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

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Introduction

Recurrent falls are cited as one of the most problematic symptoms in PD, lacking satisfactory treatment. Pirepemat enhances prefrontal cortex (pfc) neurotransmission via increased synaptic availability of dopamine (DA) and norepinephrine (NA). This addresses impairment in meso-cortical DA and NA, associated with executive dysfunction and falls in PD.

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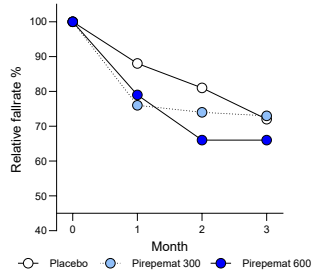
Methods

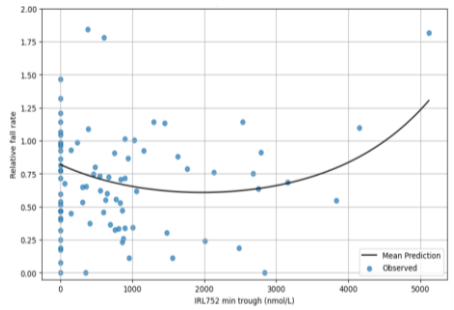
Phase IIb study REACT-PD evaluated efficacy and safety of pirepemat at two dose levels in recurrent fallers with PD. Falls were documented with daily patient diaries. Additionally, assessments for PD and balance function were performed. 104 participants were randomly assigned to pirepemat 300 mg daily, 600 mg daily, or placebo, for 12 weeks. The primary outcome measure was the relative fall rate from the baseline period (1 month) to the end of treatment. REACT-PD was conducted at 38 trial centers across France, Germany, Poland, the Netherlands, Spain, and Sweden.

Primary endpoint: Falls by dose group



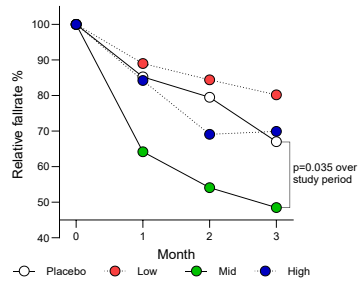
Relative fall rate by dose group analysed with negative binomial regression (NBR)

Secondary analysis: U-Shaped plasma concentration vs. response



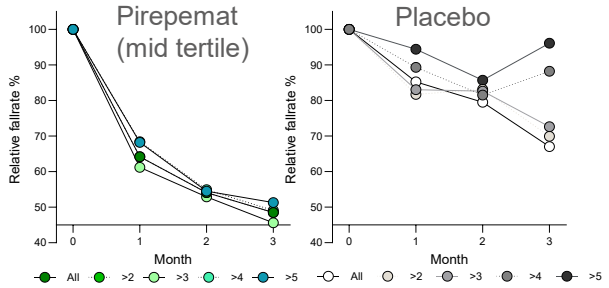
NBR model of plasma concentrations (pc) *vs.* relative fall rate

Secondary Analysis: Falls by exposure



Relative fall frequency by exposure (pc) tertile*. Analysed with NBR.

**Tertiles (low, mid, high) based on trough pc*



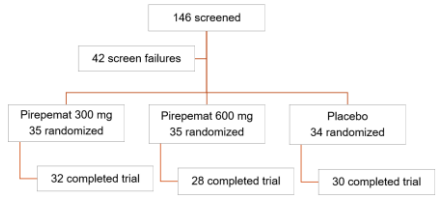
Sensitivity analysis: relative fall frequency for patients with > 2, 3, 4, or 5 falls during baseline. The effect of placebo, but not that of pirepemat, is highly sensitive to baseline falls.

Demographics by exposure

Variable	Low	Mid	High	Placebo
Age (years)	72.9 (6.6)	71.1 (6.6)	71 (8.1)	72 (7.8)
Gender n (%) Female Male	 9 (45%) 11 (55%)	 9 (45%) 11 (55%)	 6 (31.6%) 13 (68.4%)	 12 (40%) 18 (60%)
H&Y	3.2 (0.5)	3.2 (0.5)	3.4 (0.6)	3.1 (0.5)
MDS-UPDRS part 2	21.9 (8.6)	22.8 (7.3)	23.5 (5.8)	21.2 (6.6)
MDS-UPDRS part 3	43 (18.4)	39.7 (8.6)	47.3 (10.6)	41.5 (12.4)
MOCA	22.8 (3.9)	21.6 (3.1)	21.4 (3.5)	21.9 (2.9)

Baseline demographics were generally similar across exposure groups

Flowchart



Adverse events

	Pirepemat (all) (%) N=70	Placebo (%) N=34
Hepatic enzyme increased	11 (15.7)	0
Injuries	14 (20.3)	9 (26.5)
Diarrhoea	7 (10)	0
Arthralgia	5 (7.1)	3 (8.8)
Headache	4 (5.7)	1 (2.9)
Dizziness	4 (5.7)	0
Nausea	4 (5.7)	3 (8.8)
Pain in extremity	4 (5.7)	0
Urinary tract infection	4 (5.7)	0

AEs with > 5% incidence. The safety profile was in line with previous experience, and pirepemat was well tolerated.

www.clinicaltrials.gov NCT05258071

MDS-UPDRS part 2

Plasma concentration			
Low	Mid	High	Placebo
N=20	N=20	N=19	N=30
21.90 (8.58)	22.75 (7.32)	23.53 (5.81)	21.20 (6.65)
-0.21 (4.04)	-0.20 (6.67)	-1.16 (6.42)	-2.03 (5.45)
1.26, 0.2458	2.07, 0.0555	1.15, 0.2940	

Line 1: Mean (sd), Line 2: Change from baseline, Line 3: Difference vs. Placebo, p-value

MDS-UPDRS 2 was analysed with mixed model approach including covariates. For the mid tertile, showing the greatest reduction in fall rate, MDS- UPDRS 2 remained at baseline levels, while the placebo group showed a reduction vs. baseline.

For more details, meet us on-site, poster shift 2, or email susanna.waters@irlab.se

Many thanks to all patients who participated in this study along with their families, caregivers, investigators, study personnel and CROs.

Conclusions

Trial results indicate that pirepemat could significantly and clinically meaningfully reduce falls in PD, with a U-shaped concentration-response relationship. Relative fall rate was reduced by 31% *vs.* placebo in the mid tertile. The U-shaped conc-response pattern is in line with previous findings for dopaminergic compounds acting in the pfc, suggesting that dosing of pirepemat should be individualized, governed by plasma concentrations. In terms of absolute number of falls the effect at optimal concentrations corresponds to a reduction by 7 falls vs. placebo.

The reduction in falls was not contingent on any change in motor symptoms. Collectively, the study results supports further development of pirepemat