



CONFIDENTIAL

**A RANDOMISED, PLACEBO-CONTROLLED, MULTI-CENTRE
PHASE IIB STUDY EVALUATING THE EFFICACY OF PIREPEMAT
ON FALLS FREQUENCY IN PATIENTS WITH
PARKINSON'S DISEASE**

PROTOCOL

Version:	5.0
Version date:	23-JAN-2024
Superseded version:	Not applicable
Sponsor:	Integrative Research Laboratories Sweden AB (IRLAB)
Product:	Pirepemat (IRL752) [REDACTED] [REDACTED]
Study Number(s):	IRL752C003 EudraCT number: 2019-002627-16 NCT number: NCT05258071

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PROTOCOL APPROVAL PAGE

**A randomised, placebo-controlled, multicentre phase IIb study
evaluating the efficacy of pirepemat on falls frequency in patients with
Parkinson's disease**

IRL752C003 CSP version 5.0 dated 23-JAN-2024

"I agree to the terms of this Clinical Study Protocol."

Signature:

Date:

**Chief Medical Officer
IRLAB**

Signature:

Date:

**Clinical Project Manager
IRLAB**

Signature:

Date:

Signature:

Date:

INVESTIGATOR PROTOCOL APPROVAL PAGE

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

Investigator Name:
Investigator Title:
Investigator Address:

Investigator Signature:
Date:

The following amendments have been made to the Final Clinical Study Protocol version 1.0:

Amendment No.	Date of Amendment	Revised Protocol version
1. Updates in response to VHP queries during original submission	16-Nov-2021	2.0
2. Falls will be collected using a paper diary Change in schedule of activities (assessments done at Week 12 move to Week 11 to capture clinical assessments before tapering IMP and have PK sample during full treatment) Clarification in section 19.7.4 on subgroup analysis	25-Feb-2022	3.0
3. Correction of discrepancies and clarifications and update following implementation of urgent safety measure. Removal of two safety follow-up visits (V10, 3-4 days after last dose and V11, 6-7 days after last dose).	13-Sep-2023	4.0
4. Re-estimation of sample size. Blinded review of study data shows a substantially larger than anticipated baseline fall rate in the study population. This leads to an improved signal-to-noise ratio in the analysis of treatment effect on falls frequency, and hence the planned sample size has been reduced from 165 to 120 randomised subjects. Revision of analysis model for primary endpoint. The simulations used for re-evaluation of sample size indicate that the originally proposed analysis model, negative binomial regression, while adequate if study data follows an ideal distribution, is highly sensitive to outlier data. Therefore, a non-parametric method which displays similar performance overall but is less sensitive to outliers will be used for the primary analysis. Negative binomial regression will be kept as a secondary analysis. Clarification of the primary outcome measure and revision of secondary, tertiary objectives classification. Correction of discrepancies.	23-Jan-2024	5.0

2 STUDY SYNOPSIS

Study Title	
A randomised, placebo-controlled, multicentre phase IIb study evaluating the efficacy of pirepemat on falls frequency in patients with Parkinson's disease	
Study code	EudraCT No
IRL752C003	2019-002627-16
Study period	Phase of development
Estimated date of first patient enrolled: Q1 2022 Estimated date of last patient completed: Q2 2024	Phase IIb
Study design	
This will be a randomised, double-blind, placebo-controlled multi-centre study.	
Investigator study sites	
This study will be conducted at approximately 40 study sites in approximately 5 countries.	
Objectives	
Primary objective	Primary outcome measure
To evaluate the effects of pirepemat on falls frequency as compared to placebo.	Change in falls frequency from baseline period (1 month prior to randomisation) to the end of treatment as assessed by fall diary (1 month prior to dose de-escalation).
Secondary objectives	Secondary endpoint variables
To evaluate the effects of pirepemat on Parkinson's disease motor symptoms as compared to placebo.	Change in the total score of MDS-UPDRS part 2 (M-EDL) from baseline to Week 11.
To evaluate the effects of pirepemat on apathy as compared to placebo.	Change in total score (Frequency*Severity) and Caregiver distress of NPI Item G (Apathy/Indifference) from baseline to Week 11.
Other objectives	Tertiary/exploratory endpoint variables

To evaluate the effects of pirepemat on Parkinson's disease symptoms and severity as compared to placebo.	- Change in MDS-UPDRS part I from baseline to Week 11. - Change in MDS-UPDRS part II from baseline to Week 11. - Change in MDS-UPDRS part III from baseline to Week 11. - Change in MDS-UPDRS part IV from baseline to Week 11. - Change in MDS-UPDRS part IV item 4.3 (Time spent in the off state) from baseline to Week 11. - Change in sum score of MDS-UPDRS items 2.13 (Freezing) and 3.11 (Freezing of gait) from baseline to Week 11. - Change in individual scores from baseline to Week 11 for the following MDS-UPDRS part I items: 1.2 (Hallucinations and psychosis), 1.3 (Depressed mood), 1.5 (Apathy), 1.6 (Features of dopamine dysregulation syndrome), 1.8 (Daytime sleepiness), 1.9 (Pain and other sensations), 1.13 (Fatigue). - Change in individual scores from baseline to Week 11 for the following MDS-UPDRS part II items: 2.1 (Speech), 2.12 (Walking and balance). - Change in modified Hoehn & Yahr score from baseline to Week 11.
To evaluate the effects of pirepemat on postural dysfunction as compared to placebo.	- Change in scores from baseline to Week 11 for the following tests: Single leg stance test, Tandem walking test - Change in MDS-UPDRS item 3.12 (postural stability) from baseline to Week 11.
To evaluate the effects of pirepemat on cognitive function as compared to placebo.	Change in total MoCA score from baseline to Week 11.
To evaluate the safety and tolerability of pirepemat	As measured by subject incident of treatment-emergent adverse events, clinically significant changes in vital signs

	and physical examination, clinical laboratory safety tests, and ECGs.
To examine the relationship between dose and plasma concentration of pirepemat and pharmacodynamic effects.	
Number of patients planned A total number of 120 patients randomised (40 per treatment arm) will be required. The Sponsor will evaluate the actual dropout rate after 80 randomised patients have completed Visit 5 and can, if the dropout rate at this point is higher than expected, decide to increase the sample size to a total of maximum 138 randomised patients.	
Diagnosis and main eligibility criteria Male and female patients 55-85 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 55-85 years of age, inclusive. 2. Diagnosis of idiopathic Parkinson's disease, according to the UK Parkinson's disease Society Brain Bank criteria. 3. Montreal Cognitive Assessment (MoCA) score of ≥ 10 and < 26 at screening. 4. A modified Hoehn & Yahr score of ≥ 2.5 in "on". 5. Having experienced recurrent falls during the past 3 months (based on interview with the patient and/or caregiver) and at least 2 falls during the past 4 weeks before baseline. 6. On a stable regimen of anti-Parkinson's medications for at least 30 days prior to baseline, and willing to continue the same doses and regimens during study participation. 7. Able to cooperate and participate in study related procedures. This includes the ability to accurately complete a fall diary. The fall diary may also be completed by a responsible caregiver. For patients meeting DSM-IV TR criteria for Parkinson's disease dementia, the fall diary should be completed by the caregiver. 8. Availability of a responsible caregiver at least five days per week at least 2 hours per day. For patients meeting DSM-IV TR criteria for Parkinson's disease dementia, availability of a responsible live-in caregiver is required. 9. Female patients must be of non-childbearing potential (defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or post-menopausal females defined as 12 months of amenorrhoea [in questionable cases a blood sample with simultaneous follicle stimulation hormone (FSH) 25-140 IU/L and oestradiol < 200 pmol/L is confirmatory]).	

10. Fertile male patients must be willing to use condom and refrain from donating sperm during the study and until 3 months after last dosing of IMP and ensure that their fertile female partners are using contraceptive methods to prevent pregnancy¹.
11. Written informed consent for participation in the study given by the patient and the responsible caregiver.

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

1. Any of the following potential hepatic conditions:
 - a. known history of alcohol abuse, chronic liver or biliary disease, with the exception of Gilbert's syndrome
 - b. total bilirubin greater than the upper limit of the normal range (unless associated with isolated instances of suspected Gilbert's syndrome)
 - c. alkaline phosphatase (ALP) greater than 1.5 times the upper limit of the normal range
 - d. aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 2 times the upper limit of the normal range
 - e. history of repeated unexplained upper right quadrant abdominal pain and/or nausea, or jaundice
2. A positive Hepatitis B surface antigen or a positive Hepatitis C antibody result.
3. A score of 5 (wheelchair bound or bedridden) in the "on"-state on the modified Hoehn & Yahr scale.
4. Uncontrolled symptomatic orthostatic hypotension.
5. Clinically significant polyneuropathy.
6. Weight <55 kg at Screening.
7. Patients with current or past treatment with deep brain stimulation (DBS) or patients with previous history of stereotaxic brain surgery for PD.
8. A current diagnosis of any primary neurodegenerative disorder other than idiopathic PD.
9. A current diagnosis of any treatable dementia (hypothyroidism, syphilis, vitamin B12 or folate deficiency) that is verified by the investigator to be the cause of dementia.
10. A current diagnosis of a major depressive episode according to DSM-IV criteria.
11. Patient has delirium.
12. Any history of a heart condition, including prolonged QTc (>450 ms for males and > 470 ms for females, QTcF and/or QTcB), cardiac arrhythmias, any repolarisation deficits or any other clinically significant abnormal ECG as judged by the Investigator.
13. 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; renal failure, history of abnormal renal function.

¹ Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS).

14. History of seizures within two years of screening.
15. History of cancer within five years prior to screening, with the following exceptions: adequately treated non-melanomatous skin cancers, localised bladder cancer, non-metastatic prostate cancer or in situ cervical cancer.
16. History of severe allergy/hypersensitivity or on-going allergy/hypersensitivity, as judged by the Investigator, or history of hypersensitivity to drugs with a similar chemical structure or class to pirepemat.
17. Creatinine clearance <30 mL/min (calculated according to the Cockcroft-Gault formula).
18. Treatment with Warfarin within three months before study treatment.
19. Treatment with Amantadine within 6 weeks before study treatment.
20. Treatment with Selegiline within 6 weeks before study treatment.
21. Administration of another new chemical entity (defined as a compound which has not been approved for marketing) or has participated in any other clinical study that included drug treatment with less than three months between administration of last dose and first dose of IMP in this study.
22. Current or history of drugs of abuse according to DSM-IV criteria.
23. Any planned major surgery within the duration of the study.
24. Any other condition or symptoms preventing the patient from entering the study, according to the Investigator's judgement.

Where the clinical significance of an abnormal Screening test result (lab or any other tests) is considered uncertain, the test may be repeated once, at the discretion of the Investigator, as long as the repeat test result is available within the 6 weeks screening period to determine eligibility.

Methodology

On Visit 1 (Screening Visit), consenting patients will be screened for eligibility according to study-specific inclusion/exclusion criteria within 6 weeks before start of Investigational Medicinal Product (IMP) administration.

Following Visit 1 the patient and/or caregiver will be asked to complete a daily fall diary and to bring the completed diary for Visit 2.

Following baseline assessments and fall diary review at Visit 2 (Day 0) patients will be randomised to receive pirepemat 100 mg t.i.d. (three times daily; "ter in die"), pirepemat 200 mg t.i.d., or placebo t.i.d. (1:1:1). The treatment allocation will be double-blinded, 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 at home for twelve consecutive weeks; *three oral daily doses (at approximately 8 am, 2 pm and 8 pm)* as adjunct treatment to the patients' regular and stable antiparkinsonian medication. Dosing will start with half the dose for the first week of treatment (i.e. 1 tablet t.i.d.), and then continue with full dose (2 tablets t.i.d.) until Week 11. Dosing will be de-escalated according to pre-specified schedule during the last week of study treatment, ending with the last dose on Day 84 (Visit 8).

During the treatment period Visits 3-8 will be performed after Week 2, 3, 4, 6, 8, 10, and 11. Patients and/or caregiver will also receive a phone call after the first week of treatment as a reminder to increase the dose and a phone call on the last day of treatment as a reminder to stop treatment. A fall diary will be completed for the entire treatment period (between Day 1 and Day 84).

Blood samples for pharmacokinetic (PK) analysis will be collected within 15 min pre-dose and approximately two hours (± 15 min) post dose on Visit 5 and 8.

Following the last IMP dose, follow-up visits will be performed. Safety laboratory assessments will be taken at the day after last dose (Visit 9), 12-14 days after last dose (Visit 12) and 33-37 days after last IMP dose (Visit 13).

Unscheduled visits will be performed as needed during the study and should be documented in the appropriate section of the electronic Case Report Form (eCRF).

Investigational Medicinal Products (IMP), dosage and mode of administration

Pirepemat tablets, [REDACTED]

Placebo tablets, [REDACTED]

Treatment and dose allocation will be randomly assigned to pirepemat 100 mg t.i.d., pirepemat 200 mg t.i.d or placebo t.i.d.

Duration of treatment

Patients will take three daily oral doses (at approximately 8 am, 2 pm and 8 pm) of pirepemat or placebo for 84 consecutive days. Dosing will start with half maximum dose for the first week of treatment and de-escalated according to pre-specified schedule during the last week of study treatment.

Duration of each patient's involvement in the study

Patients will be screened for eligibility up to 6 weeks prior to start of study treatment (Visit 1; Screening visit).

Follow-up visits will be performed for all patients after the last IMP dose until a final visit (Visit 13) 33-37 days after the last IMP dose.

The total study duration for each patient will be approximately 21-23 weeks.

Efficacy assessments

- Fall diary
- MoCA
- MDS-UPDRS Part 1-4
- Single leg stance test, Tandem walking test
- NPI (Apathy/Indifference only)
- CGI-S and CGI-I

Safety assessments

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

Pharmacokinetic (PK) assessments

Blood samples for pharmacokinetic (PK) analysis of pirepemat and metabolites will be collected within 15 min pre-dose and approximately two hours ($\pm$ 15 min) post dose on visit 5 and 8. Plasma concentrations of pirepemat will be used as a measure of drug exposure. These data together with pharmacodynamic data will be used to explore the relation between dose and plasma concentration and pharmacodynamic effect.

Data Safety Monitoring

A medical monitor will continuously monitor safety assessments and if there are any trends or specific assessment results of concern, an independent Data Safety Monitoring Board (DSMB) will convene to review and discuss the case(s) to determine next step.

The DSMB will also convene:

- When the 25th and 75th patient has completed the Follow-Up visit
- As soon as there has been a SUSAR

Recruitment will continue throughout the DSMB assessments.

The DSMB has the right to break the blind for the involved patients, request extra assessments, and recommend to the Sponsor that the study be suspended, amended, terminated or lower doses be given, if considered appropriate.

Statistical methods

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

The Full Analysis Set (FAS) will consist of all randomised and treated patients who receive at least one dose of IMP and who provide at least one post-baseline assessment. However, given the stage of development patients will be analysed according to the treatment they receive in the event of randomisation errors and not according to the scheduled treatment assignment.

The per-protocol set (PPS) is a subset of the full analysis population and will consist of patients who complied at least 80% with the protocol and completed Visit 8. Rules for defining the PPS will be detailed in the Statistical Analysis Plan. A list of all relevant situations which constitute major protocol violations and constitute reasons for exclusion from the PPS will be described in the SAP.

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

AEs and serious Adverse Events (SAEs) will be recorded as baseline symptoms from signing of ICF and up to start of IMP administration and as Treatment Emergent AEs from start of IMP administration. Medical events occurring between screening and first treatment with IMP will be reported separately as baseline symptoms.

All AE data will be fully listed by Investigator terms and Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT). AE data will be summarised by System Organ Class (SOC) and PT.

The analysis of the primary endpoint falls will be performed using a linear model based on ranked relative fall rates, using Proc Mixed in SAS. Strata for cholinesterase inhibitor will be included as

covariate. A negative binomial regression with log(fall rate at baseline) as covariate and log (time) as the offset parameter will be performed as a secondary efficacy analysis model.

The statistical model for all continuous variables (i.e. including all scales except CGIS) will be analysed using MMRM (mixed model for repeated measures) with at least treatment and site as covariates.

PK data will be presented using summary statistics. Data will be presented in terms of number (N), arithmetic mean, standard deviation (SD), minimum and maximum value, the geometric mean and coefficient of variation (CV%).

Table 1. Schedule of study and study procedures

Visit	V1 Screening	V2	Phone call ⁶	V3	V3b	V4	V5	V6	V7	V8	Phone call ⁸ EOT	V9	V12 ¹²	V13
	Screening period	Treatment period										Safety follow-up period		
Day	Up to 6 weeks before V2	0	7	14	21	28	42	56	70	77	84	1 day after EOT	12-14 days after EOT	33-37 days after EOT
Week	-6 to -4 weeks	0	1	2	3	4	6	8	10	11	12			
Visit window		-	±1 day	±1 day	±1 day	±2 days	±2 days	±2 days	±2 days	-2 days	-			
Informed Consent	X													
Demographics	X													
Medical/surgical history	X													
Inclusion/Exclusion Criteria	X	X												
Prior and concomitant medications	X	X		X		X	X	X	X	X		X	X	X
Height	X													
Weight	X											X		
Physical Examination	X						X					X	X	
Vital Signs (incl. supine/standing BP)	X	X		X		X	X	X	X	X		X	X	
12-lead ECG	X						X			X		X	X	
Safety laboratory assessments ^{5,7,9}	X	X ¹		X ¹	X ^{1, 11}	X ¹	X ¹	X ¹	X ¹	X		X	X	X
Urine analysis ⁵	X									X		X	X	X
Dispense IMP		X ¹⁰				X ⁴		X						
IMP administration at clinical site							X			X				
IMP compliance assessment				X		X	X	X	X	X		X		
PK blood sampling, incl metabolite screening							X ²			X ²				
MDS-UPDRS	X	X					X			X				
Modified Hoehn & Yahr	X	X		X		X	X	X	X	X				
MoCA	X	X					X			X				
NPI		X					X			X				
Single leg stance test		X					X			X				
Tandem walking		X					X			X				
CGI-S		X					X			X				
CGI-I							X			X				
Randomization		X												

Visit	V1 Screening	V2	Phone call ⁶	V3	V3b	V4	V5	V6	V7	V8	Phone call ⁸ EOT	V9	V12 ¹²	V13
	Screening period	Treatment period										Safety follow-up period		
Day	Up to 6 weeks before V2	0	7	14	21	28	42	56	70	77	84	1 day after EOT	12-14 days after EOT	33-37 days after EOT
Week	-6 to -4 weeks	0	1	2	3	4	6	8	10	11	12			
Visit window		-	±1 day	±1 day	±1 day	±2 days	±2 days	±2 days	±2 days	-2 days	-			
Confirm eligibility		X												
Distribute fall diary	X	X		X		X	X	X	X	X				
Fall diary review and collection		X		X		X	X	X	X	X		X		
Adverse Events, including assessment of suicide ideation and behaviour ³	X	X		X		X	X	X	X	X		X	X	X

¹ Only liver chemistry (ALT, AST, ALP, Total bilirubin)

² Taken within 15 min pre-dose and approx. 2 hours (± 15 min) after morning dose of IMP

³ Baseline symptoms from signature of ICF up to first IMP administration, and Treatment Emergent AEs (TEAEs) from first IMP administration

⁴ Patient will continue to use tablets in the bottle dispensed at V2, but a second bottle will also be dispensed at V4 to cover for the full period until V6.

⁵ Any safety lab result outside reference range and considered clinically significant should be followed with new samples until resolution, frequency of extra samples as judged by the Investigator

⁶ Phone call to remind the patient to increase (Day 7) the dose and to remind about fall diary completion and collection of the completed diary at study visit.

⁷ Hepatitis B Surface Antigen and Hepatitis C antibody testing are only performed at V1 Screening.

⁸ Phone call to remind the patient to stop treatment.

⁹ In exceptional circumstances, safety laboratory assessments can be performed at local laboratory.

¹⁰ Note that first IMP dispensation is performed at baseline visit (Day 0) but first administration is on Day 1, the day after the visit.

¹¹ Visit 3b does not have to be a visit to the clinical site, safety laboratory assessments can be performed at local laboratory instead.

¹² Visit 10 and Visit 11 existed in previous versions of the protocol and were removed. Naming of visits is kept for V12 and V13 despite absence of V10/V11.