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. In IRL752C002, a phase IIa study in PD, signals of efficacy were observed on cognition, axial motor symptoms and falls.

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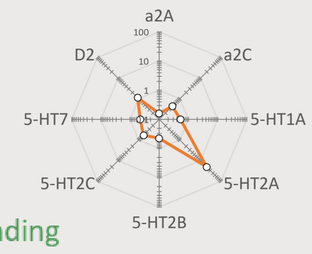


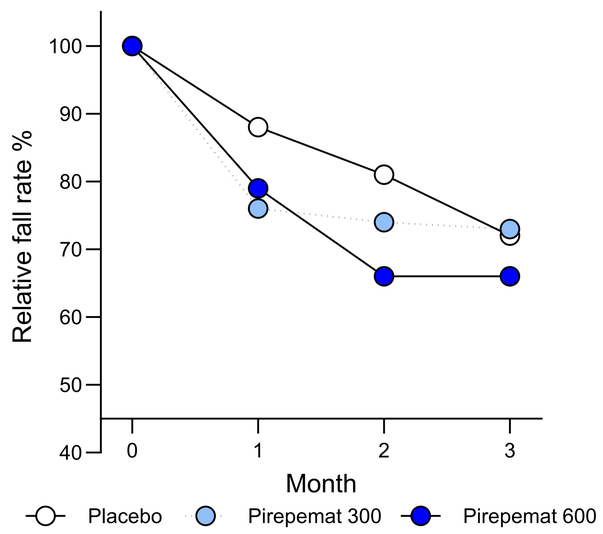
In vitro receptor binding

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 (1m) to the end of treatment. Relative fall rate = fall rate during observation period / fall rate baseline period. The relative fall rate was analysed using Negative Binomial Regression (NBR), with treatment, log fall rate during baseline, stratification variable as covariates and using log treatment days as offset. REACT-PD was conducted at 38 trial centers across France, Germany, Poland, the Netherlands, Spain, and Sweden.

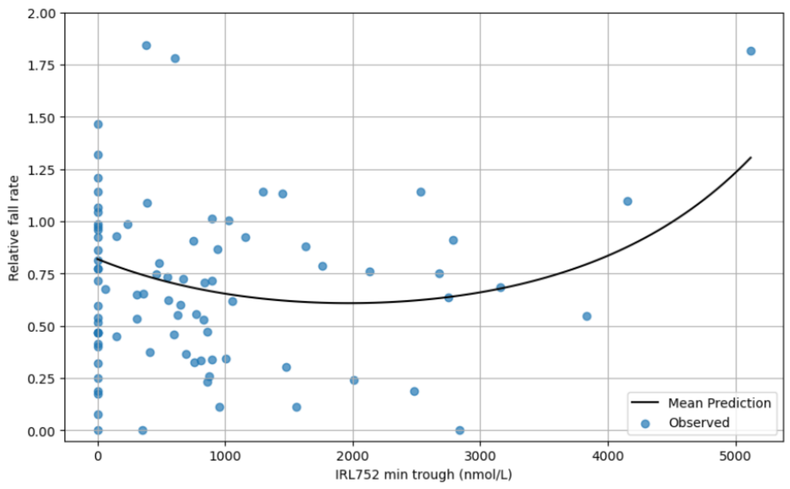
Results

Primary endpoint: Falls by dose group



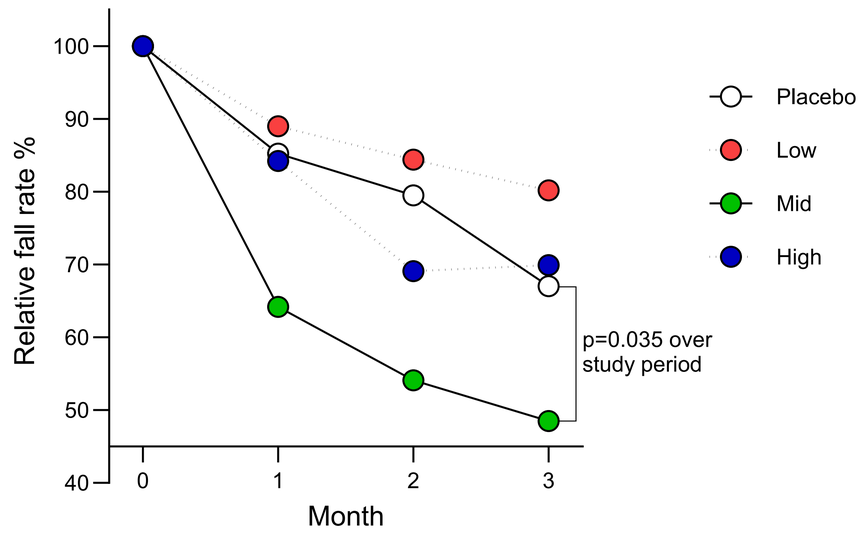
Relative fall rate by dose group analysed with NBR. No statistically significant differences between treatment groups and placebo were observed.

Secondary analysis: Plasma concentration vs. response



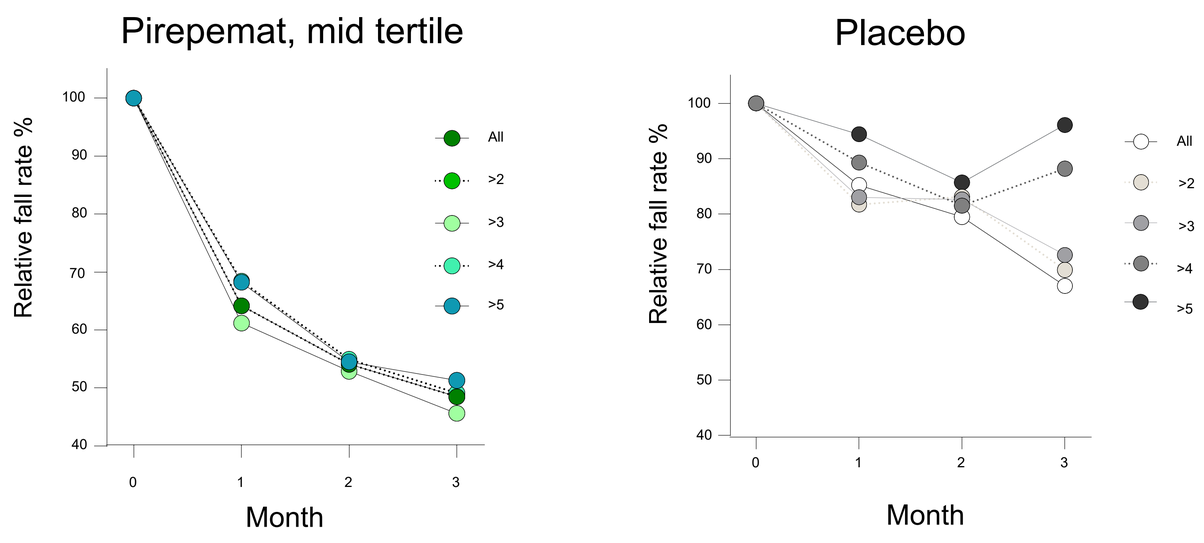
NBR model of plasma concentrations (pc) *vs.* relative fall rate showing U-shape pc vs. response pattern. NBR model included log baseline fall rate, linear and quadratic term for pc, both significant.

Secondary Analysis: Falls by exposure



Relative fall rate by exposure (pc) tertile*. Analysed with NBR. *Exposure tertiles were defined based on (low, mid, high) trough pc (Mid tertile pc 0.6 to 1.1 µM).

Sensitivity Analysis: Falls by exposure

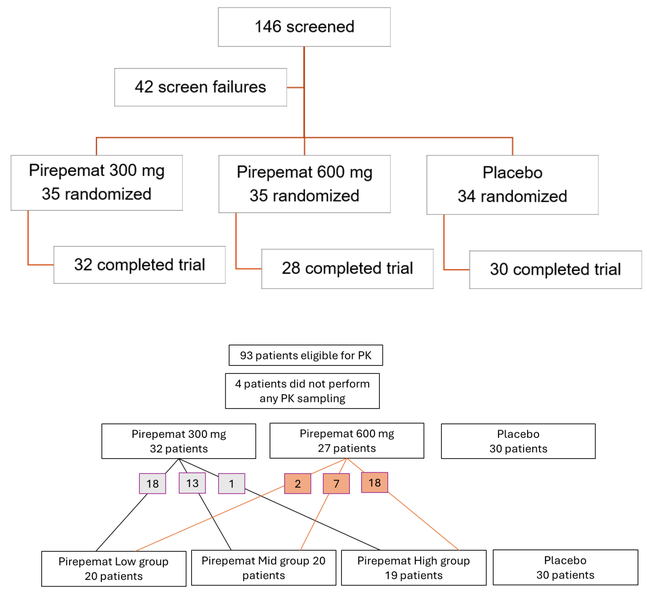


Sensitivity analysis

The impact of baseline falls on the outcome, was assessed applying different baseline thresholds: Relative fall rate for patients with > 2, >3, >4, or >5 falls during the baseline period (1 month)

- The effect of pirepemat was independent of baseline fall rate
- The effect of placebo was markedly dependent to baseline fall rate

Flowchart



Demographics & Safety

Variable	Low	Mid	High	Placebo
Age (years)	72.9 (6.6)	71.1 (6.6)	71 (8.1)	72 (7.8)
Fem gender n (%)	9 (45%)	9 (45%)	6 (31.6%)	12 (40%)
Hoehn&Yahr	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. Mean (SD) shown for continuous measures.

AE	Pirepemat (%) N=70	Placebo (%) N=34
Hepatic enzyme incr.	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.

Exploratory: Motor assessment by exposure tertiles

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	

MDS-UPDRS part 2 was analysed with MMRM 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. Shown are baseline (SD); change vs. baseline (SD); contrast *vs.* placebo, p-value. Results for MDS-UPDRS part 3 were similar (not shown).

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 compounds enhancing *pfc* neurotransmission, 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/month vs. placebo.
The reduction in falls was not contingent on any change in motor symptoms.
Collectively, the study results supports further development of pirepemat.