SYNOPSIS

Name of Sponsor: Integrative Research Laboratories Sweden AB (IRLAB) Name of Finished Product: Pirepemat (IRL752) Name of Active Ingredient: Pirepemat	**[For publication]**
TITLE OF STUDY:	A Randomised, Placebo-Controlled, Multi-Centre Phase IIB Study Evaluating the Efficacy of Pirepemat on Falls Frequency in Patients with Parkinson's Disease IRL752C003 EudraCT number: 2019-002627-16
SPONSOR	Sponsor: Integrative Research Laboratories Sweden AB (IRLAB) Arvid Wallgrens Backe 20, 413 46 Göteborg, Sweden Scientific and Public Contact Point: Joakim Tedroff, MD, PhD, Chief Medical Officer
INVESTIGATORS:	No coordinating investigator was assigned. [redacted]
STUDY CENTRES:	Patients were enrolled at 34 sites in 6 European countries (France, Germany, Netherlands, Poland, Spain, and Sweden).
PUBLICATION (REFERENCES):	Tedroff J, Vu Van O, Sonesson C, Waters N, Waters S. REACT-PD – A Randomized, Placebo-controlled Phase IIB Trial Evaluating the Efficacy of Pirepemat on Falls Frequency in Patients with Parkinson's Disease. *Advances in Science & Therapy – International Conference on Alzheimer's and Parkinson's Diseases and Related Neurological Disorders*. Lisbon, Portugal, 05- to 09-Mar-2024 (Shift 2, #0555).
STUDY PERIOD:	Date of First Consent: 15-Jun-2022 Date of Last Follow-up Visit: 14-Jan-2025
PHASE OF DEVELOPMENT:	Phase 2b
BACKGROUND AND RATIONALE FOR THE STUDY:	Falls are a frequent and serious complication of Parkinson's disease (PD). Consequences of falls in PD include fractures and injury, hospital admission, and increased caregiver burden. The cause of the high propensity for falls in PD is likely to be multifactorial, with impaired postural function and cognitive deterioration both considered to be contributing factors. Pirepemat displays a novel pharmacological profile that addresses pathological dysregulations occurring in multiple cortical transmitter systems implicated in axial motor impairment and dementias. It targets several of the key neurochemical features suggested to be underlying risk factors for falls in PD without causing unwanted adverse effects on the motor system. The present study was designed to evaluate the effects of 2 different doses of pirepemat on falls frequency as compared with placebo; additional efficacy assessments looked at the effects of pirepemat on motor symptoms, postural dysfunction, and cognitive function. Safety was also evaluated.

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OBJECTIVES:

Primary: To evaluate the effects of pirepemat on falls frequency as compared to placebo.

Secondary:

Secondary Objectives

- To evaluate the effects of pirepemat on PD motor symptoms as compared to placebo
- To evaluate the effects of pirepemat on apathy as compared to placebo

Other Objectives

- To evaluate the effects of pirepemat on PD symptoms and severity as compared to placebo
- To evaluate the effects of pirepemat on postural dysfunction as compared to placebo
- To evaluate the effects of pirepemat on cognitive function as compared to placebo
- To evaluate the safety and tolerability of pirepemat
- To examine the relationship between dose and plasma concentration of pirepemat and pharmacodynamic effects

METHODOLOGY: This was a randomised, double-blind, placebo-controlled, multi-centre study conducted in 3 parallel groups, in patients with PD, evaluating 2 doses of pirepemat.

On Visit 1 (screening visit), consenting patients were screened for eligibility according to study-specific inclusion/exclusion criteria within 6 weeks before start of investigational medicinal product (IMP) administration on Day 1.

Following Visit 1, the patient and/or caregiver was 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 were randomly allocated (1:1:1) to receive pirepemat 100 mg t.i.d. (3 times daily; “ter in die”), pirepemat 200 mg t.i.d., or placebo t.i.d. The treatment allocation was double-blinded, i.e., it was not disclosed to the patients, the site staff, or the sponsor. Starting on Day 1, the IMP was self-administered at home for 12 consecutive weeks: 3 oral daily doses (at approximately 8 am, 2 pm, and 8 pm) as adjunct treatment to the patients’ regular and stable antiparkinsonian medication. Dosing started with half the dose for the first week of treatment (i.e., 1 tablet t.i.d.), and then continued with full dose (2 tablets t.i.d.) until Week 11. Dosing was de-escalated according to prespecified 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 were performed after Week 2, 3, 4, 6, 8, 10, and 11. Patients and/or caregivers also received 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 was completed for the entire treatment period (between Day 1 and Day 84).

Blood samples for pharmacokinetic (PK) analysis were collected within 15 min before dosing and approximately 2 hours (±15 min) after dosing on Visits 5 and 8.

Following the last IMP dose, follow-up visits were performed. Samples for safety laboratory assessments were taken the day after the last dose (Visit 9), 12-14 days after last dose (Visit 12) and 33-37 days after the last IMP dose (Visit 13).

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	Unscheduled visits were performed as needed during the study and documented in the appropriate section of the electronic Case Report Form (eCRF).					
NUMBER OF PATIENTS (Planned and Analysed):	Planned	120	Screened	146	Screen Fail	42
	Enrolled	106	Randomised	104	Completed	90
	Prematurely Discontinued	16	Analysed (Efficacy – Full Analysis Set)	101	Analysed (Safety)	104
	Analysed (PK)	59				
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION AND EXCLUSION:	The study enrolled male and female patients, aged 55 to 85 years old, with a diagnosis of idiopathic PD (according to the UK Parkinson's Disease Society Brain Bank criteria), with a Montreal Cognitive Assessment (MoCA) score of ≥10 and <26, and a modified Hoehn & Yahr score of ≥2.5 in "on". Patients were required to have experienced recurrent falls during the past 3 months and had at least 2 falls during the 4 weeks before baseline. Patients were required to have had a stable anti-Parkinson's medication regime for at least 30 days before baseline. Additional eligibility criteria were included to protect patient safety (e.g., exclusion of patients with hepatic conditions, heart conditions, polyneuropathy, clinically significant medical conditions), and to avoid enrolling patients with conditions that could interfere with study evaluations (e.g., primary neurodegenerative disorders, dementia, delirium).					
TEST PRODUCTS, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:	Pirepemat tablets, [redacted] Dose: pirepemat 100 mg t.i.d. or pirepemat 200 mg t.i.d. Patients who did not tolerate the IMP for any reason were allowed to reduce the dose to 1 tablet t.i.d. at any time throughout the study. Labelled lot numbers: [redacted] Bulk capsule batch numbers: [redacted]					
DURATION OF TREATMENT:	Patients took 3 daily oral doses (at approximately 8 am, 2 pm, and 8 pm) of pirepemat or placebo for 84 consecutive days. Dosing started with half maximum dose for the first week of treatment and de-escalated according to prespecified schedule during the last week of study treatment.					
CONTROL PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:	Placebo tablets, [redacted] Dose: placebo t.i.d. Labelled lot numbers: [redacted] Bulk capsule batch numbers: [redacted]					

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ENDPOINTS:

Efficacy:

Primary Endpoint:

Change in falls rate from baseline period (approximately 1 month prior to randomisation) to the end of treatment as assessed by fall diary (28 days prior to dose de-escalation).

Secondary Endpoints:

Change in the total score of Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part II (M-EDL) from baseline to Week 11.

Change in total score (Frequency × Severity) and Caregiver distress of Neuropsychiatric Inventory (NPI) Item G (Apathy/Indifference) from baseline to Week 11.

Exploratory Efficacy Endpoints

- 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); and 1.13 (Fatigue)
- Change in individual scores from baseline to Week 11 for the following MDS-UPDRS part II items: 2.1 (Speech) and 2.12 (Walking and balance)
- Change in modified Hoehn & Yahr score from baseline to Week 11
- Change in scores from baseline to Week 11 for the following tests:
  - Single leg stance test (elapsed time for both legs in seconds)
  - Tandem walking test
- Change in MDS-UPDRS item 3.12 (Postural stability) from baseline to Week 11
- Change in total MoCA score from baseline to Week 11
- Clinician Global Impression – Severity (CGI-S) and Clinician Global Impression – Improvement (CGI-I) scores by timepoint (baseline, Week 6, Week 11)

Pharmacodynamics: Relation between dose and plasma concentration and pharmacodynamic effect

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Safety:	Safety Endpoints • Patient incident of treatment-emergent adverse events • Clinically significant changes in vital signs • Clinically significant changes in physical examination • Clinically significant changes in clinical laboratory safety tests • Clinically significant changes in ECGs
STATISTICAL METHODS:	The following analysis sets were defined: • Safety Set (SS): The Safety Set includes all patients who received at least 1 dose of IMP. • Full Analysis Set (FAS): The FAS includes all patients who were randomised and treated, who received at least 1 dose of IMP and who provided at least 1 postbaseline efficacy assessment on primary or secondary efficacy endpoints. • Per-protocol Set (PPS): The PPS includes all patients in the FAS who had at least 80% compliance of study IMP (recorded compliance between 80-120%) and completed Week 11 (Visit 8) and had no major protocol deviations that led to exclusion from the PPS set as per decision at blinded data review meeting. Assignment of patients to sets was confirmed at a blinded data review meeting held before the study database was locked. Patients who received the wrong treatment throughout the treatment period were analysed according to the treatment received. Continuous (quantitative) variable summaries include the number of patients (n) with nonmissing values (unless otherwise specified), mean, standard deviation (SD), median, minimum, maximum, lower quartile and upper quartile, as well as number of observations for both actual values and change from baseline data (for PK variables the coefficient of variation [CV%] and geometric mean are also presented). Categorical (qualitative) variable summaries include the frequency and percentage of patients who are in the particular category or each possible value. The analysis of the primary endpoint, fall rate, was performed by means of a linear model, using the ranks of the relative fall rates as dependent variable, strata for cholinesterase inhibitor use as covariate, and treatment group as a factor (SAS Proc Mixed). Results are presented as median relative event rate ratio with 95% confidence interval (CI). The relative treatment improvement was also computed using bootstrap sampling. Sensitivity analyses were also conducted. A categorical analysis of fall rate was performed. For analysis of the secondary endpoints and exploratory endpoints, treatment groups were compared for the change from baseline to Visit 8 (Week 11) using mixed model for repeated measures (MMRM). Primary and seconady efficacy endpoints were also subject to PK/PD analysis, ie assessment of concentration *vs.* response relationship. All safety analyses were performed on the Safety Set using descriptive statistics. No inferential statistical tests were performed.

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SUMMARY OF RESULTS AND CONCLUSIONS:

Patient Disposition:	Between 15-Jun-2022 and 27-Aug-2024, a total of 146 patients were screened in the present study. Among these, 42 patients failed screening. A total of 106 patients were enrolled in the study, including 2 patients who failed screening but were enrolled by error. A total of 104 were randomly allocated to receive treatment in 1 of the 3 treatment groups, including 35 patients in the pirepemat 100 mg t.i.d. group, 35 patients in the pirepemat 200 mg t.i.d. group, and 34 patients in the placebo group. Ninety (90) of the 104 randomised patients (86.5%) were considered to have completed, having completed the study period including follow-up. Reasons for discontinuing study treatment included withdrawal of consent (7 patients), AEs (3 patients), elevation of liver enzymes (3 patients), and death (1 patient).
Demography and Baseline Characteristics:	Patients in the FAS had a mean age of 71.6 years, with a range from 55 to 84 years. There were more male patients (59.4%) than female patients (40.6%). The majority of patients (98.0%) were White or Caucasian, and the remaining 2.0% were Hispanic or Latino. Patients had a mean body mass index of 27.3 kg/m^2. No clinically meaningful differences in demographic characteristics were observed across the 3 treatment groups.
Efficacy Results:	The primary efficacy endpoint was the change in falls rate from baseline period to the end of treatment as assessed by fall diary. Descriptive statistics showed that the mean weekly fall rate at baseline was lower in the placebo group (3.98) than in the pirepemat 100 mg t.i.d. group (4.95) or the pirepemat 200 mg t.i.d. group (5.57). • In analysis of the median relative fall rate ratio using bootstrap sampling, the median relative fall rates in the pirepemat 100 mg t.i.d. group and 200 mg t.i.d. group were 53.571 and 58.00, respectively, compared with 59.592 for the placebo group; relative improvement (i.e., relative to placebo) in the 2 pirepemat groups was 10.38% and 2.67%, respectively. • In analysis of the primary efficacy endpoint using a ranked linear model, the lowest mean ranked relative fall rate was in the placebo group (0.486), with mean ranked relative fall rates of 0.534, 0.531 and 0.533 in the pirepemat 100 mg t.i.d. group, 200 mg t.i.d. group, and Overall, respectively; however, no statistically significant differences were observed for the actual treatment difference relative to placebo. • Similar results were obtained in the PPS. Several sensitivity analysis of the primary efficacy endpoint were conducted.

- Negative binomial regression of the fall rate ratios in the Evaluation Period showed no statistically significant difference between the pirepemat groups and the placebo group.
- Comparing the weekly fall rate between treatment groups using MMRM showed an LS mean treatment difference (relative to placebo) in the change of weekly fall rate from baseline to the Evaluation Period was -1.281 (95% CI: -2.678 to 0.116) in the pirepemat 100 mg t.i.d. group; however, this was not a statistically significant (P = 0.1949). In addition, no statistically significant difference was observed for the pirepemat 200 mg t.i.d. group or the pirepemat overall group.
- In an analysis of ranked relative fall rates, the lowest ranked relative fall rate was observed in the placebo group (0.486, versus 0.534 in the pirepemat 100 mg t.i.d. group and 0.531 in the pirepemat 200 mg t.i.d. group). However, no statistically significant differences were observed between the pirepemat treatment groups and the placebo group.
- In a categorical analysis of relative fall rates (for the Evaluation Period relative to baseline), the number of patients with a relative fall rate of ≤25% in the Evaluation Period was greater in the placebo group (12 patients, 36.36%) than in either the pirepemat 100 mg t.i.d. group (3 patients, 8.57%) or the pirepemat 200 mg t.i.d. group (6 patients, 18.18%) (9 patients overall, 13.24%), with a Fisher's exact test showing a statistically significant difference from placebo for the pirepemat 100 mg t.i.d. group (P = 0.0070) and the pirepemat overall group (P = 0.0162). No statistically significant difference was observed for analysis of the ≤50% and ≤75% categories.

PK/PD-analysis, allocating subjects into three equal-size exposure groups based on trough plasma-levels, indicated a biphasic pattern where medium exposure of pirepemat reduced fall rates by 31% versus placebo ($p<0.05$) over the treatment period whereas lower and higher exposure of pirepemat did not significantly affect fall rates. Changes from baseline to Week 11 in the MDS-UPDRS part II total score and the NPI Item G (apathy/indifference) total score and caregiver distress score were secondary efficacy endpoints.

- In analysis of the MDS-UPDRS at Week 11, the greatest improvement in the total score was observed in the placebo group (LS mean change from baseline -2.230), but no statistically significant differences between treatment groups were observed.
- Among patients who reported apathy at baseline with the NPI Item G, analysis of the total score showed a greater improvement in the placebo group (LS mean change from baseline -3.000) than in the pirepemat 100 mg t.i.d. group (-0.418) or the pirepemat 200 mg t.i.d. group (-0.524), suggesting a greater improvement in the apathy/indifference scale in the placebo group; a statistically significant difference from placebo was observed for both dose groups (P = 0.0332 and P = 0.0312, respectively). It should be noted that the presence of apathy at baseline was not part of the eligibility criteria, thus the incidence and severity of apathy at baseline were not controlled; these results should therefore be considered with caution. No statistically significant differences between treatment groups were observed for the caregiver distress item.

Several exploratory efficacy endpoints were evaluated. While the analysis of most endpoints saw no statistically significant difference between treatment groups, several endpoints showed differences:

- For MDS-UPDRS part III, the LS mean change from baseline saw a greater improvement in the placebo group (-6.315) than in the pirepemat 100 mg t.i.d. group (-0.804) or the pirepemat 200 mg t.i.d. group (-0.224),

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which was a statistically significant difference (P = 0.0136 and P = 0.0097, respectively).

- For MDS-UPDRS item 2.12, LS mean changes from baseline to Week 11 were small for each treatment group; however, while there was little change (0.071) in the pirepemat 100 mg t.i.d. group, a small decrease was observed in the placebo group (-0.428, indicating an improvement). This was found to be a statistically significant difference in the MMRM analysis (P = 0.0113).
- For the MDS-UPDRS part 1 item 1.8 (daytime sleepiness), the LS mean change from baseline was close to 0 (-0.007) in the placebo group, while decreases were observed in the pirepemat 100 mg t.i.d. group (-0.434) and the pirepemat 200 mg t.i.d. group (-0.207), with the MMRM showing a statistically significant difference from placebo for the pirepemat 100 mg t.i.d. group (P = 0.0219).
- For the modified Hoehn and Yahr score, the LS mean change from baseline to Week 11 showed a small decrease in the placebo group (-0.284) consistent with an improvement in functional disability, while little change was seen in the 2 pirepemat groups; a statistically significant difference from placebo was shown for both dose groups (P = 0.0273 and P = 0.0470 in the pirepemat 100 mg t.i.d. group and the pirepemat 200 mg t.i.d. group, respectively).

No statistically significant differences between treatment groups were observed for the following exploratory endpoints:

- MDS-UPDRS part I total score
- MDS-UPDRS part IV total score, and part IV item 4.3
- MDS-UPDRS item 2.13 and 3.11 (summed)
- MDS-UPDRS item 2.1
- Change from baseline in tandem walking test and single leg stance test
- CGI-S and CGI-I
- For secondary and exploratory endpo0ints, PK/PD-analysis, allocating subjects into three equal-size exposure groups based on trough plasma-levels, was also performed. These analyses indicated that in the medium tertile, showing the greatest reduction in fall rates, there were no changes in MDS-UPDRS scores or other motor assessment including the balance tests (single leg stance test, tandem walking). Thus the improvement in falls in the medium exposure range was not accompanied by any change in motor performance, or other assessments responsive to levodopa.

Pharmacokinetic Results: Measurement of plasma concentrations of pirepemat showed evidence of dose-proportionality, with exposure in the pirepemat 200 mg t.i.d. group approximately twice that observed in the pirepemat 100 mg t.i.d. group when measured predose and at 2 hours after dosing at Week 6 and Week 11.

Safety Results: Treatment-emergent AEs were reported in 74 patients (71.2%) overall, with a greater incidence observed in pirepemat-treated patients (53 patients [75.7%] in the pirepemat overall group) than in the placebo group (21 patients, 61.8%).

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Overall, the most frequently reported TEAEs at the System Organ Class (SOC) level were injury, poisoning and procedural complications; these events were reported in 24 patients (23.1%) overall, and with a greater incidence in the placebo group (10 patients, 29.4%) than in the pirepemat overall group (14 patients, 20.0%). The majority of these events were consistent with injuries sustained during falls, such as contusion and head injury (5 patients each overall, 4.8%), joint injury (4 patients, 3.8%), and fall and skin abrasion (3 patients each, 2.9%); in general, the incidence of these events (at the preferred term [PT] level) was comparable between the treatment groups.

Events in the SOCs investigations and nervous system disorders were reported in 23 patients (22.1%) and 22 patients (21.2%) overall, respectively. Investigations events were reported in 20 patients (28.6%) in the pirepemat overall group, compared with 3 patients (8.8%) in the placebo group, with the difference between groups accounted for largely by the incidence of hepatic enzyme increased, reported in 11 patients (15.7%) in the pirepemat overall group compared with 0 patients in the placebo group. Nervous system disorders were also reported with a greater incidence in the pirepemat overall group (17 patients, 24.3%) than in the placebo group (5 patients, 14.7%). Several events in this SOC can be considered as symptoms of PD, such as somnolence, on and off phenomenon, and bradykinesia

Treatment-related TEAEs were reported in more pirepemat-treated patients (29 patients [41.4%] in the pirepemat overall group) than placebo-treated patients (9 patients, 26.5%); this disparity was accounted for largely by the incidence of treatment-related hepatic enzyme increased, reported in 11 patients (15.7%) and 0 patients, respectively.

For the majority of patients in the study, TEAEs were not severe; mild and moderate events were reported as the greatest severity TEAEs in 30 patients (28.8%) and 33 patients (31.7%), respectively. Severe events were reported in 10 patients (9.6%) overall, and in a greater proportion in the pirepemat overall group (8 patients, 11.4%) than in the placebo group (2 patients, 5.9%). Among 15 severe events, 5 events were reported that were related to the liver (hepatitis toxic, hepatic enzyme increased, and hepatitis cholestatic), all of which were reported in the pirepemat overall group.

One patient died during the study. A patient in the placebo group died on Study Day 22 due to an event reported by the investigator as “death”; no other details were available. However, the event was not considered to be related to treatment with the IMP.

A total of 11 patients (10.6%) overall experienced serious adverse events (SAEs) during the study, with a similar incidence observed in the pirepemat overall group (8 patients, 11.4%) and the placebo group (3 patients, 8.8%). The SAEs reported included a wide range of PTs across a wide range of SOCs, with hepatobiliary disorders and nervous system disorders the only SOCs to include more than 1 SAE. Two events were reported as SAEs in the hepatobiliary disorders SOC; hepatitis toxic was reported in 1 patient in the pirepemat 100 mg t.i.d. group, and hepatitis cholestatic was reported in 1 patient in the pirepemat 200 mg t.i.d. group.

A total of 7 patients discontinued treatment with the IMP due to TEAEs. These included 3 pirepemat-treated patients who discontinued treatment with the IMP due to events associated with the liver (hepatitis toxic, hepatitis cholestatic, and hepatic enzyme increased).

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Safety laboratory assessments were conducted at each site visit. For haematology assessments, descriptive statistics showed no clinically meaningful changes from baseline for any of the haematology parameters, and there were no clinically meaningful differences in median values between the pirepemat treatment groups and the placebo group.

Among the clinical chemistry parameters, increases in the median values for alkaline phosphatase, ALT, and AST were observed in the pirepemat treatment groups, early on during patients' treatment with IMP, primarily during the first 4 to 6 weeks. After this period, median liver enzyme values were comparable to baseline values. Importantly, median values of alkaline phosphatase, ALT and AST were all within the normal range in the follow-up period, covering 1 to 37 days after the end of treatment with the IMP.

Additional safety assessments included evaluation of vital signs (including orthostatic changes), 12 lead ECGs, and physical examinations. None of these evaluations demonstrated any safety signals.

CONCLUSIONS:

- Analysis of the primary efficacy endpoint, change in falls rate from baseline period to the end of treatment as assessed by fall diary, a ranked linear showed no statistically significant differences between the pirepemat treatment groups and the placebo group. Three sensitivity analyses supported this finding, while a fourth sensitivity (of categorical responses) indicated a placebo effect.
- Analysis of the effect of pirepemat on PD motor symptoms and apathy showed no statistically significant difference between treatment groups for the MDS UPDRS part II total score (motor experiences of daily living). In the evaluation of effects on apathy, analysis of the NPI Item G score showed a greater improvement in the placebo group than the pirepemat groups, indicating a placebo effect on apathy in these patients. Additional evidence of a placebo effect was observed for several exploratory efficacy endpoints (MDS-UPDRS part III and items 2.12 and 3.12, modified Hoehn and Yahr).
- PK/PD-analysis, allocating subjects into three equal-size exposure groups based on trough plasma-levels, indicated a biphasic pattern where medium exposure of pirepemat reduced fall rates significantly compared to placebo, ($p<0.05$) whereas lower and higher exposure of pirepemat did not significantly affect fall rates. The marked reduction in fall rates in the medium exposure range was not accompanied by any change in motor endpoints, or correlated, levodopa responsive endpoints. MDS-UPDRS part 4 demonstrated improvement from baseline to end of treatment in pirepemat treated subjects, reaching statistical significance versus placebo in the high exposure group.
- Evaluation of the safety and tolerability of pirepemat in patients with PD showed no new safety signals. Overall, treatment was safe and well toleratedThe most frequently reported TEAE was hepatic enzymes increased, , in accordance with previous experience occurring around two to four weeks after start of dosing, and in most cases resolving spontaneously. There was no case of Hy's law.

DATE OF THE REPORT: 10-Oct-2025