (Visit 5, Week 12).

Secondary efficacy endpoints

- Change from baseline in average daily hours of ON-time without troublesome dyskinesia for each individual dose level (2.5 mg, 5 mg, 7.5 mg b.i.d.), as well as all active doses grouped compared to placebo.
- Change from baseline in mean score or average daily hours with mesdopetam compared to placebo for the following measures:
    - ON-phase dyskinesia assessed with the sum score of the modified UDysRS (parts 1, 3 and 4).
    - Disability associated with ON-phase dyskinesia assessed with the sum score of parts 1b and 4 of the UDysRS.
    - ON-phase dyskinesia assessed by MDS-UPDRS part 4 questions 4.1 (Time spent with dyskinesias) and 4.2 (Functional impact of dyskinesias).
    - Motor symptoms of PD assessed with MDS-UPDRS total score of part 2 (M-EDL).
    - Daily OFF-time, daily ON-time with troublesome dyskinesia and daily total ON-time (defined as the sum of ON-time with and without troublesome dyskinesia).
    - CGI-S of ON-phase dyskinesia.

Exploratory endpoints

- Change from baseline with mesdopetam compared to placebo in:
    - CGI-S of overall PD symptoms.
    - Total MMSE score.

Safety endpoints

- Frequency and nature of Adverse Events (AEs), laboratory results, vital signs, physical examinations, Columbia-Suicide Severity Rating Scale (C-SSRS) and 12-lead electrocardiograms (ECG) at each visit from baseline to follow-up.

Pharmacokinetic endpoints

- Plasma concentrations of mesdopetam and its two main metabolites at pre-dose and 2 hours post-dose at 8 and 12 weeks of treatment.

Diagnosis and main eligibility criteria:

Male and female patients 30-79 years of age with PD according to the specified inclusion and exclusion criteria will be recruited.

Inclusion & Exclusion criteria:

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

1. Male or female ≥30 and ≤79 years of age at the time of screening.
2. Signed a current Ethics Committee approved informed consent form (ICF).
3. PD, per UK Parkinson's Disease Society (UKPDS) Brain Bank Clinical Diagnostic Criteria.
4. Minimal amount of 2 hours of levodopa-induced daily "ON-time with troublesome dyskinesia" during waking hours.
5. Functional impact of dyskinesias determined as a score of ≥2 as per Question 4.2 of the MDS-UPDRS.
6. On a stable regimen of antiparkinson medications for at least 30 days prior to first home diary completion which must include a levodopa preparation administered 3-8 times/day (excluding nighttime levodopa), and willing to continue the same doses and regimens during study participation. Rescue medications such as Madopar dispersable and Apomorphine injections are allowed if prescribed PRN prior to study entry.
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 first home diary completion 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. Able to complete 24-hour patient home diaries of which two valid diaries must be presented at Visit 1.

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

1. History of neurosurgical intervention related to PD (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, localized bladder cancer, non-metastatic prostate cancer or in situ cervical cancer.
6. Presence of cognitive impairment, as evidenced by a Mini-Mental State Examination (MMSE) score of less than 24 during screening.
7. A Hoehn and Yahr stage of 5.
8. Ongoing treatment with amantadine at time of screening or within 6 weeks prior first home diary completion.
9. Treatment with Inbrija (levodopa inhalation powder) at time of screening or within 4 weeks prior first home diary completion.

10. 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.
11. 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 (a fall and/or a discomfort); clinically significant hepatic disease, severe renal impairment, i.e. creatinine clearance <30 mL/min (stage IV or V).
12. Any history of a neurological disorder other than PD or a psychiatric disorder, including history of Diagnostic and Statistical Manual of Mental Disorders (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.
13. 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.
14. Drug and/or alcohol abuse.
15. History of severe drug allergy or hypersensitivity.
16. If female, is pregnant or lactating, or has a positive pregnancy test result pre-dose.
17. Patients unwilling to use two forms of contraception (one of which being a barrier method (see Section 8.1) during the treatment period and 90 days for men and 30 days for women after last IMP dose.
18. Any planned major surgery within the duration of the study.
19. Any other condition or symptoms preventing the patient from entering the study, according to the Investigator's judgement.

Methodology:

This is a multicentre study where 140 patients with PD exhibiting ON-phase dyskinesia will be randomized to receive Investigational Medicinal Product (IMP) or placebo, respectively.

At the screening visit consenting patients will be screened for eligibility according to study specific inclusion/exclusion criteria within 8 weeks before start of Investigational Medicinal Product (IMP) administration. A diary concordance training will be performed, either during the screening visit or during a separate scheduled visit prior start of the baseline diary completion period.

Following the screening visit and the diary concordance training, the patient will be asked to self-administer three 24-hour home diaries and to bring the completed diaries to the baseline visit (Visit 1, Day 1), for assessment prior to randomization.

At the baseline visit (Visit 1, Day 1), patients will be randomized 1:1:1:1 to receive one of three doses of mesdopetam (2.5 mg, 5 mg or 7.5 mg) or placebo b.i.d.

During the first week (Day 1 evening dose to Day 9 morning dose) a run-in phase with either 5 mg mesdopetam or placebo b.i.d. will take place, during which all patients allocated to

mesdopetam will receive 5 mg mesdopetam b.i.d. and patients allocated to placebo will receive placebo b.i.d. At Visit 2 (Day 9), patients will receive mesdopetam 2.5 mg, 5 mg or 7.5 mg or placebo b.i.d., as randomized.

Patients will continue the same dose for the rest of the treatment period until EOT (Visit 5, Week 12, Day 84). Dose reductions will only be allowed if the patient manifests increased parkinsonism and/or a consistent increase in motor OFF-time. The dose can only be reduced once (and only by 2.5 mg b.i.d.). Dose reductions are permitted from Visit 2 until Visit 3 (i.e. Day 9 - Day 28 ±4 days), where after the dose should be kept stable until EOT (Visit 5, Week 12, Day 84).

The treatment allocation will be double-blind, i.e. it will not be disclosed to the patients, the site staff or the Sponsor. Starting on Day 1, the IMP will be self-administered by the patient at home for 12 consecutive weeks: *two oral daily doses (approximately 8 hours apart)* as adjunct treatment to the patients' regular and stable antiparkinsonian medication.

During the treatment period at Visits 3-5, changes in disease state and ON-phase dyskinesia will be assessed using the MDS-UPDRS, the modified UDysRS (i.e. parts 1, 3 and 4), and Clinician's Global Impression of Severity (CGI-S). Furthermore, patients will self-administer three 24-hour home diaries prior to Visit 3 (Week 4), Visit 4 (Week 8) and Visit 5 (Week 12) to assess daily motor function.

Blood samples for pharmacokinetic (PK) analysis will be collected within 15 min pre-dose (trough) and approximately 2 hours (± 15 min) post dose on Visit 4 (Week 8) and Visit 5 (Week 12). PK data collected at 2 hours post dose will be used as an estimate of the maximum concentration (C_{max}).

Visit 6 (follow-up) will be performed for all patients, including any patients that discontinue the IMP early, 5-8 days after last administration of IMP.

IMP dosage and mode of administration:

Mesdopetam capsules: 2.5 mg, 5 mg and 7.5 mg free base equivalent: White hard Hydroxypropyl Methylcellulose (HPMC) capsule, coni snap size 3, colour white containing mesdopetam x ½ L-tartrate for oral administration.

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

Mesdopetam 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 84 consecutive days. The starting dose will be 5 mg b.i.d. (mesdopetam or placebo) during the dose run-in period (one week) and thereafter mesdopetam 2.5 mg, 5 mg or 7.5 mg or placebo b.i.d as randomized. The minimum dose is 2.5 mg b.i.d. and the maximum dose is 7.5 mg b.i.d.

Duration of each patients' involvement in the study:

Patients will be screened for eligibility up to 8 weeks prior start of IMP treatment at Day 1. IMP treatment will last for twelve weeks. A follow-up visit will be performed approximately 1 week after the last IMP dose.

Efficacy assessments

- 24-hour patient home diary
- Modified UDysRS (i.e. parts 1, 3 and 4)
- MDS-UPDRS
- Clinical Global Impression of Severity (CGI-S) Rating
- MMSE

Safety assessments

- Frequency, seriousness and intensity of AEs
- Physical examination
- 12-lead ECG recordings
- Vital signs (blood pressure (BP) and heart rate)
- Clinical laboratory measurements
- Columbia-suicide severity rating scale (C-SSRS)

PK assessments

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

Statistical methods:

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

Power and sample size:

140 patients (35 per group), are enough to demonstrate a treatment difference of 3 hours, pooled standard deviation 3.5, between a single dose level of active treatment and control (i.e. 2.5 mg, 5 mg or 7.5 mg mesdopetam vs placebo b.i.d.) for the primary endpoint with 92% power and type 1 error rate 0.05 (two tailed). The sample size calculation is based on an expected dropout rate of 10%. The Sponsor will evaluate the actual dropout rate after 70 randomized patients have completed Visit 3 (Week 4) and can, if the dropout rate in the study is higher than expected, decide to increase the sample size to a total of maximum 154 randomized patients (+10%).

Randomization will be performed via a web-based Interactive Response System (IRS), using a dynamic balancing (minimization) algorithm. Randomization will be stratified by the average daily hours spent in ON-time with troublesome dyskinesia (<6 hours and ≥6 hours) at baseline.

Demographics and baseline characteristics:

All demographic information and baseline characteristics relating to patients with PD exhibiting ON-phase dyskinesia will be summarized to describe the population of patients recruited to the study.

Efficacy analyses

The primary efficacy analysis will be conducted on the Full Analysis Set (FAS), defined as all randomized subjects who have received at least 1 dose of IMP and have at least 1 post baseline assessment.

The primary efficacy assessment is the change in average daily hours of ON-time without troublesome dyskinesia with mesdopetam compared to placebo as assessed with 24-hour patient home diaries from baseline to EOT (Visit 5, Week 12). This will be analyzed using a mixed model repeated measures (MMRM) analysis that includes changes from baseline to Visit 3 (Week 4), Visit 4 (Week 8) through to EOT (Visit 5, Week 12). The model will include randomized treatment, visit (Visits 3, 4 and 5 (EOT)), and treatment by visit interaction as explanatory variables. Treatment, visit and treatment by visit interaction will be fixed effects in the model. Baseline value for average daily hours of ON-time without troublesome dyskinesia will be included as a continuous covariate along with the baseline stratification factor of daily hours spent in ON-time with troublesome dyskinesia (<6 hours and ≥-6 hours).

Model assumptions will be examined and alternative analyses (e.g. analysis after data transformation or non-parametric analysis) may be performed as appropriate.

The main comparison will be a contrast between treatment groups at EOT (Visit 5, Week 12). Estimates for each individual dose level, as well as all active doses grouped vs. placebo will be obtained from the model. Least squares means, 95% confidence intervals, and p-values of the treatment comparisons along with basic arithmetic summary statistics (mean, median, standard deviation, min and max) will be provided.

Sensitivity analyses will be performed for the Primary efficacy endpoint to assess the robustness of the observed result. In the first instance, the Primary analysis will be repeated for all subjects without a major protocol deviation, followed by analysis by treatment received following Visit 3 (Week 4, Day 28) to EOT. An alternative analysis using Analysis of covariance (ANCOVA) may also be performed. Methods to assess the impact of missing data (including last observation carried forward or multiple imputation) may also be applied where appropriate.

Key secondary efficacy assessments include the change in score of subsets of the UDysRS (parts 1+3+4 and parts 1+4) as well the MDS-UPDRS part 2 total score, the daily hours of OFF-time, the daily hours of ON-time with troublesome dyskinesia and the change in score of questions 4.1 and 4.2 of the MDS-UPDRS.

Change from baseline (Visit 1, Day 1) through EOT (Visit 5, Week 12) will be derived, summarized and analyzed. EOT (Visit 5, Week 12) is considered the primary time-point of interest.

All secondary and exploratory efficacy endpoints (including CGI-S data) will be analyzed per the Primary efficacy endpoint. Summary statistics (mean, median, standard deviation, min and max), least squares means, 95% confidence intervals, and p-values of the treatment comparisons will be provided for descriptive purposes.

PK analyses

PK variables measured in plasma are: Plasma concentrations of mesdopetam parent drug and two of its metabolites (IRL902 (N-dealkylated) and IRL872 (acetylated)).

Samples are obtained pre-dose (trough) and 2 hours post dose (C_{max}) on Visit 4 (Week 8) and EOT (Visit 5, Week 12) and results will be summarised by timepoint, visit, and mesdopetam dose level.

If appropriate, the PK relationship between the treatment doses and plasma exposure (trough concentrations and C_{max}) of mesdopetam and its metabolites will be assessed using a power model.

Safety analyses

Safety evaluations include AE and concomitant medication reporting, complete physical examination, vital signs, 12-lead ECG, C-SSRS and clinical safety laboratory tests (serum chemistry, haematology, urinalysis and coagulation). All will be presented as data summaries. No formal statistical analyses will be performed.

AEs (overall, by seriousness, by severity, by relationship) and concomitant medications (overall) recorded throughout the investigation will be reported following classification according to Medical dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT) and World Health Organisation Drug dictionary (WHODD) Anatomical Therapeutic Chemical (ATC) Classification System respectively.

All other safety evaluations performed at screening and Visits 1-6 (EOS/EW) will be summarized accordingly.

Unscheduled safety laboratory samples assayed at the local hospital will be listed according to Site.

Schedule of study and study procedures

Visit	Screening	Phone calls	Visit 1 (Baseline)	Visit 2	Phone call	Phone calls	Visit 3	Phone calls	Visit 4	Phone calls	Visit 5 (EOT)	Visit 6 (EOS/EW) [1]
		Baseline diary period	Dose run-in	Treatment period								Follow up
Day	**-56 to -10**	**-9 to -1**	**Day 1**	**9**	**14**	**21**	**28**		**56**		**84**	**5-8 days after EOT**
Week				**Week 1**	**2**	**3**	**4**	**7**	**8**	**11**	**12**	
Time window	**-**	**-[2]**	**-**	**+ 2 days**	**± 2 days**	**± 2 days[2]**	**± 4 days**	**-[2]**	**± 4 days**	**-[2]**	**-2 to 0 days**	
Informed Consent	X								X[3]			
Demographics/Medical History	X											
Inclusion/Exclusion Criteria	X		X									
Hoehn and Yahn scale	X											
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X
Height	X											
Weight	X											X
Vital Signs (incl supine/standing BP)	X		X[5]				X		X		X	X
Physical Examination	X										X	X
12-lead ECG	X[4]		X[5]						X		X	X
Haematology / Clinical Chemistry	X		X[5]						X		X	X
CYP2D6 genotyping									X			
Dipstick Urinalysis	X		X[5]						X		X	X
Pregnancy Test[6/6a]	X[6]		X[6]				X[6a]		X[6a]		X[6]	
MDS-UPDRS	X[7]		X				X[8]		X		X	
24-hour patient home diary training	X[9]											

[1] Safety follow-up visit to be performed (if possible) for early IMP discontinuations (5-8 days after last dose of IMP)
[2] Site to call the patient the working day before the first 24-hour diary completion period, as a reminder, and the working day after the last 24-hour diary completion period to encourage compliance.
[3] CYP2D6 genetic informed consent must be signed prior CYP2D6 blood sample testing. Note: the CYP2D6 testing is optional
[4] Triplicates separated by at least one minute
[5] If 29 days or more between the Screening visit and Visit 1 (Baseline), safety parameters (Vital Signs, single ECG, Haematology/Clin Chem and Urinalysis) are included also at Visit 1 (Baseline).
[6] Serum hCG; Only applicable for women with childbearing potential (as defined in section 8.1)
[6a] Urine hCG; Only applicable for women with childbearing potential (as defined in section 8.1)
[7] Part 4 question 4.2
[8] Part 2 (M-EDL) and part 4 questions 4.1 and 4.2
[9] Diary concordance training (takes approx. 2.5 hours). Could be done either at the screening visit or during a separate scheduled visit after receipt of the screening lab results and prior start of the baseline diary completion period.

Visit	**Screening**	**Phone calls**	**Visit 1 (Baseline)**	**Visit 2**	**Phone call**	**Phone calls**	**Visit 3**	**Phone calls**	**Visit 4**	**Phone calls**	**Visit 5 (EOT)**	**Visit 6 (EOS/EW)** [1]
		Baseline diary period	**Dose run-in**	**Treatment period**								**Follow up**
Day	**-56 to -10**	**-9 to -1**	**Day 1**	**9**	**14**	**21**	**28**		**56**		**84**	**5-8 days after EOT**
Week				**Week 1**	**2**	**3**	**4**	**7**	**8**	**11**	**12**	
Time window	**-**	**-[2]**	**-**	**+ 2 days**	**± 2 days**	**± 2 days[2]**	**± 4 days**	**-[2]**	**± 4 days**	**-[2]**	**-2 to 0 days**	
24-hour patient home diaries hand out/collection	X[10]		X[10 11]				X[10 11]		X[10 11]		X[11]	
24-hour patient home diary entry[12]		X				X		X		X		
Patient motor function review							X					
Modified UDysRS			X				X		X		X	
MMSE	X										X	
CGI-S			X				X		X		X	
C-SSRS			X				X		X		X	
Adverse Event (AE)	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Event (SAE) collection/reporting	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[13]			X									
PK sample[14]									X		X	
Dispense IMP			X	X			X					
Collect empty bottles of IMP				X			X[15]		X		X	
Compliance				X	X	X	X	X	X	X	X	

[10] Three empty diaries handed out
[11] Three completed diaries collected
[12] Three 24-hour home diaries to be completed during separate days during the week (can be three consecutive days or any combination of days during the week) prior V1, V3, V4 and V5 (i.e. in total 12 diaries during the study). Set dates for the patient complete diaries to be agreed in advance. Clinic to call the patient the working day before the first 24-hour diary completion period, as a reminder, and the working day after the last 24-hour diary completion period to encourage compliance.
[13] First dose to be taken in the evening at day 1
[14] Taken within 15 min pre-dose and approx. 2 hours (± 15 min) after morning dose of IMP
[15] Only collect the bottle if dose is reduced

CONTACT NAME AND ADDRESS

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2. ABBREVIATIONS

ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
AE	Adverse Event
AIM	Abnormal Involuntary Movements
ANCOVA	Analysis of covariance
ATC	Anatomic Therapeutic Chemical classification system
AUC	Area under the concentration time curve
b.i.d.	Twice daily
BMI	Body Mass Index
BP	Blood Pressure
CA	Competent Authority
CGI-S	Clinical Global Impression of Severity
C_{max}	Maximum concentration
CMO	Chief Medical Officer
CNS	Central Nervous System
CRF	Case Report Form
CRO	Clinical Research Organisation
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochromes
DSM	Diagnostic and Statistical Manual of Mental Disorders (DSM)
ECG	Electrocardiogram
ED50	Median Effective Dose
EOS	End of study
EOT	End of treatment
EW	Early withdrawal
FAS	Full Analysis Set
ICH GCP (R2)	International Conference on Harmonisation Good Clinical Practice (Revision 2)
Hb	Haemoglobin
HPMC	Hydroxypropyl Methylcellulose
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRL	Integrative Research Laboratories
IUD	Intrauterine Device
IUS	Intrauterine System
LID	Levodopa-Induced Dyskinesia
MAD	Multiple Ascending Dose
MDS-UPDRS	Movement Disorder Society – Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini–Mental State Examination
NTEAE	Non-Treatment Emergent Adverse Event
PD	Parkinson's Disease
PDP	Parkinson's Disease Psychosis
PK	Pharmacokinetic

PPS	Per Protocol Set
PT	Preferred Term
SAE	Serious Adverse Event
SAD	Single Ascending Dose
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SOC	System Organ Class
SS	Safety Set
SUSAR	Suspected Unexpected Serious Adverse Reaction
T_{max}	Time to maximum concentration
TEAE	Treatment Emergent Adverse Event
UAE	Unexpected Adverse Event
UKPDS	UK Parkinson's Disease Society
UDysRS	Unified Dyskinesia Rating Scale
WHODD	World Health Organisation Drug dictionary

Enrolled/screened patient:	*Patient who has signed the informed consent*
Screening failure:	*Enrolled patient not included*
Included patient:	*Patient randomized*
Withdrawn patient:	*Patient randomized but not completed*
Completed patient:	*Patient completed the study period, including follow-up*

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4. BACKGROUND INFORMATION AND STUDY RATIONALE

Parkinson's disease (PD) is a relatively common neurodegenerative disorder characterized 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 [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 PD. 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 PD, about 50% of patients (and after 10 years almost all patients) develop involuntary movements appearing when the patient is in ON-phase, so called LIDs. [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].

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 PD.

4.1. Investigational agent

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

Some specific desired properties of this compound are:

- Efficacy in preclinical PD models of levodopa-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, mesdopetam 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 mesdopetam. The specific antidyskinetic and antipsychotic effects of mesdopetam suggest its use in the treatment of LID

and psychosis (PDP) in PD. This trial is aimed at assessing mesdopetam as a treatment for LID. Its role as a treatment for PDP will be assessed in future trials.

4.1.1. Mechanism of action

Mesdopetam 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's monoaminergic systems without suppressing locomotor activity in normal un-pretreated rats. *In vitro* mesdopetam 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.

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

4.1.2. Efficacy

Behaviourally, mesdopetam can 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, mesdopetam significantly reduced LID but left the levodopa-dependent motor activation intact.

Furthermore, in a Phase 1b and a Phase 2a study, patients with advanced PD experiencing LID were randomized to receive mesdopetam or placebo as adjunct treatment for 28 days. In the Phase 1b study, 13 patients completed the study, with 9 patients on mesdopetam and 4 patients on placebo. In the Phase 2a study, 72 patients completed the study, with 37 patients on mesdopetam and 35 patients on placebo. For both studies, mesdopetam was safe and well tolerated following individual dose adjustments. It was also shown that the adjunct treatment of mesdopetam to otherwise stable antiparkinsonian medication reduced ON-phase dyskinesia without compromising general mobility.

4.1.3. Preclinical data

The safety of mesdopetam has been evaluated in a standard battery of non-clinical studies, including *in vitro* and *in vivo* genotoxicity tests, repeat oral dose toxicity studies of up to 13 weeks duration in rats and dogs, male fertility assessment in rats, and safety pharmacology studies on the cardiovascular, central nervous and respiratory systems. Mesdopetam is not genotoxic. Histopathological findings in the rat were either a probable effect on dopamine modulation of prolactin levels (effects on mammary gland, prostate gland, female reproductive organs and adrenal gland), related to metabolizing enzymes (liver finding) or a high-dose phenomena (stomach lesions and increased apoptosis in pancreas and parotids, 1-month study), all of which were partially or fully reversible. The principal clinical signs seen in the rat safety studies were C_{max}-related and attributable to the pharmacological action of mesdopetam. The main dose limiting events were tremors, hypoactivity, hunched posture, abnormal or unsteady gait and reduced food consumption and body weight gain. The clinical signs recorded in the dog toxicity studies were of a similar nature to those in the rat, i.e. locomotor/postural and behavioural signs. In dogs, histopathological findings were seen only in the high-dose group in

the 1-month study (40 mg/kg/day). These were arteritis/periarteritis in small arteries mainly in the alimentary tract in one female (which had been preterminally sacrificed due to convulsions), and capillary dilation associated with an increased thickness of the alveolar walls in one male. These findings are considered to be adverse until their nature has been clarified. In the 3-month dog study, histopathological changes were only noted in the adrenal gland, and considered to be of adaptive nature and non-adverse. In the 1-month study in rat the NOAEL was considered to be 25 mg/kg/day (corresponding to mean C_{max} of 10.8 µM; mean $AUC_{0\text{-}24h}$ of 47.2 µM•h). The NOAEL for microscopic findings is considered to be 55 mg/kg/day (corresponding to mean C_{max} of 19 µM; mean $AUC_{0\text{-}8h}$ of 106 µM•h), while for the 3-month study the NOAEL was considered to be 55 mg/kg/day (including microscopic finding, corresponding to mean C_{max} of 27.4 µM; mean $AUC_{0\text{-}24h}$ of 204 µM•h).

In the 1- and 3-months studies in dog the NOAEL was considered to be 18 mg/kg/day (corresponding to mean C_{max} of 8.9/10.6 µM and mean $AUC_{0\text{-}24h}$ of 84 /87.6 µM•h, for the 1-month/3-month studies, respectively).

Mesdopetam has low affinity for Human Ether-à-go-go-Related Gene (hERG) (IC_{50}; 223.9 µM) and is therefore predicted to have low liability for QT prolongation. Mesdopetam was tested for excitability, automaticity, cardiac wavelength, TRIaD and proarrhythmia in the Hondeghem model using rabbit isolated hearts [7]. Mesdopetam was concluded to be safe in the dose range tested (0.5 to 45 µM).

Mesdopetam had no effects on cardiovascular parameters in dogs. No potential adverse effects were identified in the core battery safety pharmacology studies. Mesdopetam did not modify mating behavior, gonadal function and reproductive capacity of male rats.

The phototoxicity potential of mesdopetam is assessed to be low, and the risk for phototoxic reactions is considered to be minimal in the planned clinical study.

The major metabolites IRL902 and IRL872 are not considered to be pharmacologically active. The contribution of IRL902 and IRL872 to the overall assessment of general toxicity of mesdopetam has been investigated, by the presence of these metabolites in the 1- and 3-month studies in rats (IRL902 and IRL872) and dogs (IRL902) at significantly greater plasma concentrations (C_{max}, AUC) than those occurring in humans (MAD study). Hence, the *in vivo* toxicity of IRL902 and IRL872 has been adequately characterized, and it is considered that these metabolites have been qualified in the pivotal toxicity studies in rats and dogs. The IRL902 and IRL872 metabolites are considered to be of no genotoxic concern in the proposed clinical study based on negative results in standard Ames test and *in vitro* micronucleus assays [8].

4.2. Risks / benefits

Collectively, the data from nonclinical and clinical studies indicate that mesdopetam is likely to have an acceptable safety profile. Studies in humans have not identified any safety issues for the doses studied and the highest obtained plasma concentration of mesdopetam in healthy volunteers was below the highest recommended level. Possible adverse effects associated with mesdopetam include mild increase in parkinsonism and potential increases in plasma prolactin at higher dose levels.

The dose levels to be used in this study have been selected based on analysis of previous clinical studies (see Section 4.6). A dose run-in phase for one week with a starting dose of 5 mg b.i.d.

and a subsequent dose allocation to three dose levels of mesdopetam (i.e. 2.5 mg, 5 mg or 7.5 mg) b.i.d. or placebo b.i.d. is expected to retain a pronounced margin of safety. To mitigate the risk for intolerability, a one-step dose reduction is allowed but only once and only due to increased parkinsonism and/or consistent increase in motor OFF-time. There will be a careful monitoring of the patient's well-being including regular collection of Adverse Events (AEs).

4.2.1. 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 (baseline), 9, 28, 56 and 84 for monitoring of safety variables. PK sampling will occur on Days 56 and 84. Phone calls will be made between Screening and Visit 1 and on Weeks 2, 3, 7 and 11 to collect information on any AEs and changes in concomitant medication, as well as instructing the user to complete three 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 patient home diaries, patient study identification, 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 BP cuff and frequent blood-sampling, can cause transient discomfort but the risk is deemed to be low and ethically justifiable.

The Sponsor acknowledges the impact of global pandemic of COVID-19 on any health system and broader society, and the impact it may have on this clinical study and study participants. Extraordinary measures may need to be implemented and study adjusted due, among others, to study participants being in self-isolation/quarantine, limited access to public places (including hospitals) due to the risk of spreading infection, and health care professionals being committed to critical tasks.

These challenges could have an impact on the conduct of the study such as the completion of study assessments, completion of study visits and the provision of the IMP. The ability to confirm eligibility and to conduct key safety assessments and study evaluations is of particular importance.

If needed, actions will be proportionate and based on benefit-risk considerations, on contingency provisions taken nationally and locally by the authorities, with priority given to the impact on the health and safety of the study participant. Necessary actions may be that for example Visit 2 (Day 9) is performed as a home visit or a phone visit with the new bottle of IMP sent to the patient via a courier or importer as per local regulatory requirement, or that in case of dose reduction (i.e. allowed between Day 9 - Day 28) the new bottle of IMP could be sent to the patient via a courier or importer as per local regulatory requirements. The possibility to access source documents during remote monitoring could be considered necessary, but need to be regulated as per local requirements (or temporary national emergency measures).

4.3. Dose rationale

The pharmacological effects of mesdopetam have been evaluated in a range of preclinical animal models. As to the suggested indication, LID in PD, the 6-hydroxydopamine (6-OHDA) Abnormal Involuntary Movements (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, mesdopetam has been studied in two independent tests, both in-house and by an external laboratory. Mesdopetam showed significant efficacy in reducing AIMs (active doses <10 mg/kg s.c. with a Median Effective Dose (ED50) of 3.7 mg/kg s.c.), without compromising beneficial effects of levodopa. Taken together, a dose range of around 1-4 mg/kg in the rat (C_{max} ≈ 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 mesdopetam is also likely to be personalized. Flexible dosing has been explored in two of the clinical studies (phase 1b and phase 2a). In this study (phase 2b) a dose-response analysis will be performed to evaluate three dose levels of mesdopetam (i.e. 2.5 mg, 5 mg and 7.5 mg b.i.d.). The dose-response analysis will give knowledge of the relationship among dose, drug-concentration in blood and clinical response (effectiveness & safety).

The dose levels to be used in this study have been selected based on previous clinical studies (see Section 4.6) where data indicates that clinically relevant efficacy may be achieved at the dose levels selected. The most commonly reported adverse event in patients randomized to mesdopetam in the phase 2a study was increased parkinsonism (during titration phase), and the finding of a possible dose dependent increase in OFF-time strongly suggest that lower doses than 10 mg b.i.d. should be explored in this forthcoming study. The finding of a strong trend towards improved general motor function in patients allocated to 7.5 mg b.i.d. or lower indicate that the efficacy of mesdopetam may extend beyond that of reducing peak dose dyskinesia.

The treatment starts with a one-week dose run-in period where all patients are randomized to a starting dose of 5 mg mesdopetam or placebo (twice daily). Thereafter the patients are allocated to one of three doses of mesdopetam or placebo. Given the plasma half-life of about 7 hours, enough coverage during the waking hours of the day is expected.

4.4. Trial conduct

This study will be conducted in compliance with the protocol and according to International Conference on Harmonisation Good Clinical Practice Revision 2 (ICH GCP (R2)) 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.

4.5. Population

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 ON-phase involuntary movements, so called 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 may also develop over time in a substantial proportion of patients. There are few options for the treatment and prevention of such long-term complications.

Mesdopetam was discovered and developed in a project aimed at finding a treatment for LID and psychosis 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 affecting the basic efficacy of antiparkinsonian medications.

4.6. Previous clinical studies

Mesdopetam has been investigated in the following three clinical studies:

- IRL790C001, a randomized, double-blind, placebo-controlled, phase 1 single ascending dose (SAD) and multiple ascending dose (MAD) study in male healthy volunteers.

- IRL790C002, a randomized, double-blind, placebo-controlled, phase 1b study evaluating the safety and tolerability of mesdopetam in patients with PD experiencing LID.

- IRL790C003, a randomized, double-blind, placebo-controlled phase 2a study evaluating the efficacy and tolerability of mesdopetam in patients with PD experiencing LID.

IRL790C001 (Phase 1)

In the SAD part of IRL790C001, 16 subjects were divided into two cohorts. Within each cohort the subjects were randomized to one of four treatment sequences, which included three dose levels of IMP. One of the dose levels was repeated once, taken with a standardized meal, all other doses were taken without food. In each of the six administered dose levels (5, 15, 40, 80, 120 mg mesdopetam), six subjects received active drug and two subjects received matching placebo.

In the MAD part of this study, 23 subjects were treated with IMP. In the first cohort, 9 subjects received mesdopetam, 40 mg/day for 10 consecutive days and 3 subjects received matching placebo. In the second cohort, 9 subjects received mesdopetam, 80 mg/day for 10 consecutive days and 3 subjects received matching placebo.

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

In agreement with preclinical findings, the PK 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.

IRL790C002 (Phase 1b)

In the Phase 1b study (IRL790C002), 15 patients with advanced PD experiencing LID were randomized to receive mesdopetam or placebo (3:1 randomization) 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 (15) patients were randomized to treatment, 11 to mesdopetam and 4 to placebo. Generally, AEs were of mild intensity and transient after dose adjustments. Ten (10) patients in the mesdopetam treated group and 4 patients in the placebo group reported at least one related AE. Nervous system disorder was the most common AE (31% of all reported AEs). Five patients treated with mesdopetam reported transient worsening of parkinsonism during dose titration, an adverse effect which was mitigated by dose reduction. Thirteen (13) patients completed the study, 9 patients on mesdopetam and 4 patients on placebo. Two (2) patients treated with mesdopetam discontinued treatment due to AEs.

IRL790C003 (Phase 2a)

In the Phase 2a study (IRL790C003), 75 patients with advanced PD experiencing LID were randomized to receive mesdopetam or placebo as adjunct treatment for 28 days, 39 to mesdopetam and 36 to placebo. 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, the dosing was kept stable for the remaining two weeks.

Generally, AEs were of mild intensity and transient after dose adjustments. Parkinsonism was the most common AE. Nine patients in the mesdopetam treated group reported parkinsonism during titration only and 2 patients in the mesdopetam treated group reported parkinsonism during steady state. 72 patients completed the study, with 37 patients on mesdopetam and 35 patients on placebo. 3 patients discontinued treatment in advance due to AEs (two on mesdopetam and one on placebo).

Vital signs, laboratory measurements and cardiovascular functions were unaffected by mesdopetam treatment.

At EOT the number of daily hours spent in ON-phase with troublesome dyskinesia was significantly reduced for mesdopetam treated patients as compared to placebo. General mobility was unaltered by the treatment, there were no evidence for changes in time spent in OFF-state or in the total score of MDS-UPDRS parts 2 or 3.

The clinical studies show that, following individualized dose adjustment, mesdopetam is well tolerated in patients with advanced PD and seem to act to reduce dyskinesia without compromising general motility.

5. STUDY OBJECTIVES AND ENDPOINTS

5.1. Primary objective and endpoint

Primary objective:

- To evaluate the effectiveness of adjunctive treatment with mesdopetam dosed at 2.5 mg, 5 mg or 7.5 mg b.i.d. (permitting a single 2.5 mg dose reduction to a minimum

dose of 2.5 mg, up to Day 28) compared to placebo in patients with PD exhibiting troublesome ON-phase dyskinesia.

Primary endpoint:

- Change in average daily hours of ON-time without troublesome dyskinesia with mesdopetam compared to placebo as assessed with 24-hour patient home diaries from baseline to end of treatment (EOT) (Visit 5, Week 12).

5.2.Secondary and exploratory objectives and endpoints

Secondary objectives:

- To establish the dose response relationship with 3 dose levels of mesdopetam.
- To evaluate the effects of mesdopetam on severity of ON-phase dyskinesia and motor symptoms of PD.
- To evaluate the effects of mesdopetam on the daily hours spent in different motor states.
- To evaluate the safety and tolerability of mesdopetam given twice daily during 84 consecutive days.
- To evaluate trough and 2-hour post dose plasma concentrations of mesdopetam and its two main metabolites (IRL902 (N-dealkylated) and IRL872 (acetylated)).

Exploratory objectives:

- To assess overall PD symptoms.
- To assess cognitive function.

Secondary endpoints:

- Change from baseline in average daily hours of ON-time without troublesome dyskinesia for each individual dose level (2.5 mg, 5 mg, 7.5 mg b.i.d.), as well as all active doses grouped compared to placebo.
- Change from baseline in mean score or average daily hours with mesdopetam compared to placebo for the following measures:
    - ON-phase dyskinesia assessed with the sum score of the modified UDysRS (parts 1, 3 and 4).
    - Disability associated with ON-phase dyskinesia assessed with the sum score of parts 1b and 4 of the UDysRS.
    - ON-phase dyskinesia assessed by MDS-UPDRS part 4 questions 4.1 (Time spent with dyskinesias) and 4.2 (Functional impact of dyskinesias).
    - Motor symptoms of PD assessed with MDS-UPDRS total score of part 2 (M-EDL).
    - Daily OFF-time, daily ON-time with troublesome dyskinesia and daily total ON-time (defined as the sum of ON-time with and without troublesome dyskinesia).
    - CGI-S of ON-phase dyskinesia.

Exploratory endpoints:

- Change from baseline with mesdopetam compared to placebo in:
    - CGI-S of overall PD symptoms.
    - Total MMSE score.

Safety endpoints:

- Frequency and nature of AEs, laboratory results, vital signs, physical examinations, C-SSRS and 12-lead electrocardiograms (ECG) at each visit from baseline to follow-up.

Pharmacokinetic endpoints:

- Plasma concentrations of mesdopetam and its two main metabolites at pre-dose and 2 hours post-dose at 8 and 12 weeks of treatment

6. STUDY DESIGN

6.1. Overall study design and plan description

This is a multi-centre, randomized, double-blind, placebo-controlled study with the primary objective to evaluate the efficacy of 84 days' treatment with mesdopetam on ON-time without troublesome dyskinesia in patients with PD.

At the screening visit, consenting patients will be screened for eligibility according to study-specific inclusion/exclusion criteria (see Sections 7.2 and 7.3) within 10-56 days before start of IMP administration. Diary concordance training will be performed, either during the screening visit or in the period prior to first diary completion. Patients will be instructed to self-administer three 24-hour home diaries (before Baseline, Visit 1) for assessment of daily motor function and to bring the completed diaries to the clinic at the next visit (Baseline, Visit 1). Screen failed patients will not complete any diaries. To be eligible for randomization the patient should have completed at least two valid 24-hour home diaries.

Following baseline assessments, patients will be randomized 1:1:1:1 to receive one of three doses of mesdopetam (2.5 mg, 5 mg or 7.5 mg) or placebo b.i.d. During the first week (Day 1 evening dose to Day 9 morning dose) a dose run-in phase will take place, during which all patients allocated to mesdopetam will receive mesdopetam 5 mg b.i.d. and patients allocated to placebo will receive placebo b.i.d.

At Visit 2 (Day 9), patients will be dispensed mesdopetam 2.5 mg, 5 mg or 7.5 mg or placebo b.i.d., as randomized. The patients will continue the same dose for the rest of the treatment period until EOT (Day 84). Dose reductions will only be allowed if the patient manifest increased parkinsonism and/or consistent increase in motor OFF-time. The dose can only be reduced once (and only by 2.5 mg b.i.d.) (see Table 3). Dose reduction is only permitted from Visit 2 (Day 9) until Visit 3 (Day 28 ±4 days), where after the dosing should be kept stable until the EOT visit (Day 84).

The treatment allocation will be double-blind, i.e. it will not be disclosed to the patients, the site staff or the Sponsor. Starting on Day 1 the IMP will be self-administered by the patient at home for 12 consecutive weeks; *two oral daily doses (approximately 8 hours apart*) as adjunct treatment to the patients' regular and stable antiparkinsonian medication.

During the treatment period at Visits 3-5, changes in disease state and ON-phase dyskinesia will be assessed using the MDS-UPDRS, the modified UDysRS (i.e. parts 1, 3 and 4) standardized for levodopa intake and time of the day and Clinician's Global Impression of Severity (CGI-S). The MDS-UPDRS part 2 will be assessed at all clinical visits. Part 3 will be assessed with the patient in ON at Visit 1 and Visits 4 and 5.

Furthermore, patients will self-administer three 24-hour home diaries prior to Visit 3 (Week 4), Visit 4 (Week 8) and Visit 5 (Week 12) to assess daily motor function. Dates for the patient to complete home diaries will be agreed in advance. The clinic will call the patient the working day before the first scheduled 24-hour home diary completion period, as a reminder, and the working day after the last 24-hour home diary completion period to encourage compliance. Patients must bring all three diaries to the clinic at each visit.

At Visit 4 and Visit 5, the morning IMP dose will be administered at the clinic. Blood samples for PK analysis will be collected within 15 min pre-dose and approximately two hours (± 15 min) post dose.

Various parts of the safety assessments will be performed at all visits. The morning dose at Day 84 (Visit 5, EOT) will be the last dose of IMP.

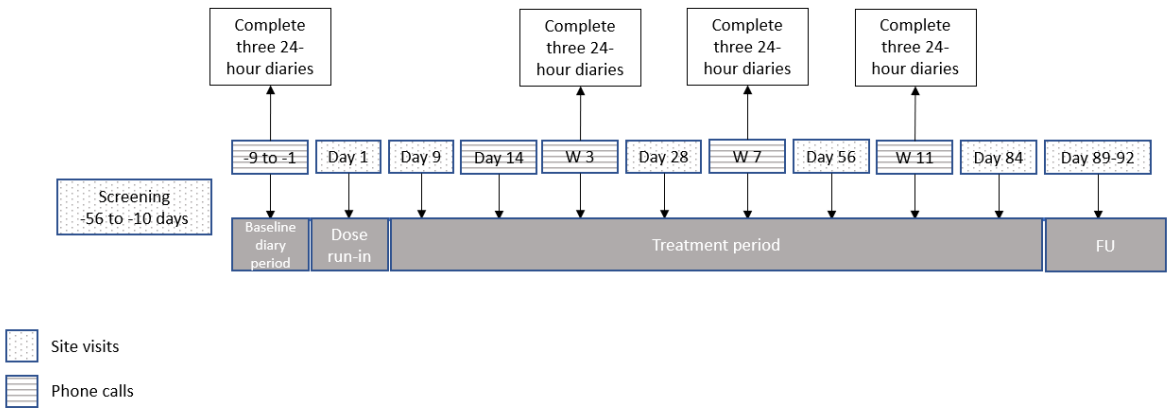
Visit 6 (follow-up) will be performed for all patients, including any patients that discontinue the IMP early, 5-8 days after last administration of IMP.

Unscheduled visits will be performed as needed during the study and should be documented in the appropriate section of the Case report form (CRF).

Each assessment is further described in Section 10.

6.1.1. Study Schematic

Patient path - primary endpoint



6.2. Rationale for study design and dose selection

The pharmacological effects of mesdopetam 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 producing 100-200 nM in plasma concentration.

Individualized dosing has been explored in two previous clinical studies (phase 1b and phase 2a). In this phase 2b study a dose-response analysis will be performed to evaluate three dose levels of mesdopetam (i.e. 2.5 mg, 5 mg and 7.5 mg b.i.d.). The dose-response analysis will give knowledge of the relationship among dose, drug-concentration in blood and clinical response (effectiveness & safety). The dose levels to be used in this study have been selected based on previous clinical studies (see Section 4.6) where data indicates that clinically relevant efficacy may be achieved at the dose levels selected. The most commonly reported AE in patients randomized to mesdopetam in the phase 2a study was increased parkinsonism (during titration phase), and the finding of a possible dose dependent increase in OFF time strongly suggest that lower doses than 10 mg b.i.d. should be explored in this forthcoming study. The finding of a strong trend towards improved general motor function in patients allocated to 7.5 mg b.i.d. or lower indicate that the efficacy of mesdopetam may extend beyond that of reducing ON-phase dyskinesia.

6.3. 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. The study will be double blind and placebo controlled. Patients will be randomized, in equal proportions, to placebo or to one of the three doses (2.5 mg, 5 mg or 7.5 mg b.i.d.) of the active dose regimen (mesdopetam), to permit analyses of the dose response relationship. For patients to adjust to the new medication, IMP treatment will start with a run-in period of one week. During this initial week, patients randomized to mesdopetam will receive 5 mg b.i.d. and patients randomized to placebo will receive placebo b.i.d. Results from previous clinical studies show that 5 mg b.i.d. is well tolerated by a vast majority of patients. Following the initial one-week run-in, patients randomized to mesdopetam will continue with their assigned dose (2.5 mg, 5 mg, or 7.5 mg b.i.d.) and patients randomized to placebo will continue with placebo.

7. PATIENT SELECTION CRITERIA

7.1. 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 early termination/withdrawal should be stated for all patients included but not completed.

140 randomized patients are required for this study.

7.2. Inclusion criteria

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

1. Male or female ≥30 and ≤79 years of age at the time of screening.
2. Signed a current Ethics Committee approved informed consent form.
3. PD, per UK Parkinson's Disease Society (UKPDS) Brain Bank Clinical Diagnostic Criteria.
4. Minimal amount of 2 hours of levodopa-induced daily "ON-time with troublesome dyskinesia" during waking hours.
5. Functional impact of dyskinesias determined as a score of ≥2 as per Question 4.2 of the MDS- UPDRS.
6. On a stable regimen of antiparkinson medications for at least 30 days prior to first home diary completion, which must include a levodopa preparation administered 3-8 times/day (excluding nighttime levodopa) and willing to continue the same doses and regimens during study participation. Rescue medications such as Madopar dispersable and Apomorphine injections are allowed if prescribed PRN prior to study entry.
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 first home diary completion 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. Able to complete 24-hour patient home diaries of which two valid diaries must be presented at Visit 1.

7.3. Exclusion criteria

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

1. History of neurosurgical intervention related to PD (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, localized bladder cancer, non-metastatic prostate cancer or in situ cervical cancer.
6. Presence of cognitive impairment, as evidenced by a Mini-Mental State Examination (MMSE) score of less than 24 during screening.
7. A Hoehn and Yahr stage of 5.
8. Ongoing treatment with amantadine at time of screening or within 6 weeks prior first home diary completion.
9. Treatment with Inbrija (levodopa inhalation powder) at time of screening or within 4 weeks prior home first diary completion.

10. 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.
11. 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 (a fall and/or a discomfort); clinically significant hepatic disease, severe renal impairment, i.e. creatinine clearance <30 mL/min (stage IV or V).
12. Any history of a neurological disorder other than PD 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.
13. 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.
14. Drug and/or alcohol abuse.
15. History of severe drug allergy or hypersensitivity.
16. If female, is pregnant or lactating, or has a positive pregnancy test result pre-dose.
17. Patients unwilling to use two forms of contraception (one of which being a barrier method see Section 8.1) during the treatment period and 90 days for men and 30 days for women after last IMP dose.
18. Any planned major surgery within the duration of the study.
19. Any other condition or symptoms preventing the patient from entering the study, according to the Investigator's judgement.

7.4. Patient withdrawal and early IMP discontinuation

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 discrimination, 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 and discontinue the IMP early 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

- Any AE 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

If a patient discontinues the IMP early for any reason, if possible, a safety follow-up visit (according to Visit 6) should be scheduled within 5-8 days after the last intake of the IMP. The Investigator must complete the "Study termination" section of the CRF explaining all reasons for withdrawal.

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

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

7.4.1. Replacements

Patients who are screened but not randomized will be classed as Screen Failures. The Sponsor will evaluate the actual dropout rate after 70 randomized patients have completed Visit 3 (Week 4) and can, if the dropout rate at this point is higher than expected, decide to increase the sample size to a total of maximum 154 randomized patients (+10%).

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

8. RESTRICTIONS DURING THE STUDY

8.1. General restrictions

Contraception Requirements:

The patient must be reminded to use two forms of contraception (one of which being a barrier method) for six months (180 days) for men and four months (120 days) for women from the time of the first administration of IMP.

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 of IMP until three months following administration of the last dose of IMP. Male patients must also refrain from donating sperm from the time of first administration of IMP until three months after last dosing of IMP. 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*

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

Female patients
Female patients of childbearing potential must use medically acceptable methods of contraception from the time of the first administration of treatment or IMP until four weeks following administration of the last treatment or dose of IMP. A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

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.*

Blood donation:

The patients must not donate blood or plasma during the study conduct or until three months after the final medical examination at the follow-up visit.

8.2.Concomitant medication

Permitted concomitant medication:

Patients included in the study must be on stable antiparkinsonian medications for at least 30 days prior to first 24-hour patient home diary completion and during the study. Rescue medications such as Madopar dispersable and intermittent Apomorphine injections are allowed if prescribed PRN prior to study entry. Other medications considered necessary for the patient's safety and well-being may be given at the discretion of the Investigator.

All concomitant therapy used within the four weeks prior to the screening period and during the study must be recorded on the CRF.

Non-permitted concomitant medication:

Inbrija (levodopa inhalation powder) is not allowed as a rescue medication during the study. No other drug under investigation may be used concomitantly with the IMP.

Treatment with amantadine is not allowed within 6 weeks before completion of the first 24-hour patient home diary and during the study.

Available *in vitro* data indicate that CYP2D6 and CYP1A2 are the main enzymes involved in the metabolism of mesdopetam. However, the exact contribution from each of these two enzymes in the elimination is not known, and there may be a risk for significant increase of exposure when mesdopetam is used together with a combination of medications being strong inhibitors of CYP2D6 and CYP1A2 (see Table 1). Therefore, a combination of such inhibitors, i.e. a CYP1A2 strong inhibitor and a CYP2D6 strong inhibitor concurrently, should be avoided throughout the study. A CYP2D6 genotyping testing will be performed at Visit 4 (Day 56).

Mesdopetam and its two main plasma metabolites M1 (IRL902) and M2 (IRL872) have been shown *in vitro* to not be inhibitors of the main drug metabolizing CYP450 enzymes to a significant degree. Restrictions on concomitant medications being CYP450 substrates are therefore not considered necessary during the study.

Mesdopetam and metabolite M2 (IRL872) are also not inhibitors or substrates to a significant extent to main drug membrane transporters. Restrictions on concomitant medications being substrates or inhibitors of drug transporters are not considered necessary during the study.

Table 1: Examples of clinical inhibitors of CYP2D6- and CYP1A2-mediated metabolism

Isoenzyme (cytochrome P450)	Strong Inhibitors	
CYP1A2	ciprofloxacin, enoxacin, fluvoxamine, zafirlukast	A combination of a CYP1A2 inhibitor and a CYP2D6 inhibitor is not permitted during the study.
CYP2D6	bupropion, fluoxetine, paroxetine, quinidine, terbinafine	

9. TREATMENT(S)

9.1. Appearance and content

Mesdopetam capsules, 2.5 mg, 5 mg and 7.5 mg free base equivalent: White hard HPMC capsule, coni snap size 3, colour white containing mesdopetam x ½ L-tartrate.

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

9.2. Dosage and administration

The IMP (1 capsule b.i.d.) will be swallowed together with 200 mL of water in the morning and in the afternoon approximately 8 hours apart on each administration day, except for Day 56 and Day 84 when the dose will be taken in the morning at the clinic visit after trough PK sampling.

Dose run-in phase and treatment phase

Treatment allocation throughout the run-in and treatment dosing periods will be managed through the Interactive Response System (IRS) system. During the 9-day run-in phase, the IRS system will ensure all patients allocated to active dose regimen will receive 5 mg mesdopetam b.i.d, followed by the randomized dose at Visit 2 (Day 9). Patients allocated to placebo will receive placebo during the first week run-in and then continue placebo during the whole treatment period. Any dose reduction will also be managed through the IRS system to ensure that blinding is maintained.

If a patient experiences **increased parkinsonism** and/or **consistent increase in motor OFF-time**, during the treatment period from Visit 2 up to Visit 3 (i.e. Day 9 – Day 28 ±4 days), the dosing can be reduced by 2.5 mg b.i.d. A dose reduction is allowed at only one occasion. A review of motor function will be performed at Visit 3.

The following tables give additional information on the two dose phases (Table 2) and the dose decrease guidance (Table 3).

Table 2: Treatment period – dosing phases

Dose phase	Details
Dose run-in phase: Randomization Day 1. First dose taken Day 1 (evening dose) and last dose taken Day 9 (morning dose).	All patients randomized to mesdopetam will receive 5 mg b.i.d. All patients randomized to placebo will receive placebo b.i.d.
Dosing following Visit 2: First dose taken Day 9 (evening dose) and last dose taken Day 84 (morning dose/at the clinic due to PK sampling)	All patients randomized to mesdopetam will receive mesdopetam 2.5 mg, 5 mg or 7.5 mg b.i.d., as randomized. All patients randomized to placebo will continue with placebo b.i.d.

Table 3: Dose decrease guidance

Treatment period	Dose decrease guidance
Applicable for treatment from Visit 2 (Day 9) until Visit 3 (Day 28 ±4 days):	Decision to reduce the dosing is only allowed from Visit 2 (Day 9) until Visit 3 (Day 28 ± 4 days), and dose reduction is only allowed once. A dose reduction is only allowed if the patient experiences an increase in parkinsonism and/or a consistent increase in motor OFF-time. Increased parkinsonism is manifested as consistent increase in disability associated with parkinsonian symptoms (i.e. bradykinesia, tremor and/or rigidity). The following steps are permitted if the dose is decided to be reduced: Patients allocated to 7.5 mg b.i.d. → dose is reduced to 5 mg b.i.d. Patients allocated to 5 mg b.i.d. → dose is reduced to 2.5 mg b.i.d. Patients allocated to 2.5 mg b.i.d. → dose is maintained (i.e. 2.5 mg b.i.d.). Patients allocated to placebo b.i.d. → placebo b.i.d. is maintained.

	If parkinsonism is still increased following this dose reduction, the patient and Investigator need to decide if the patient could continue with the same dose in the study (since the dose cannot be reduced further) or if the patient have to withdraw the IMP and the study. Dose reduction will be managed through the IRS system.
Patient motor function review performed at Visit 3 (Day 28 ±4 days)	This review is based on the 24-hour patient home diaries completed in the week prior to Visit 3 and the MDS-UPDRS part II assessment completed during site Visit 3. Diaries and MDS-UPDRS data are reviewed and compared to baseline. If there is a clinically relevant increase in OFF-time, the Investigator must determine if the increase has been consistent over time and if it is predominantly related to non-motor or motor OFF-time (according to the Investigator's clinical judgement). Evaluation of results from MDS-UPDRS part 2 (M-EDL) should be weighted in the decision. Adherence to prescribed antiparkinsonian medications should also be reviewed. Should a consistent increase in motor OFF-time, and/or a clinically significant worsening of mobility due to parkinsonism be assessed as likely due to the IMP, the dosing should be reduced by 2.5 mg b.i.d. at this visit. If the patient has already had a dose reduction prior to Visit 3, the dose cannot be reduced further at this visit, and the Investigator must determine whether the patient can continue in the study (i.e. continue in the study with the same dose). Other AEs not relating to the core symptoms of parkinsonism (such as, fatigue, headache, dystonia and other) do not qualify for dose reduction.

The reason for any dose adjustments must be recorded in the CRF. There will be no treatment with mesdopetam available after end of study participation.

9.3. Packaging and labelling

Finished product of IMP (active drug and placebo) will be packed and labelled by Catalent Pharma Solutions.

Labels will comply with applicable Good Manufacturing Practice (GMP) requirements (EudraLex Volume 4, Good manufacturing practices, ANNEX 13, Manufacture of Investigational Medicinal Products) and applicable local regulatory guidelines. Labels will be translated into local languages.

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

9.4. Blinding and randomization

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 mesdopetam and placebo (capsules of mesdopetam and placebo will be of identical appearance.)

At the baseline visit (Visit 1, Day 1) patients will be randomized 1:1:1:1 to receive one of three doses of mesdopetam (2.5 mg, 5 mg or 7.5 mg) or placebo b.i.d.

During the first week (Day 1 evening dose to Day 9 morning dose) a run-in phase with either 5 mg mesdopetam or placebo b.i.d. will take place, during which all patients allocated to mesdopetam will receive 5 mg mesdopetam b.i.d. and patients allocated to placebo will receive placebo b.i.d. At Visit 2 (Day 9), patients will receive mesdopetam 2.5 mg, 5 mg or 7.5 mg or placebo b.i.d., as randomized.

Randomization will be performed via a web-based Interactive Response System (IRS), using a dynamic balancing (minimization) algorithm. Randomization will be stratified by average (based on at least two valid home diaries) of <6 daily hours or ≥6 hours of daily ON-time with troublesome dyskinesia at baseline.

During the one-week run-in phase, the IRS system will ensure all patients allocated to mesdopetam treatment will receive 5 mg mesdopetam b.i.d, followed by the randomized dose during the treatment period. Patients allocated to placebo will receive placebo during the first week run-in and then continue placebo during the whole treatment period. Any dose reduction will also be managed through the IRS system to ensure that blinding is maintained.

Interactive Randomization System (IRS):

The IRS will manage the randomization, stratification 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 will be used to track patient activities in real time throughout study visits. Real-time web reports and alerts platform (such as email and fax) give access to compliance feedback for continuous transparency of study progress. Patient unblinding is also contained within the IRS system to allow the unblinding of patients for safety purposes within the protocol via web or phone. If emergency unblinding is required, this responsibility lies solely with the Investigator. Unblinding for other safety 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

Minor increases in prolactin levels may be present in participants randomized to mesdopetam. It should be noted that this elevation in prolactin is not expected to be clinically significant but could be potentially detectable if comparing Visit 5 (EOT) results to screening. For this reason, prolactin is not included in the safety lab measurements at Visit 4 and laboratory analysis results for the prolactin value at Visit 5 will be blank (i.e. not revealed to the Investigator).

PK Samples

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

Breaking the Blind

Mesdopetam and placebo (capsules of identical appearance.) will be dispensed in identical containers according to a blinded randomization scheme. Study patients, Investigators, study staff and the Sponsor will remain blinded to the randomization 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 an SAE, 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 have access to the IRS system with the permissions 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 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.

9.5. Treatment compliance and accountability

Patients will be instructed to bring the IMP to the study site at each applicable visit and treatment compliance will be checked. If a subject shows significant non-compliance (<80% compliance) between any two scheduled visits, Medical Monitor should be contacted for further assessment. In the event that a subject is permanently unable to return study drug to the site (i.e. drug is lost, destroyed, or discarded), the subject testimony is to be used in determining compliance.

Unused medication and empty containers will be returned to the study site at each applicable visit. The investigators will maintain a Drug dispensing log detailing the dates and quantities of IMP received, dispensed to and used by each patient as well as IMP returned or destroyed at the end of the study. Any discrepancies between dispensed and returned IMP must be explained and documented. Products deliberately and/or accidentally destroyed by the investigator/pharmacy/Catalent or the patient must be accounted for.

9.6.Drug storage

The IMP should be stored at room temperature (not to exceed +30ºC/+86ºF).

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

10.STUDY PLAN

10.1. Continuous Assessments

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

- AEs including SAEs
- Concomitant Medications
- IMP compliance

10.2. Screening (-56 to -10 days prior to randomization)

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)
- Hoehn and Yahr scale
- Concomitant Medications
- Height
- Weight
- Vital Signs (including supine/standing BP)
- Physical Examination
- 12-lead ECG (triplicates separated by at least one minute)
- Haematology/Serum Chemistry/Coagulation
- Dipstick Urinalysis
- Serum Pregnancy Test (if applicable)
- MDS-UPDRS question 4.2
- 24-hour patient home diary completion training (minimum 2.5 hours). Could be done either at the screening visit or during a separate scheduled visit after receipt of the screening lab results and prior start of the baseline home diary completion period. An approved 24-hour diary trainer must perform the diary concordance session and the patient must achieve at least 75% overall diary concordance including at least one OFF interval (see section 11.2.3.1).

- Three 24-hour patient home diaries are handed out. Patients will be instructed to complete 24-hour home diaries for assessment of daily motor function on three days in the week before Visit 1 and bring the completed diaries to the clinic (see section 11.2.3.1. Set dates for the patients to fill in the diaries to be decided.
- MMSE
- AEs/SAEs

- **General Practitioner Letter**

If appropriate, the patient's General Practitioner will be informed of the patient's entry into the clinical trial.

10.3. Phone calls (-9 to -1 days prior to randomization)

Several phone calls will take place during the baseline diary completion period to remind the patient about the 24-hour home diary completion.

- Three 24-hour patient home diaries to be completed during the week (-9 to -1 days) prior Visit 1. Clinic to call the patient the working day before the first 24-hour diary completion period, as a reminder, and the working day after the last 24-hour diary completion period to encourage compliance. Screen failed patients will not complete any diaries.
- Concomitant Medications
- AEs/SAEs

10.4. Visit 1 (Baseline, Day 1)

Inclusion and Exclusion criteria will be re-assessed. Eligible patients will be randomized to either trial drug (mesdopetam) or placebo.

The following procedures and assessments will be carried out at Visit 1:

- Inclusion/Exclusion criteria
- Concomitant Medications
- Vital Signs (including supine/standing BP)*
- 12-lead ECG (single assessment)*
- Haematology/Serum Chemistry/Coagulation*
- Dipstick Urinalysis*
- Serum Pregnancy test (if applicable)
- MDS-UPDRS (all parts)
- Modified UDysRS (part 1, 3 and 4)
- Three completed 24-hour patient home diaries collected and assessed for eligibility
- Three empty 24-hour patient home diaries handed out
- CGI-S
- C-SSRS
- AEs/SAEs
- Randomization. Managed through IRS system.
- Dispense IMP. First dose of IMP to be taken in the evening at Day 1.

* If 29 days or more between Screening Visit and Visit 1 (Baseline)

- **Patient Information Card**

All study patients randomized 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

10.5. Visit 2 (Day 9 + 2 days)

The following procedures and assessments are to be carried out at Visit 2:

- Allocation of randomized dose of mesdopetam/placebo. Managed through IRS system.
- Dispense and collect empty bottle of IMP
- Concomitant Medications
- AEs/SAEs
- IMP compliance

10.6. Phone call (Day 14 ± 2 days)

The purpose of the phone call is to check the general status of the patient. The following procedures and assessments are to be carried out during the phone call:

- Concomitant Medications
- AEs/SAEs
- IMP compliance

10.7. Phone calls (Week 3, Day 21 ± 2 days)

Several phone calls will take place during Week 3 to remind patients about the 24-hour patient home diaries completion and to check the general status of the patient.

- Three 24-hour patient home diaries to be completed during the week prior Visit 3. Clinic to call the patient the working day before the first 24-hour diary completion period, as a reminder, and the working day after the last 24-hour diary completion period to encourage compliance.
- Concomitant Medications
- AEs/SAEs
- IMP compliance

10.8. Visit 3 (Day 28 ± 4 days)

The following procedures and assessments are to be carried out at Visit 3:

- Concomitant Medications
- Vital signs (including supine/standing BP)
- Urine pregnancy test (if applicable)
- MDS-UPDRS part 2 (M-EDL) and part 4 questions 4.1 and 4.2
- Modified UDysRS (part 1, 3 and 4)
- Three 24-hour patient home diaries collected
- Three empty 24-hour patient home diaries handed out

- Patient motor function review (see Table 3)
- CGI-S
- C-SSRS
- AEs/SAEs
- Dispense IMP
- IMP compliance

10.9. Phone calls (Week 7)

Several phone calls will take place during Week 7 to remind about the 24-hour patient home diary completion and to check the general status of the patient.

- Three 24-hour patient home diaries to be completed during the week prior Visit 4. Clinic to call the patient the working day before the first 24-hour diary completion period, as a reminder, and the working day after the last 24-hour diary completion period to encourage compliance.
- Concomitant Medications
- AEs/SAEs
- IMP compliance

10.10. Visit 4 (Day 56 ± 4 days)

The following procedures and assessments are to be carried out at Visit 4:

- Concomitant Medications
- Vital signs (including supine/standing BP)
- 12-lead ECG
- Haematology/ Serum Chemistry (prolactin should not be included) /Coagulation
- CYP2D6 genetic testing. Note: A genetic ICF must be signed prior testing.
- Dipstick Urinalysis
- Urine pregnancy test (if applicable)
- MDS-UPDRS (all parts)
- Modified UDysRS (part 1, 3 and 4)
- Three 24-hour patient home diaries collected
- Three empty 24-hour patient home diaries handed out
- CGI-S
- C-SSRS
- PK sample 15 min pre-dose and approximately two hours (± 15 min) post dose. Patient need to bring the IMP morning dose to the site.
- AEs/SAEs
- Collect empty bottle of IMP
- IMP compliance

10.11. Phone calls (Week 11)

Several phone calls will take place during Week 11 to remind about the 24-hour patient home diary completion and to check the general status of the patient.

- Three 24-hour patient home diaries to be completed during the week prior Visit 5. Clinic to call the patient the working day before the first 24-hour diary completion

period, as a reminder, and the working day after the last 24-hour diary completion period to encourage compliance.
- Concomitant Medications
- AEs/SAEs
- IMP compliance

10.12. Visit 5 (End-of-Treatment, Day 84, -2 to 0 days)

The following procedures and assessments are to be carried out at Visit 5:
- Concomitant Medications
- Vital signs (including supine/standing BP)
- Physical Examination
- 12-lead ECG
- Haematology/Serum Chemistry (including prolactin) /Coagulation
- Dipstick Urinalysis
- Serum Pregnancy test (if applicable)
- MDS-UPDRS (all parts)
- Modified UDysRS (parts 1, 3 and 4)
- Three 24-hour patient home diaries collected
- CGI-S
- C-SSRS
- PK sample 15 min pre-dose and approximately two hours (± 15 min) post dose
- MMSE
- AEs/SAEs
- IMP compliance
- Collect empty bottle of IMP

10.13. Visit 6 (Follow Up 5-8 days after End-of-Treatment)

The following procedures and assessments are to be carried out at Follow Up:
- Concomitant Medication
- Weight
- Vital Signs (including supine/standing BP)
- Physical Examination
- 12-lead ECG
- Haematology/Serum Chemistry (including prolactin)/Coagulation
- Dipstick Urinalysis
- AEs/SAEs

NOTE: Patients that discontinue IMP early for any reason should if possible, undergo Visit 6 assessments 5-8 days after the last dose of IMP.

10.14. Early Termination Visits

Patients have the right to withdraw from the trial at any time and for any reason. If a patient discontinues the IMP early, a safety follow-up visit (according to follow-up, Visit 6) should if possible be scheduled within 5-8 days after the last intake of the IMP.

11.STUDY PROCEDURES / EVALUATIONS

Signed informed consent must be obtained before any screening procedures are initiated. The informed consent procedure is further described in Section 17.

11.1. Clinical evaluations

11.1.1. Demographics/Medical History

The following demographic data will be recorded: gender, age, ethnicity and race.
Medical/surgical history including smoking will be obtained by interview in order to verify that the eligibility criteria are met.
Diagnosis of PD must have been made as per the UKPDS Brain Bank Clinical Diagnostic Criteria.
The duration of the patients' PD will be assessed by the following endpoints:

- Years from diagnosis
- Years from symptom onset

11.1.2. Hoehn and Yahr scale

The Hoehn and Yahr scale is a five point scale for describing the severity of Parkinson's disease. The scale will be administered at screening and a Hoehn and Yahr stage of 5 is a study exclusion criterion.

Stage	Hoehn and Yahr Scale
0	Asymptomatic
1	Unilateral involvement only
2	Bilateral involvement without 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

11.1.3. Height/Weight

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

11.1.4. 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.

11.1.5. Vital Signs

Pulse and systolic/diastolic BP will be measured in supine position after five minutes of rest and then after 1 minute and 3 minutes in standing position, without sitting in between. Any symptomatic orthostatic reaction will be noted in the CRF (no/yes).

11.1.6. Resting 12-lead ECG

12-lead ECGs will be recorded in a supine position after five minutes of rest. PR, QRS, QT, and QTcF intervals will be recorded. Three ECGs will be recorded at screening visit, separated by at least one minute. Single ECG for all other visits. The time of the ECG recordings must be noted in the CRF.

11.2. Evaluations & assessments

11.2.1. Clinical laboratory evaluations

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

Any remaining laboratory samples will be disposed of after analyses.

Blood samples for analysis of serum chemistry, haematology and coagulation parameters will be collected at screening, Visit 1 (if 29 days or more between the Screening Visit and Visit 1), Visit 4, 5 and 6 and sent to the certified Central laboratory for analysis. Screening laboratory test results will be taken into consideration for assessing subject's eligibility. Urine analysis will be performed at the clinic using dip sticks.

The following safety laboratory variables will be assessed:

Clinical Chemistry	**Haematology**
Alanine aminotransferase (ALT)	Basophils
Alkaline phosphatase (ALP)	Eosinophils
Amylase	Haematocrit
Aspartate aminotransferase (AST)	Haemoglobin (Hb)
Calcium	Lymphocytes
Albumin	Monocytes
Total bilirubin	Neutrophils
Creatinine	Platelet count
Creatinine kinase	Red blood cell (RBC) count
Lactate dehydrogenase (LDH)	White blood cell (WBC) count with differential count
Random Glucose	
Total cholesterol	**Coagulation**
Magnesium Phosphate	International Normalized Ratio (INR)
Potassium	**Urinalysis (dip stick)**
Prolactin*	Glucose
Sodium	Hb/erythrocytes
Thyroid-stimulating hormone (TSH)	Nitrite

Triiodothyronine (Free T3)	Protein
Thyroxine (T4)	U-hCG***
Triglycerides	
Urea nitrogen	**CYP2D6 genetic testing****
human Chorionic Gonadotropin (hCG)**	

NOTE: *Prolactin at screening, Visit 1 (if lab sampling is applicable), Visit 5 and Visit 6

**hCG is only required for women with childbearing potential (as defined in section 8.1). S-hCG at Screening, Baseline and Visit 5 (if applicable)

***U-hCG is only required for women with childbearing potential (as defined in section 8.1). U-hCG at Visit 3 and Visit 4 (if applicable)

****CYP2D6 genetic test at Visit 4 (optional testing). Signed genetic informed consent required.

11.2.2. Columbia Suicide Severity Rating Scale (C-SSRS)

Suicidality will be assessed by trained study personnel using the C-SSRS [9].
The C-SSRS is a standardized suicidality rating system conducted by a certified rater. The interview measures presence of suicidality and consists of 4 categories: suicidal ideation, intensity of ideation, suicidal behaviour, and actual/potential lethality. This scale will be used for baseline as well as to assess for the occurrence of any suicidal ideation and/or behaviour during the study.

11.2.3. Assessments related to the primary endpoint

11.2.3.1. 24-hour patient home diary

Home diaries have gained wide acceptance as endpoints for clinical development of therapeutics aiming to reduce treatment-related motor complications [10]. Motor fluctuations and dyskinesia are associated with compromise in activities of daily living (ADL) 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 (without troublesome dyskinesia) or ON with troublesome dyskinesia. The patient will also denote the time when he or she has been asleep.

It has been demonstrated that OFF-time and ON-time with troublesome dyskinesia are generally considered by patients to be “bad time” with regard to motor function, whereas ON-time without troublesome dyskinesia are generally considered to be “good ON-time” [11].

In general, an “OFF” time reduction or “good ON-time” increase of 1 hour may be considered clinically significant and has been used as an assumption in power calculations in clinical trials [10]. Therefore, it can be assumed that shift towards more “good ON-time” of a minimum of 1-hour daily represents a clinically meaningful effect, considering the total time spent in the daily ON state (ON with and without troublesome dyskinesia) is not negatively affected by the treatment.

For this trial, patient diary concordance training to improve accuracy and compliance is essential. Patients will be instructed and trained on how to complete the home diary at the screening visit or during a separate scheduled visit after receipt of the screening lab results and

prior start of the baseline diary completion period. The Investigator must ensure that each patient understands how and when to complete diaries before leaving the clinic.

The patient will receive instruction on how to complete the 24-hour home diary, including the definitions of ON and OFF. The definitions of ON and OFF will be reviewed, including ON time according to dyskinesia categories "without troublesome dyskinesia" and "with troublesome dyskinesia", with emphasis on the need for the patient to be consistent in their use of the definitions when rating their status in the 24-hour home diary during the study.

When instructions appear to have been understood by the patient, a diary concordance session will be initiated during which the patient and the diary trainer/rater will concurrently complete separate training diaries for at least 4 consecutive half-hour intervals (minimum 2 hours). During the diary concordance session, the patient must experience both ON and OFF. The 2-hour session may be extended, as needed, so that the patient experiences OFF. If the patient is OFF at the beginning of the diary concordance session, they may be administered their next dose of levodopa-containing medication in order to experience ON.

When the session is completed, the diary trainer/rater will review and assess the patient's diary concordance with the trainer/rater. The patient is required to reach at least 75% overall diary concordance with the trainer/rater including at least one OFF interval. If the concordance criteria are not achieved, the trainer/rater will schedule a second diary training and diary concordance session within the 8-week screening period and prior start of the baseline diary completion period, unless the patient declines further participation.

Following successful completion of the 24-hour home diary training and diary concordance session, patients will be required to complete 24-hour home diaries on three prespecified days (24-hour periods starting at midnight) prior the baseline visit (Visit 1).

Patients that have not been able to complete at least two valid diaries at baseline (Visit 1) will not be included. Patients not completing at least two valid diaries at Visit 1 may be rescheduled for Visit 1 following additional diary completion training. For diaries completed prior to Visits 3-5, one valid diary is required for each visit for data to be captured. It is important that the Investigator take all possible measure for patients to complete all three of the weekly diaries.

The 24-hour home diaries will be captured on three days during one week at the baseline diary completion period (prior to Visit 1) and Weeks 3, 7, and 11 (i.e. the week's prior Visits 3, 4 and 5). Set dates for the patient to complete diaries are to be agreed in advance. The clinic will call the patient the working day before the first 24-hour registration period, as a reminder, and the working day after the last 24-hour registration period to check for diary completion.

At Visit 1, 3, 4 and 5, the Investigator (or designee) will register the data from all valid diaries in the appropriate sections of the CRF.

A valid diary will not have ≥2 hours of invalid data entries (i.e. ≥4 invalid entries) over a given 24-hour period. An invalid diary entry is defined as more than one entry recorded in each half-hour interval, an unreadable entry, or the absence of an entry in each half-hour interval. The average diary information from 3 valid diaries (if available) for each visit will be used to calculate diary-based efficacy endpoints. If there are only 2 valid diaries for a visit, then the average information from the 2 valid diaries will be used. If only one diary is valid, information

from the single valid diary will be used. If no valid diaries are available for a patient visit, then the diary information is considered missing.

11.2.4. Assessments related to the secondary and other endpoints

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

The MDS-UPDRS parts 1-4 will be administered at Visit 1, Visit 4 and Visit 5 (Day 84, EOT). Additionally, MDS-UPDRS part 4 (question 4.2) will be administered at screening and part 2 (M-EDL) and part 4 (questions 4.1 and 4.2) will be administered at Visit 3. The MDS-UPDRS part 3 should be administered with the patient in ON-phase. The ON-phase 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-phase agrees with the patient's perception of best mobility. Preferably, the same rater should complete MDS-UPDRS part 3 at Visit 1 (baseline), Visit 4 and Visit 5 (EOT).

11.2.4.2. Modified Unified Dyskinesia Rating Scale (UDysRS)

Assessment of ON-phase dyskinesia will be administered according to the modified UDysRS, (i.e. parts 1, 3 and 4) at Visit 1, 3, 4 and 5 (Day 84 EOT) to assess impairment and disability of ON-phase dyskinesia. Rating of patient ON-dyskinesia will be performed in the ON-phase at so called peak dose dyskinesia following a regular levodopa dose at a similar time of day (± 1 hour), preferably before noon. The timing of the preceding levodopa intake and the subsequent assessment must be noted in the CRF. Likewise, it is important that morning dose of IMP is taken at the same time in the morning for these visits. The timing of morning intake of the IMP should be noted in the CRF.

Dyskinesia assessment should be administered by a specialist physician (or specialist nurse) with previous experience using the scale in movement disorders and who has received appropriate training.

The objective evaluation of dyskinesia impairment and disability will be captured while observing the patient in the following situations and scoring performed according to rating scale instructions [12]:

1. Communication: Instruct patient to look at evaluator 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.

11.2.4.3. Clinical Global Impression of Severity (CGI-S)

Two different assessments of the CGI-S will be administered at Visits 1 and Visits 3-5.

The first CGI-S assessment is related to the patient's physical functioning related to PD. The Investigator will rate, considering his or her total clinical experience with the PD population,

the severity of the patient's disease, based on a 1-7 point weighted scale ranging from "normal", not at all ill" (1) to "among the most extremely ill patients" (7).

The second CGI-S assessment is related to the patient's ON-phase dyskinesia. The Investigator will rate, considering his or her total clinical experience with the PD population, the severity of the patient's ON-phase dyskinesia, based on a 1-7 point weighted scale ranging from "normal", not at all ill" (1) to "among the most extremely ill patients" (7).

11.2.4.4. Mini-Mental State Examination (MMSE)

The MMSE will be administered at screening and at Visit 5 (EOT).

11.2.4.5. Pharmacokinetic samples

Venous blood samples (approximately 5 mL) for the determination of concentrations of mesdopetam and its metabolites IRL902 (N-dealkylated) and IRL872 (acetylated) in plasma will be collected 15 minutes before and two hours (for trough and C_{max}) after IMP administration at the specified time-points (Visits 4 and 5). 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 mesdopetam and its metabolites in plasma will be analyzed 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.

11.2.5. Specimen preparation, handling and shipping

11.2.5.1. Instructions for specimen preparation, handling and storage

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

Any remaining laboratory samples will be disposed of after analyses.

If a patient withdraws consent to the use of biological samples donated, the samples will be disposed of/destroyed, if not already analyzed 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 Laboratory Manual.

12.ADVERSE EVENT REPORTING

12.1. Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and SAEs. Open-ending and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problem since your last visit /contact?"
- "Have you taken any new medicines other than that are provided for this study since your last visit/contact?"

12.2. 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 AE 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 IMP.

Adverse Drug Reaction (ADR)

Untoward and unintended responses to an IMP related to any dose administered.

All AEs 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

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

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 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 12.5) and are both unexpected and serious. The Sponsor or designee is responsible for determining whether a reported SAE meets the definition of a SUSAR.

12.3. Expectedness

An expected adverse reaction is an adverse reaction, the nature or severity of which is consistent with the applicable product information (Investigator's Brochure [8]), 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 PD (Phase 2a), AEs are likely to predominantly be CNS related. Adverse reactions in patients with advanced PD are listed below:

Table 4: Potential AEs associated with mesdopetam 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			

Nervous system	Cardiac	General disorders and administration site condition	Musculoskeletal and connective tissue disorders
Concentration difficulties			
Gait freezing			
Fall			

12.4. Intensity of adverse event

The grading of the severity of AEs will follow the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [13]. 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 AE 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.*

12.5. Causality assessment

The Investigator must assess the causal relationship between an AE and the IMP using the definitions below and record it on the AE Form in the CRF as well as on the SAE 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.

12.6. Action taken regarding the IMP

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

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

12.7. Outcome

The Investigator must assess the outcome of an AE using the definitions below and record it on the AE 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*

12.8. Recording adverse events

AEs 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 AEs starts after the patient signs the ICF 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 must be followed up until resolution or the follow-up assessment, whichever comes first.

AEs must be recorded on an AE 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 times (only applicable for AEs with start date on the day of first IMP administration); intensity; causal relationship to IMP; action taken, and outcome.

If the AE is serious, this must be indicated on the AE Form in the CRF. Furthermore, the Investigator must fill out the SAE Report Form and report the SAE to Worldwide Clinical Trials as described in Section 12.9.

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 AE 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.

It is the responsibility of the Investigator to follow up on all SAEs until the patient has recovered, stabilized, 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.

The SAE reporting period starts at the time of the signature of the ICF until 30 days after the last follow-up visit. 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.

12.9. Serious adverse Events

All SAEs must be reported to the Clinical Research Organisation (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 Trial Master File (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 Worldwide Clinical Trials:
Email: drugsafety@worldwide.com

Fax number: Fax US: 1-866 387 5539, Fax ROW: +44 208 043 4813

Pregnancies occurring during the study must be reported immediately by email or fax using the Pregnancy Form.

The Sponsor and Worldwide Clinical Trials will keep the Investigator informed of all SUSARs 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, IECs/IRBs 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 IECs/IRBs will be notified as soon as possible and within three days of the decision.

The Sponsor will submit Safety Reports to the CAs and IEC/IRBs annually or more frequently if so requested.

12.10. Reporting of SUSARs

Worldwide Clinical Trials will report SUSARs occurring in the trial to the CA and to the relevant Independent Ethics Committees (IEC(s))/Institutional Review Boards (IRB(s)) in line with the applicable regulatory requirements.

13. 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. Computerized 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.

Quality control check of the data entry will be performed on the CRFs.

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

13.1. Trial documentation and trial confidentiality

13.1.1. Trial documentation, CRFs and document keeping

The Investigator must generate and maintain adequate records (patient medical records, CRFs, 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-randomization period). CRFs are to be completed either at the time of the patient's visit or as soon as possible after the visit (no later than 72 hours) 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 (SDV) 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 author of an entry in the source documents must 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. The possibility to access source documents during remote monitoring, is regulated as per local requirements.

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. Source documents will be created and maintained in accordance with ALCOA-C (Attributable, Legible, Contemporaneous, Original, Accurate, Complete) criteria that is the standard for data integrity.

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 authorized 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 AE, reasonable efforts must be made to clearly document the outcome.

The Principal Investigator will allow authorized 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.

13.1.2. Confidentiality of trial documents and patient records

The Investigator must ensure the patients' anonymity is maintained. On CRFs or other documents submitted to the CRO/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 the CRO /the Sponsor/third party contractor, e.g. patients' written consent forms, must be maintained by the Investigator in strict confidence.

14. 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 utilized, planned analyses (with any sensitivity analyses), together with master table and listing shells and outline figures for reporting.

14.1. General considerations

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

All data will be described and analyzed according to allocated treatment group (mesdopetam 2.5 mg, 5 mg, 7.5 mg and placebo b.i.d.), and visit. In addition, PK data will also be described and analyzed according to time-point, as appropriate (pre and post dose). Each data summary will be supported by individual patient listings.

All quantitative, continuous data will be summarized by the number of non-missing observations, mean, median, standard deviation, and minimum and maximum for both actual values and, for all data except PK assessments, change from baseline data. All categorical (qualitative binary, ordinal) data will be summarized by presenting the frequency and percent. Percentages will be based on the number of non-missing observations or the patient population unless otherwise specified. For each variable, all categories will be shown. Zero frequencies (but not the percent) within a category will be presented.

Statistical methods applied will be appropriate to the nature and distribution of the data. A (two-sided) 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 (mesdopetam 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.

Baseline will be defined as the last non-missing assessment (either scheduled, unscheduled or repeat) that is completed prior to dosing. Baseline average daily time spent for each patient will be calculated by taking the arithmetic mean of daily time spent in each state from the three 24-hour patient home diaries completed before the baseline visit.

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.

14.2. Sample size/power calculation

140 patients (35 per group), are enough to demonstrate a treatment difference of 3 hours, pooled standard deviation 3.5, between a single dose level of active treatment and control (i.e. 2.5 mg, 5 mg or 7.5 mg mesdopetam vs placebo b.i.d.) for the primary endpoint with 92% power and type 1 error rate 0.05 (two tailed). The sample size calculation is based on an expected dropout rate of 10%. The Sponsor will evaluate the actual dropout rate after 70 randomized patients have completed Visit 3 (week 4) and can, if the dropout rate in the study is higher than expected, decide to increase the sample size to a total of maximum 154 randomized patients (+10%).

14.3. Analysis sets

14.3.1. Safety analysis set

The Safety Analysis Set (SS) will include all randomized patients who received at least 1 dose of IMP. All safety and tolerability evaluations will be presented by the treatment received for the SS population.

14.3.2. Full analysis set

The Full Analysis Set (FAS) will include all randomized patients who received at least 1 dose of IMP and who provided at least one post baseline assessment. All efficacy analyses will be presented by allocated treatment for patients in the FAS population.

14.3.3. Per protocol analysis set

The Per Protocol Analysis Set (PPS) will consist of patients from the FAS but exclude those with major protocol violations. Situations which constitute a major protocol violation may include (but are not limited to) those subjects who:

- Did not satisfy all of the inclusion/exclusion criteria
- Any subjects with treatment administration errors
- Any subjects taking inadmissible concomitant medication

Patients who are to be included in and excluded from the PPS will be identified and listed following a Blind Data Review (BDR) performed prior to the conclusion of the clinical investigation, database lock and unblinding. Any deviation considered to have a serious impact on the efficacy results will lead to the relevant subject being excluded from the PPS.

14.4. Study population

All basic information regarding the sample of patients recruited to represent the PD population with dyskinesia will be summarized. This will include all assessments performed prior to the start of treatment (screening) including demographics (gender, age, ethnicity and race), medical history (including smoking), 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.

14.5. 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 randomization process.

14.6. Treatment compliance

At the conclusion of treatment period an assessment of compliance with the required dosing schedule will be performed and summarized by treatment group. Compliance (%) will be calculated by the following: ((total prescribed - total returned)/total prescribed*100%).

14.7. Efficacy endpoints

The primary efficacy variable is the 24-hour patient home diaries, total daily hours of ON-time without troublesome dyskinesia. Improvement is defined as an increase in the daily hours spent in this motor state.

The 24-hours motor function is recorded in 30-minute intervals, beginning at midnight. For each 30-minute interval the patient will rate the state he or she has predominantly 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.

The secondary efficacy variables involve a subset of the UDysRS, MDS-UPDRS and the 24-hour patient home diaries (Table 5).

UDysRS has two primary sections: Historical and Objective Part. In this study the Part 1 of the Historical part will be administered and the part 2 will be omitted.

The full Objective part will be administered: [Part 3 (Impairment) and Part 4 (Disability)] including 11 items with each item having 0-4 ratings, where 0 = normal, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe. The subtotals of the Objective parts are summed to give an overall score.

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 secondary efficacy rating scales used, a higher score indicates worse symptoms.

Table 5: Key secondary endpoints

Scale	Component	Attribute
UDysRS	Sum score (parts 1, 3 + 4)	Sum score
UDysRS	Sum score (parts 1b and 4)	Sum score
MDS-UPDRS	Part 4 Question 4.2	Score
	Part 2 (M-EDL)	Total score
24-hour patient home diaries	OFF-time	Total daily hours
24-hour patient home diaries	ON-time with troublesome dyskinesia	Total daily hours

Table 6: Other endpoints

Scale	Component	Attribute
CGI-S (ON-phase dyskinesia)	Clinicians assessment	7-point scale
CGI-S (Parkinson's disease severity)	Clinicians assessment	7-point scale
24-hour patient home diaries	ON-time (with and without troublesome dyskinesia)	Total daily hours

MDS-UPDRS	Part 3 (Motor Examination)	Total score
MDS-UPDRS	Part 1 (Non-Motor Aspects of Experiences of Daily Living (nM-EDL)	Total Score
MDS-UPDRS	Part 4 (Motor Complications)	Total score
MDS-UPDRS	2.13 (Freezing) + 3.11 (Freezing of gait) sum score	Sum score
MDS-UPDRS	Question 1.6 (Features of dopamine dysregulation syndrome)	Single item score
MMSE	Clinicians assessment	Total score

All the outcome measures are measured at Baseline and at Visit 5 or during the intervening period for the 24-hour patient home diaries. In addition, UPDRS Part IV Question 4.1 and 4.2, UDysRS, CGI-S, and 24-hour patient home diaries (during the intervening period) are measured at Visit 3 and Visit 4.

The change from Baseline to EOT (Visit 5, Day 84) for each patient will be derived for each endpoint and each endpoint summarized descriptively (according to treatment group and day of assessment (Baseline, EOT). The EOT/last assessment available will be analyzed as Interval data. For assessments performed at Visit 3 and Visit 4, the change from Baseline to Visit 3 and Visit 4 for each patient will also be derived.

14.8. Pharmacokinetic endpoints

PK variables measured in plasma include: mesdopetam parent drug and two of its metabolites, IRL902 (N-dealkylated) and IRL872 (acetylated).

Samples obtained pre-dose and 2 hour post dose (as an estimate of C_{max}) on Day 56 and Day 84 will be summarized by timepoint, visit, and mesdopetam dose level using descriptive statistics: number (n), arithmetic mean, standard deviation, minimum, median, maximum, geometric mean, and coefficient of variation (CV%).

If appropriate, the PK relationship between the treatment doses and plasma exposure (based on trough concentrations and C_{max}) of mesdopetam and its metabolites will be assessed using a power model.

Details of the PK analysis will be included in the SAP.

14.9. Efficacy analyses

All efficacy analyses will be performed by allocated treatment group for patients in the FAS.

MMRM analysis will allow estimation of the size of treatment effects as well as magnitude of differences between the active treatment and control (mesdopetam 2.5 mg, 5 mg, 7.5 mg vs placebo).

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.

14.9.1. Primary analyses

Per protocol, patients will be required to complete three 24-hour patient home diaries prior to Baseline (Visit 1), and Visits 3, 4 and 5 (EOT). Average daily ON-time without troublesome dyskinesia will be calculated by taking the arithmetic mean of daily ON-time without troublesome dyskinesia reported in each individual diary at each visit. Change from Baseline will be calculated by subtracting the mean values at each visit (Visits 3, 4 and 5 (EOT)) from the Baseline mean value for each individual patient.

The primary endpoint will be analyzed using a mixed model repeated measures (MMRM) analysis that includes all average daily ON-time without troublesome dyskinesia changes from baseline to Week 4 (Visit 3) through to Week 12 (Visit 5/EOT) for all patients in the FAS. The model will include randomized treatment, visit (Visits 3, 4 and 5/EOT), and treatment by visit interaction as explanatory, fixed effect variables. Baseline value for average daily hours of ON-time without troublesome dyskinesia will be included as a continuous covariate along with the baseline stratification factor of daily hours spent in ON-time with troublesome dyskinesia (<6 hours and ≥6 hours).

The treatment by visit interaction will remain in the model regardless of significance. The patient effect will be assumed to be random and an unstructured covariance structure will be assumed for within patient variation.

The main comparison will be a contrast between treatment groups at EOT (Visit 5, Week 12). Estimates for each individual dose level, as well as all active doses grouped vs. placebo will be obtained from the model. Least squares means, 95% confidence intervals, and p-values of the treatment comparisons along with basic arithmetic summary statistics (mean, median, standard deviation, min and max) will be provided.

14.9.2. Sensitivity analyses

Sensitivity analyses will be performed for the Primary efficacy endpoint to assess the robustness of the observed result. In the first instance, the Primary analysis will be repeated for all subjects without a major protocol deviation, followed by analysis by treatment received following Visit 3 (Week 4, Day 28) to EOT. An alternative analysis using ANCOVA may also be performed.

14.9.3. Handling of dropouts and missing observations

Methods to assess the impact of missing data (including last observation carried forward or multiple imputation [14]) may also be applied where appropriate. Full details will be given in the study Statistical Analysis Plan (SAP).

14.9.4. Multiplicity

Multiple dose levels have been included in the study design to evaluate the dose response relationship of mesdopetam with the hypothesis that the 7.5 mg b.i.d. dose will be the most efficacious of the dose levels studied.

In order to control the overall Type I error rate at 5% for the Primary efficacy analysis, a fixed sequence testing procedure will be applied. Each test will be performed at 5% in decreasing dose sequence (mesdopetam 7.5 mg b.i.d, 5 mg b.i.d and 2.5 mg b.i.d vs placebo), until a null hypothesis cannot be rejected, after which the remaining null hypotheses also cannot be rejected.

In view of the stage of development of the drug, no statistical adjustments for multiplicity of analysis testing are planned. The clinical relevance of any significant result will be discussed.

14.9.1. Secondary analyses

All secondary and exploratory efficacy endpoints (including CGI-S data) will be analyzed per the Primary efficacy endpoint for all patients in the FAS. Summary statistics (mean, median, standard deviation, min and max), least squares means, 95% confidence intervals, and p-values of the treatment comparisons will be provided for descriptive purposes.

Where appropriate, alternative methods suited to the distribution of data may be applied. Full details will be provided in the SAP.

14.10. Safety Analyses

Safety evaluations include AEs and concomitant medications reporting, complete physical examination, vital signs, 12-lead ECG (at rest), C-SSRS rating and clinical safety laboratory tests (clinical chemistry, haematology, urinalysis and coagulation). All will be presented as data summaries. No formal statistical analyses will be performed.

AEs and concomitant medications are recorded throughout the investigational period with the rest performed at screening, Visits 3, 4 and 5 and Visit 6 (follow-up) 5-8 days after last administration of IMP).

All safety and tolerability evaluations will be presented by the treatment received for the SS population.

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.

14.10.1. Extent of exposure

Duration of exposure will be calculated as the last date of dosing minus first day of dosing plus 1 and summarized by treatment group. No adjustment will be made for breaks in therapy.

14.10.2. Adverse events

All AEs will be summarized according to TEAE or NTEAEs following classification of the verbatim terms according to the MedDRA dictionary, as presented in section 12. 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 (see section 12).

14.10.3. Concomitant medications

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

14.10.4. Physical examinations

Physical examination results will be summarized as the number and percentage of patients by body system, treatment group and assessment day.

In addition, body weight measured at the follow up visit will be summarized with descriptive statistics for actual values and change from baseline by treatment group.

14.10.5. Vital signs

For BP and pulse rate, descriptive statistics of actual values and change from baseline will be summarized by treatment group and assessment day. Categorically classified (Normal/Abnormal) results will also be summarized.

14.10.6. ECG (12-Lead) at rest

ECG findings will be summarized according to actual values and change from baseline using descriptive statistics and will be presented by treatment group and assessment visit. Overall interpretation findings (Normal, Abnormal (NCS), Abnormal CS) will also be summarized.

14.10.7. Clinical laboratory tests

All haematology, clinical chemistry and coagulation laboratory tests run at the central laboratory will be summarized using descriptive statistics for actual values and change from baseline and presented by treatment group and assessment day.

Results will be classified as below, within, or above normal range, based on ranges supplied by the central laboratory used. Shift tables for baseline and follow-up measurements will be presented by treatment group and assessment visit.

Results from dipstick urinalysis will be summarized as reported on the CRF.

Unscheduled safety laboratory samples assayed at the local hospital will be listed according to site.

15. INDEPENDENT ETHICS COMMITTEE APPROVAL

The study proposal will be submitted to the IEC/IRB in accordance with the national requirements.

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

16. REGULATORY REQUIREMENTS

The Sponsor is responsible for submission of study documents to the applicable National Competent Authorities according to local regulatory requirements.

National approval must be obtained in writing from National Competent Authority before the first study patient can be recruited in a country.

Enrolment of patients will not commence until approval has been received from both the IECs/IRBs and Competent Authorities.

The study will be conducted in accordance with the Declaration of Helsinki, ICH GCP (ICH E6 (R2) and all other national requirements.

17. INFORMED CONSENT

It is the responsibility of the Investigator or an authorized 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 emphasized 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 IEC/IRB.

18. 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.

19. STUDY MONITORING AND MANAGEMENT

19.1. 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) utilized.

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.

19.2. Clinical monitoring

The study site will be periodically monitored at times agreed on by the Investigator and the Monitor based on the risk-based monitoring plan. 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 Standard Operating Procedures (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.

19.3. 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 24-hour patient home diary, MMSE, MDS-UPDRS, UDysRS, CGI-C and C-SSRS 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 IECs/IRBs, as required.

19.4. 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.

19.5. Study timetable 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 3, 2020 and to be completed by Quarter 1, 2022.

20. QUALITY ASSURANCE

Authorized representatives of Sponsor, Competent Authority (CA) or IEC/IRB may perform audits or inspections at the study site, including 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, analyzed, and accurately reported according to the Clinical Study Protocol, ICH GCP (ICH E6 (R2) guidelines and any applicable regulatory requirements. The Investigator will contact the Sponsor immediately if contacted by a CA about an inspection at the study site.

21. 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.

22. CONFIDENTIALITY

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 Investigators and any other persons involved in the study will protect the confidentiality of this proprietary information belonging to 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 the General Data Protection Regulation (GDPR) 2016/679 and other applicable regulations 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.

23. 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.

24. 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.

25. PUBLICATION OF RESULTS

25.1. Clinical study report

Sponsor will post clinical trial results in the EudraCT and ClinicalTrials.gov database within the required timeline.

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 Statistician and the Sponsor.

25.2. Annual safety report

The Sponsor will submit an annual safety report to the CA and to the IEC/IRB. 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.

25.3. 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.

25.4. 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.

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