Efficacy, Safety and Tolerability of Tavapadon (PF-06649751) in Subjects With Early Stage Parkinson's Disease: A Randomized, Placebo-Controlled Trial

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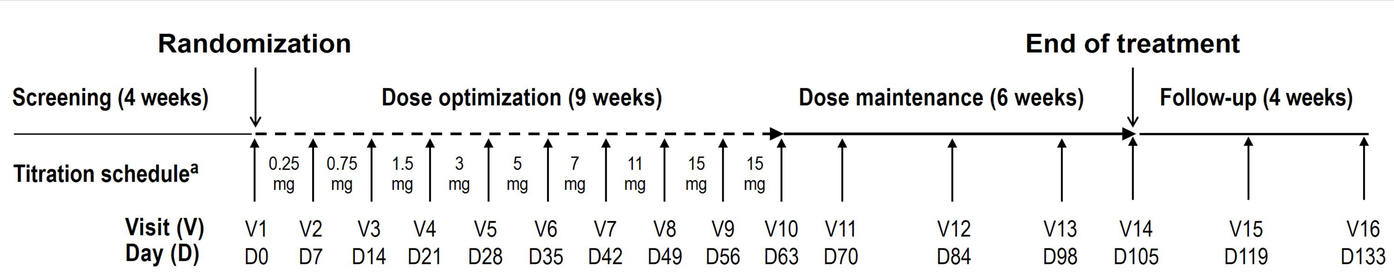
Rationale

- Despite the availability of multiple classes of drugs, many people with Parkinson's experience suboptimal efficacy and/or medication-related side effects.
- There is evidence that selective activation of D1-like receptors may be an important new therapeutic option for Parkinson's disease.
- PF-06649751 (Tavapadon, CVL-751) is a selective partial activator of D1/D5 receptors being investigated as a potential first in class new medicine for PD symptoms.

Methods

- This phase 2, double-blind, randomized, placebo-controlled, 15-week study was conducted to assess the efficacy and safety of flexible-dose PF-06649751 in subjects with early stage Parkinson's disease (clinicaltrials.gov NCT02847650).
- The study included a 30-day screening period, a 15-week double-blind treatment (9 week dose optimization and 6 week dose maintenance), and a 28-day follow-up.
- The recommended dosing schedule was as follows: 0.25 mg (days 1-7), 0.75 mg (days 8-14), 1.5 mg (days 15-21), 3 mg (days 22-28), 5 mg (days 29-35), 7 mg (days 36-42), 11 mg (days 43-49), and 15 mg (from day 50 onward).

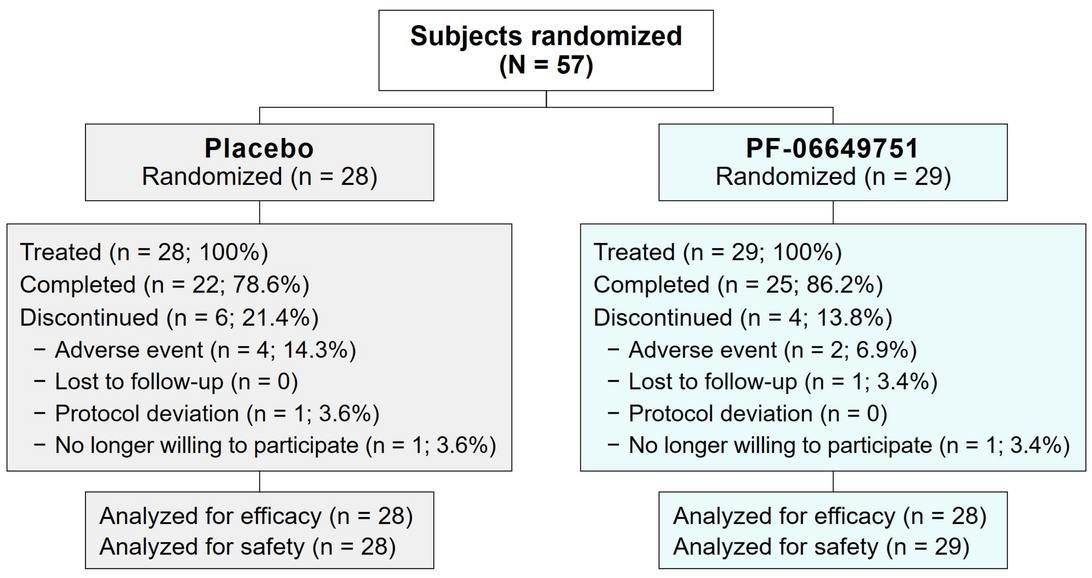


a Maximum allowed dose at each interval of the dose optimization period is shown. From Visits 3-10, the dose could be increased or decreased 1 level, or remain unchanged to balance tolerability and motor symptom control. Subjects received their optimized dose from Visit 10-14. See methods for details. V5, V7, V9, V11, V13, and V16 were by phone.

- The primary endpoint was change, from baseline, in MDS-UPDRS Part III at week 15. Scores were also compared between treatment groups at weeks 3, 5, 7, 9, and 12.
- Safety and tolerability measures included adverse event (AE) reporting, clinical laboratory parameters, vital signs, ECG parameters, the Beck Depression Inventory-II, Epworth Sleepiness Scale (ESS), the Columbia Suicide Severity Rating Scale, the Questionnaire for Impulsive Compulsive Disorders in Parkinson's Disease-Rating Scale, and the Physician Withdrawal Checklist.[1-5]

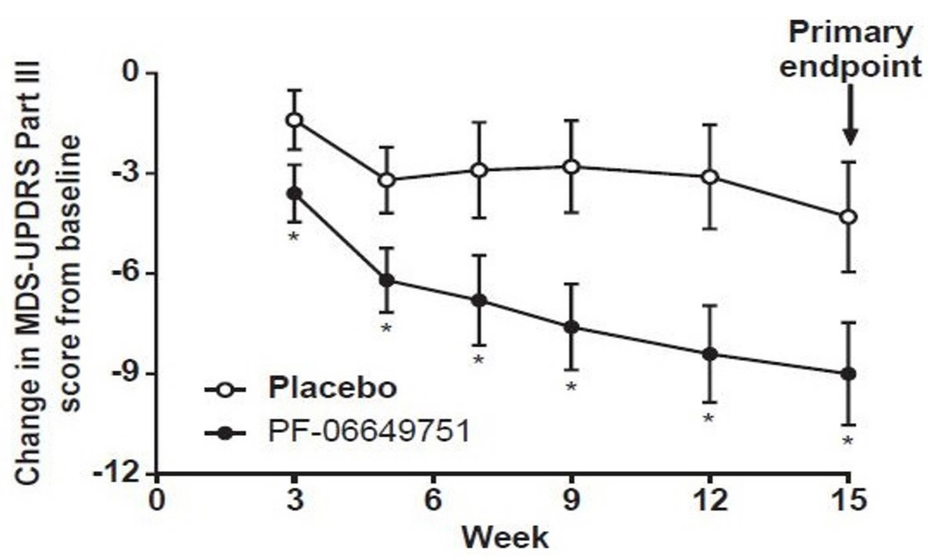
Results

- Enrollment was terminated early for reasons unrelated to the trial. Overall, 57 subjects received study medication.



- Despite early termination, the study met its primary endpoint with the PF-06649751 group showing statistically significant improvement from baseline in the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III score at week 15 compared to placebo.
- The PF-06649751 group exhibited a mean (SE) change, from baseline to week 15, in MDS-UPDRS Part III score of –9.0 (1.54) compared to –4.3 (1.65) for placebo. This corresponds to a least squares mean (SE) [90% CI] improvement over placebo of 4.8 (2.26) [1.0, 8.6] for the PF-06649751 group (2-sided P = 0.0407).

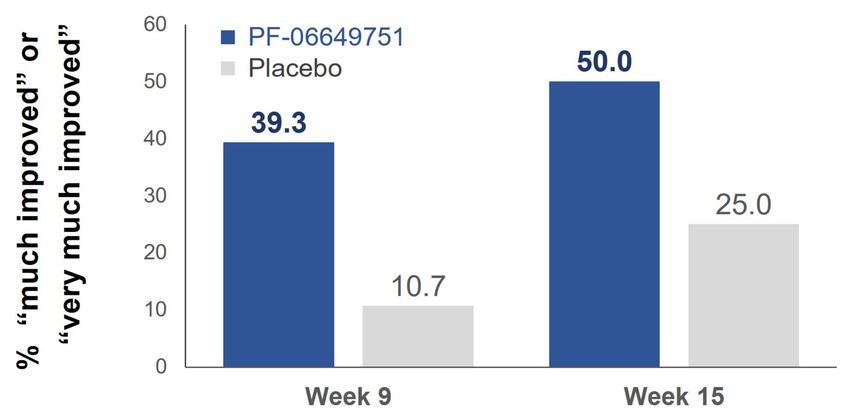
Change in MDS-UPDRS Part III Score Over Study



Data shown are mean ± standard error.
* 2-sided P ≤ 0.1 vs placebo; 2-sided P value at week 15 (primary endpoint) was 0.0407

- More subjects rated their Parkinson's symptoms as "much improved" or "very much improved" on PF-06649751 than on placebo.

Patient Global Impression of Change



- The safety profile of PF-06649751 was similar to that observed in prior studies, with the majority of adverse events reported as mild or moderate. The most common adverse events in the PF-06649751 group were nausea, headache, dry mouth, somnolence, and tremor.
- PF-06649751 did not increase sleepiness as measured by the Epworth Sleepiness Scale.

Summary of Adverse Events

	Placebo (N = 28)	PF-06649751 (N = 29)
Number of all causality AEs	57	149
Number of treatment-related AEs	19	82
Subjects with ≥1 all causality AE, n (%)	18 (64.3)	25 (86.2)
Subjects with ≥1 treatment-related AE, n (%)	10 (35.7)	22 (75.9)
Subjects with ≥1 serious AE, n (%)	0	1 (3.4)
Subjects discontinued due to AE, n (%)	4 (14.3)	2 (6.9)
Deaths, n (%)	0	0

Epworth Sleepiness Scale Data[5]

Visit	Treatment	N	LS Mean D from PBO (SE)	p value
Week 9	PF-9751	28	0.1 (0.75)	0.90
	PBO	26		
Week 15	PF-9751	26	-0.7 (0.69)	0.30
	PBO	22		

PF-06649751 Baseline (Std. Dev) = 5.1 (3.02)
Placebo Baseline (Std. Dev.) = 4.3 (2.95)

Conclusions

In this study, once-daily oral PF-06649751 resulted in significant improvement of motor symptoms and was generally well tolerated in subjects with early stage Parkinson's disease.

This warrants further development of the D1-selective partial agonist PF-06649751 for the treatment of Parkinson's disease.

Additional Information and Acknowledgments

- Cerevel Therapeutics LLC is now developing PF-06649751, which has been renamed CVL-751.
- One or more authors report potential conflicts which are described in the program.
- We gratefully and sincerely acknowledge the support, courage, and dedication of the study participants and staff who made this research possible.

About Cerevel

Cerevel is a new biopharmaceutical company formed through a partnership between Bain Capital and Pfizer focused on developing drug candidates to treat disorders of the central nervous system.

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