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ORIGINAL RESEARCH ARTICLE

A Phase I Study of the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of the Novel Dopamine D1 Receptor Partial Agonist, PF-06669571, in Subjects with Idiopathic Parkinson's Disease

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Abstract

Background and Objectives There is an unmet medical need for additional treatment options for Parkinson's disease. This was a Phase I, double-blind clinical trial assessing safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple doses of the novel dopamine D1 receptor partial agonist, PF-06669571, in subjects with idiopathic Parkinson's disease on a stable dose of L-DOPA.

Methods Subjects received PF-06669571 (or matching placebo) titrated from 1 mg to 3 mg over 7 days. The primary pharmacodynamic endpoint was the change from baseline in Movement Disorder Society-Unified Parkinson's Disease Rating Scale Part III total motor score at the pharmacodynamic time of maximum change from baseline on day 7.

Results Twenty subjects were randomized and 19 completed the study. Maximum plasma concentrations (C_{max}) of PF-06669571 were reached 3.35 and 3.19 h post-dose on day 1 and day 7. Geometric mean C_{max} and area under the plasma concentration–time profile from time 0 to 24 h post-dose on day 7 were 92.51 ng/mL and 1626 ng·h/mL, respectively. The primary pharmacodynamic endpoint did not meet the pre-specified criteria for significant improvement; however, the criteria were met in a sensitivity analysis excluding data from a L-DOPA outlier (L-DOPA dose of 2550 mg/d). The most common adverse events (AEs) were nausea (experienced by 2 subjects each in the PF-06669571 and placebo groups). There were no permanent discontinuations or dose reductions due to AEs.

Discussion Multiple daily doses of PF-06669571 were safe and well tolerated with no notable safety concerns. The pharmacodynamic endpoint did not meet the pre-specified criteria for significant improvement.

Clinicaltrials.gov identifier NCT02565628.

Key Points

Parkinson's disease is characterized by disruption of brain signaling via the neurotransmitter, dopamine.

Dopamine replacement can partly alleviate the symptoms of Parkinson's disease, but is associated with side effects that limit its use.

Our study provides initial information on a novel compound that acts on the dopamine signaling pathway via the dopamine D1 receptor, a therapeutic approach that may lead to new treatments for Parkinson's disease.

1 Introduction

Idiopathic Parkinson's disease is a progressive and debilitating neurodegenerative disorder characterized by limb bradykinesia, rigidity, tremor, and postural instability that affects 1% of the population over the age of 60 years [1]. Parkinson's disease is associated with loss of dopaminergic neurons in the substantia nigra and striatum and a progressive decrease in dopamine levels within the striatum [2]. This reduction in dopamine neurotransmission results

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in an imbalance in striatal output through the direct and indirect pathways, which regulate thalamic output to the motor cortex. Activation of the direct and indirect pathways is mediated by stimulation of dopamine D1 receptor (D1R) and dopamine D2 receptor (D2R), respectively [3].

The current standard treatment for Parkinson's disease is Levodopa (L-DOPA); however, prolonged treatment of 3 or more years can lead to motor fluctuations in up to 40% of treated patients, representing a substantial source of disability [4]. There is, therefore, an unmet medical need for new Parkinson's disease therapies that can replace or augment treatment with L-DOPA.

PF-06669571 is a novel D1R partial agonist with a non-catechol-based structure that has demonstrated efficacy in pre-clinical models of Parkinson's disease symptoms. In vitro binding studies demonstrated that PF-06669571 (MW = 389.36 g/mol) displayed potent binding affinity for recombinant dopamine receptors hD1 (Ki = 10 nM) and hD5 (Ki = 11 nM) [Pfizer, data on file]. In a study conducted in monkeys with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced Parkinsonism, PF-06669571 (0.075 and 0.15 mg/kg, PO) showed efficacy, improving scores in an observational test battery of Parkinsonian behaviors, similar to L-DOPA (Pfizer, data on file). After demonstration of a favorable nonclinical profile, PF-0669571 was progressed to safety and pharmacokinetics assessments in a dose-ranging Phase I study in healthy volunteers (NCT02184429), which showed that single and multiple doses of PF-06669571 (titrated up to 3 mg) were safe and well tolerated.

Following on from the study in healthy volunteers, we describe the results of a Phase I clinical trial (NCT02565628) to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of PF-06669571 in subjects with idiopathic Parkinson's disease.

2 Methods

2.1 Study Design

This was a double-blind, sponsor-open, randomized, parallel-group, multiple-dose study examining the safety, tolerability, pharmacokinetics, and pharmacodynamics of PF-06669571 in subjects with idiopathic Parkinson's disease. The dose of the L-DOPA/DOPA decarboxylase inhibitor remained stable during the active study treatment period, with the exception that the dose may have been decreased by the investigator if clinically indicated due to unacceptable dopaminergic side effects including nausea, emesis, worsening of dyskinesia, or hallucinations.

The study was designed with a total maximum duration of approximately 7 weeks during which the subjects were to attend the investigator site on 3 occasions, 1 of which was an inpatient stay. The study consisted of the following stages: (1) a screening period consisting of a screening visit approximately 5–28 days prior to randomization; (2) an inpatient period of up to 11 days during which the L-DOPA Responsiveness Test was performed prior to an active treatment period in eligible subjects; and (3) a follow-up visit, approximately 7–14 days after the last dose of PF-06669571.

Subjects were randomized and assigned to treatment group in a double-blinded manner provided they satisfied inclusion/exclusion criteria and had a Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III total motor score ≥ 20 during the OFF state (after approximately a 12-hour pause of all prior anti-Parkinsonian medication) and at least a 25% reduction in MDS-UPDRS Part III total motor score during the ON state (after L-DOPA dosing).

After randomization, subjects received PF-06669571 1 mg (days 1–3) then 3 mg (days 4–7) or matching placebo. On days in which MDS-UPDRS assessments were conducted (day 1 and day 7), study drug was administered after a 12-hour washout of L-DOPA. On other study days, adjunctive L-DOPA was given as required.

2.2 Determination of Sample Size

Based on analysis of previous in-house data, the assumption that the mean change from baseline in MDS-UPDRS Part III total motor score was -10.91 and -1.18 in PF-06669571 and placebo, respectively, and a common standard deviation (SD) of 7.21, 8 completers per arm were needed to reach 90% power. A significant signal was defined as follows: (1) upper bound of 1-sided 90% confidence interval (CI) of PF-06669571 versus placebo model-based contrast < 0; (2) observed effect size (i.e. adjusted mean difference between PF-06669571 vs placebo) < -4.8.

2.3 Diagnosis and Main Criteria for Inclusion and Exclusion

Eligible subjects, aged 45 to 85 years, had a clinical diagnosis of idiopathic Parkinson's disease with the presence of at least 2 out of 3 cardinal characteristics (tremor, rigidity, and/or bradykinesia) and were required to be on stable dose (determined clinically) of at least 300 mg of an L-DOPA-based dopaminergic agent for at least 90 days prior to screening (visit 1). Subjects were also required to have a body mass index (BMI) of 17.5 to 38 kg/m^2, a total body weight > 50 kg (110 pounds), and a score of ≥ 24 on the Mini-Mental State Examination and were required to be of non-child-bearing potential or were using a highly

effective method of contraception. All subjects provided informed consent and were willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

Reasons for exclusion included (but were not limited to) the following: history or clinical feature of atypical Parkinsonian syndrome such as ataxia, dystonia, clinically significant orthostatic hypertension; history of surgery for Parkinson's disease (pallidotomy, thalamotomy, deep brain stimulation, etc.); presence or history of epilepsy, seizures, psychotic symptoms, head trauma, suicidal ideation, or clinically significant medical or psychiatric condition that may have increased risk associated with study participation. Serious medical conditions such as malignancy, cardiovascular disease, or renal or hematological diseases were also reasons for exclusion.

2.4 Pharmacokinetics

PF-06669571: Blood samples (approximately 4.0 mL) to provide a minimum of 2.0 mL plasma for pharmacokinetic analysis were collected pre-dose and serially for 12 h after the PF-06669571 dose on day 1 and day 7, and additionally at 24 h after the dose on day 7 only.

L-DOPA: Blood samples (approximately 4.0 mL) to provide approximately 1.2–1.5 mL plasma for pharmacokinetic analysis were collected pre-dose and serially for 12 h after the L-DOPA/DOPA decarboxylase inhibitor dose on day − 1.

Pharmacokinetic samples were analyzed for PF-06669571 or L-DOPA concentrations as applicable using validated, sensitive, and specific high-performance liquid chromatography tandem mass spectrometric methods in compliance with Pfizer standard operating procedures.

Pharmacokinetic parameters were calculated for PF-06669571 (days 1 and 7) and L-DOPA (day − 1) using non-compartmental analysis of plasma concentration–time data.

2.5 Pharmacodynamics

The pharmacodynamic primary endpoint was defined as the change from baseline in the MDS-UPDRS Part III total motor scores at pharmacodynamic time of maximum change from baseline (T_{max}) on day 7, after washout of L-DOPA. Pharmacodynamic T_{max} was the time point at which the mean change from baseline (defined as the last pre-dose measurement prior to administration of PF-06669571 or placebo on day 1) in the PF-06669571 group was largest.

The key secondary pharmacodynamic endpoint was change from baseline in MDS-UPDRS Part III total motor score at pharmacodynamic T_{max} on day 1, after L-DOPA washout. Exploratory endpoints included the Hopkins Verbal Learning Test-Revised (HVLT-R) [5], the Apathy Evaluation Scale-Self Report (AES-S) [6], the Trail Making Test (TMT) Parts A (attention) and B (executive function) [7], forwards and backwards Digit Span (working memory) [8], and the Snaith Hamilton Pleasure Scale (SHAPS) [9], which were assessed on study days 0 and 6, during which the subjects received their typical dose of adjunctive L-DOPA. These exploratory assessments were included to collect preliminary data with the instruments in this population to inform their incorporation into future studies with the compound. Additional details of these exploratory endpoints are included in the "Appendix".

2.6 Safety

Safety variables included adverse events (AEs), clinical monitoring, clinical laboratory, vital signs (blood pressure and pulse rate), electrocardiograms (ECGs), physical and neurological examinations, and the assessment of suicidal ideation and behavior.

2.7 Statistical Methods

Treatment effect of PF-06669571 as measured by change from baseline in MDS-UPDRS Part III total motor score was tested using a mixed model for repeated measures with a restricted maximum likelihood method for the estimation of the covariance parameters. The model included treatment, time (day), and treatment by time (day) interaction as fixed categorical effects as well as baseline MDS-UPDRS motor score as a fixed-effect continuous covariate. Subject was also included in the model as a random effect. An unstructured covariance matrix was used to model the within-subject errors. Differences between PF-06669571 and placebo group were compared using appropriate contrasts of least-squares (LS) means. Mean and 90% 1-sided upper confidence interval (CI) of the model-based contrast were generated. The analysis was conducted on the full analysis set (FAS).

Plasma PF-06669571 pharmacokinetic parameters (days 1 and 7) were summarized descriptively by day. Plasma L-DOPA pharmacokinetic parameters (day − 1) were summarized descriptively by treatment (PF-06669571 or placebo).

For HVLT-R, AES-S, TMT, Digit Span, and SHAPS, the treatment effect of PF-06669571 was evaluated using an analysis of covariance model. The dependent variable was the change from baseline of each assessment. The model included treatment as fixed categorical factor and the baseline scores as fixed continuous effect covariate. Difference between treatment groups for each of the endpoints specified above was compared using appropriate contrasts of LS means.

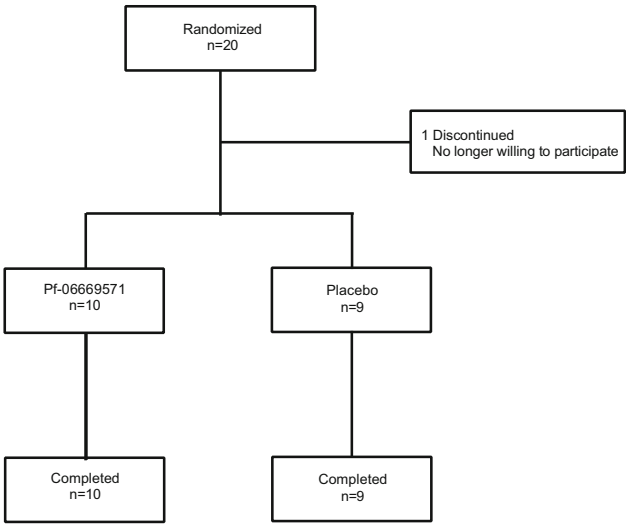

Fig. 1 CONSORT flow diagram

3 Results

3.1 Subject Disposition and Demographics

Of 20 subjects randomized, 19 were treated (Fig. 1, Table 1). All 19 subjects completed the study and were included in the pharmacokinetic, pharmacodynamic, and safety analyses.

3.2 Pharmacokinetics

PF-06669571: Following a dose titration consisting of 3 days of 1 mg and 4 days of 3 mg oral PF-06669571 doses administered once daily (QD), C_{max} was reached at a median time (T_{max}) of 3.35 h on day 1 and 3.19 h on day 7 (Table 2). Geometric mean C_{max} and area under the plasma concentration–time profile from time 0 to 24 h post-dose ($AUC_{0–24}$) on day 7 of QD dosing were 92.51 ng/mL and 1626 ng·h/mL, respectively. Variability for PF-06669571 exposure was moderate based on geometric percent coefficients of variation (%CV) values for C_{max} and AUC in the range of 28–38% (Fig. 2).

L-DOPA: During the inpatient period, subjects were provided with an "L-DOPA equivalent" dose of L-DOPA decarboxylase inhibitor based on their daily current anti-Parkinsonian medication, with the exception of from 20:00 on day −2, day 0, and day 6 to approximately 20:00 pm on day −1, day 1, and day 7, respectively. With the different doses administered, there was a wide range of individual L-DOPA C_{max} and area under the plasma concentration–time curve from 0 to 12 h ($AUC_{0–12}$) values, especially in the PF-06669571 treatment group. However, the median values were similar between the PF-06669571 (6270 ng·h/mL and 2530 ng/mL for $AUC_{0–12}$ and C_{max}, respectively) and placebo (6430 ng·h/mL and 2610 ng/mL for $AUC_{0–12}$ and C_{max}, respectively) groups (Table 3), suggesting similar background levels of L-DOPA doses in both groups. The L-DOPA $AUC_{0–12}$ and C_{max} for the L-DOPA dose outlier were 40,600 ng·h/mL and 14,700 ng/mL, respectively.

Table 2 Plasma PF-06669571 pharmacokinetics

Parameter (units)	Day 1 ($n = 10$)	Day 7 ($n = 10$)
$AUC_{0–12}$ (ng·h/mL)	150.8 (28)	917.5 (35)
$AUC_{0–24}$ (ng·h/mL)	NA	1626 (38)
C_{max} (ng/mL)	16.87 (30)	92.51 (31)
T_{max} (h)	3.35 (1.40–8.42)	3.19 (1.42–5.42)

$AUC_{0–12}$ area under the plasma concentration–time profile from time 0 to 12 h post-dose; *$AUC_{0–24}$* area under the plasma concentration–time profile from time 0 to 24 h post-dose; *C_{max}* maximum plasma concentrations, *NA* not available, *T_{max}* time of maximum change from baseline

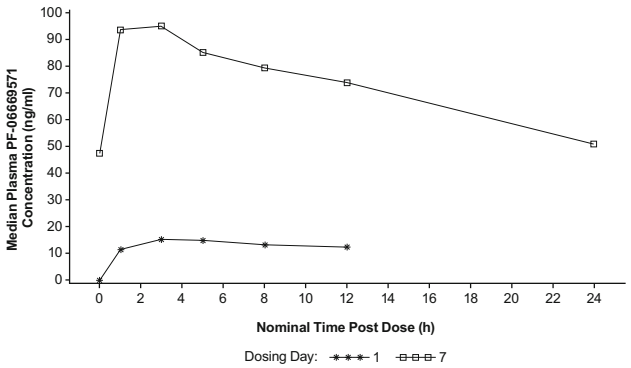

Fig. 2 Median PF-06669571 plasma concentration–time profile on day 1 and day 7

Table 1 Demographics and baseline characteristics

Characteristic	PF-06669571 ($n = 10$)	Placebo ($n = 9$)	Total ($n = 18$)
Gender, male	6	4	10
Age, mean (SD)	65.5 (7.4)	67.9 (5.9)	66.6 (6.6)
Weight, mean (SD), kg	77.2 (10.7)	72.9 (12.3)	75.2 (11.4)
Height, mean (SD), cm	168.0 (7.9)	165.3 (10.7)	166.7 (9.1)
BMI, mean (SD), kg/m^2	27.3 (3.0)	26.6 (3.0)	27.0 (2.9)

BMI body mass index, *SD* standard deviation

Table 3 L-DOPA pharmacokinetics

Parameter (units)	PF-06669571 ($n = 10$)	Placebo ($n = 9$)
AUC_{0-12} (ng·h/mL)	6270 (1550–40,600)	6430 (1830–11,300)
C_{max} (ng/mL)	2530 (445–14,700)	2610 (930–7440)
T_{max} (h)	0.924 (0.417–3.33)	0.500 (0–1.33)

AUC_{0-12} area under the plasma concentration–time profile from time 0 to 12 h post-dose

These values are well above the median values of the PF-06669571 group and are a result of the substantially higher L-DOPA dose in this subject.

3.3 MDS-UPDRS Part III

The LS mean estimate [standard error (SE)] of change from baseline in MDS-UPDRS Part III total motor score at day 7 pharmacodynamic T_{max} (1 h) was −11.13 (3.52) and −6.63 (3.71) for the PF-06669571 and placebo groups, respectively. The difference (SE) of PF-06669571 versus placebo was −4.49 (5.11) ($p = 0.3918$) with a 90% 1-sided upper bound of 2.33 (Fig. 3). The comparison of PF-06669571 against placebo at pharmacodynamic T_{max} on day 7 did not meet the pre-specified criteria for significance as the observed effect size was not < -4.8 and the 90% upper bound was not < 0. One subject was considered to be an L-DOPA dose outlier (2550 mg/d) and his/her MDS-UPDRS Part III total motor score was directionally opposite to other subjects treated with PF-06669571. This subject was excluded from the FAS in a sensitivity analysis: the LS mean estimate (SE) of change from baseline in MDS-UPDRS Part III total motor score, with the exclusion of that subject at day 7 pharmacodynamic T_{max} (1 h), was −13.47 (3.44) and −6.75 (3.44) for the PF-06669571 and placebo groups, respectively. This resulted in a difference (SE) versus placebo of −6.72 (4.87) ($p = 0.1873$) with a 90% 1-sided upper bound of −0.20, thereby meeting the pre-specified criteria for significance in this sensitivity analysis when this subject was excluded (Fig. 4).

For day 1, at pharmacodynamic T_{max} (3 h), the LS mean estimate (SE) of change from baseline in MDS-UPDRS Part III total motor score was −11.73 (3.36) for the PF-06669571 group and −7.86 (3.55) for placebo: a difference (SE) of −3.87 (4.89) ($p = 0.4397$) (Fig. 3). When excluding the L-DOPA outlier, the LS mean change was −14.47 (3.11) and −7.98 (3.11) for the PF-06669571 and placebo groups, respectively: a difference (SE) of −6.49 (4.41) ($p = 0.1601$) (Fig. 4).

3.4 Exploratory Endpoints

For the HVLT-R total recall score, the LS means (SE) of changes from baseline HVLT-R were −4.81 (1.28) and

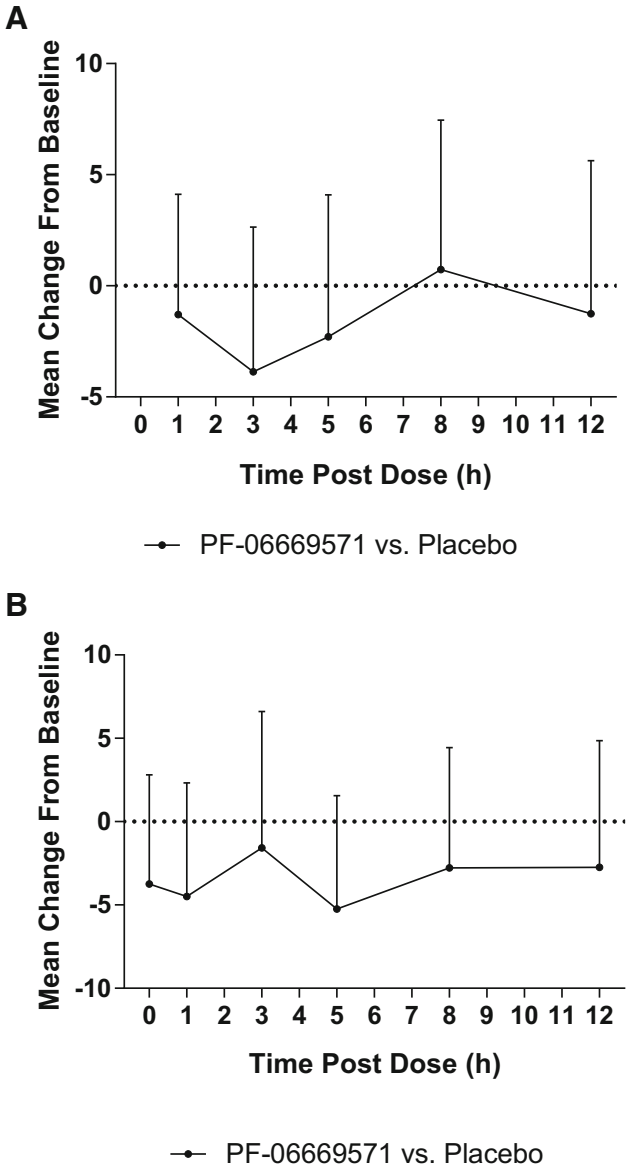

Fig. 3 Least squares mean difference (PF-06669571 vs placebo) in change from baseline in MDS-UPDRS Part III total motor score at day 1 (**a**) and day 7 (**b**). *MDS-UPDRS* Movement Disorder Society-Unified Parkinson's Disease Rating Scale

−0.65 (1.35) for the PF-06669571 and placebo treatment groups, respectively; and for the delay recall score, the LS means (SE) of changes were −2.08 (0.71) and −1.69 (0.75), respectively. The LS mean difference (80% CI) between PF-06669571 and placebo of changes in total recall score and delayed score were −4.16 (−6.72, −1.59) and −0.39 (−1.77, 1.00), respectively.

The AES-S LS mean difference (80% CI) between PF-06669571 and placebo of changes for AES-S was 3.78 (0.59, 6.97). The result was greatly impacted by an outlier (not the same outlier as described previously) in the PF-06669571 group (for whom the change from baseline

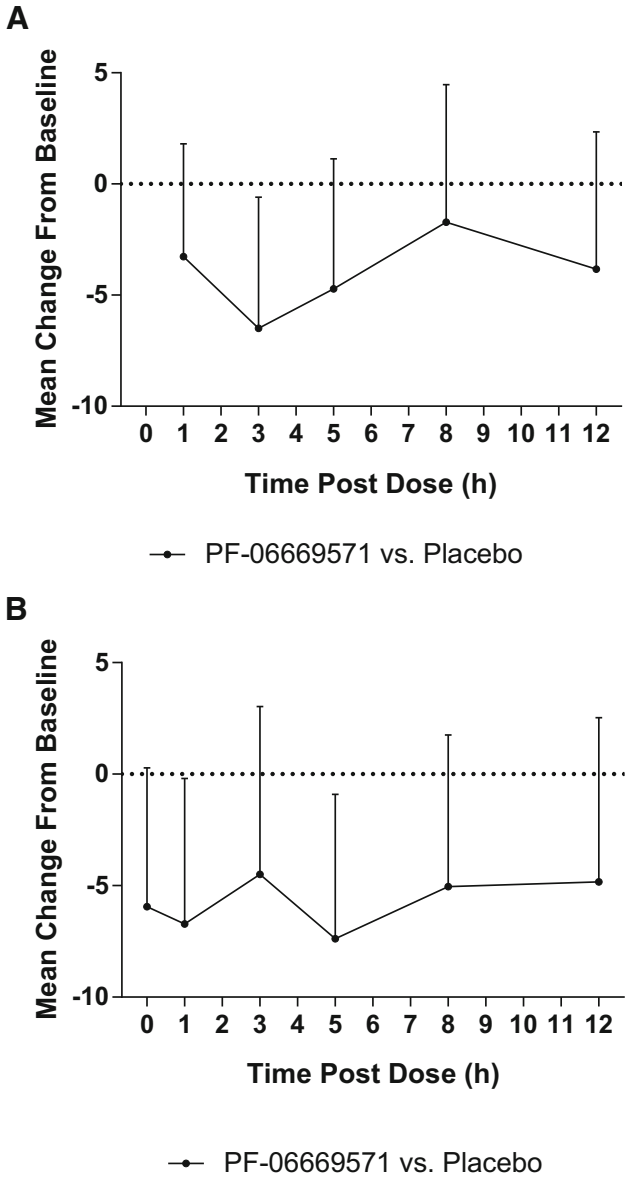

Fig. 4 Least squares mean difference (PF-06669571 vs placebo) in change from baseline in MDS-UPDRS Part III total motor score at day 1 (**a**) and day 7 (**b**) excluding L-DOPA outlier. *MDS-UPDRS* Movement Disorder Society-Unified Parkinson's Disease Rating Scale

score = 19). When the outlier was excluded from the analysis, the LS mean difference (80% CI) between the PF-06669571 and placebo was 2.24 (− 0.11, 4.60).

The LS mean differences (80% CI) between PF-06669571 and placebo of changes in time to complete the TMT Part A trails and Part B trails were − 16.89 (− 55.99, − 22.22) and 3.67 (− 37.59, 44.93) for the TMT Part A and Part B trials, respectively, and − 0.11 (− 1.57, 1.35) and − 0.57 (− 2.32, 1.19) for the Digit Span forward and backward trials. The LS mean difference (80% CI) between PF-06669571 and placebo of changes for SHAPS was − 0.37 (− 4.16, 3.42).

3.5 Safety

There were no serious adverse events (SAEs), severe AEs, or AEs leading to subject permanent discontinuations, dose reductions, or temporary discontinuations. Most of the treatment-emergent AEs were judged to be treatment-related, and the majority were mild in severity. The most commonly reported AE was nausea, experienced by 2 subjects each (all treatment-related) in the PF-06669571 and placebo groups, respectively (Table 4).

There were 8 (out of 10) subjects and 5 (out of 9) subjects with laboratory abnormalities in the PF-06669571 and placebo groups, respectively. The most commonly reported abnormality was the elevation of urine leukocyte esterase (experienced by 3 subjects each in the PF-06669571 and placebo groups, respectively). A few vital sign abnormalities meeting categorical criteria were reported and a treatment-related AE of hypotension was experienced by 1 subject in the PF-06669571 group.

There were no clinically important abnormalities in ECG, physical, or neurological examinations reported and, in general, there were no consistent differences in clinically significant laboratory, vital signs, and ECG abnormalities between the active and placebo treatments. No subjects had any suicidal behavior or any suicidal ideation during the study.

4 Discussion

Activation of the direct pathway in brain is expected to improve motor performance in patients with Parkinson's disease. Previous attempts at developing D1 agonists for treatment of Parkinson's disease have failed due, in part, to poor oral bioavailability [10]. PF-06669571 is a partial D1R agonist that has been developed for the treatment of conditions with impaired central dopaminergic (D1R) activation. PF-06669571 is a potent D1R partial agonist with a terminal elimination half-life that supports QD dosing (> 24 h). Previously, a Phase 1 study in healthy volunteers showed that multiple doses of PF-06669571 titrated up to doses of 3 mg were safe and well-tolerated in heathy individuals, with C_{max} and $AUC_{0–24}$ values on day 14 of 101.7 ng/mL and 1820 ng·h/mL, respectively. The current clinical study was conducted to evaluate the pharmacodynamic activity of the compound in patients with Parkinson's disease.

PF-06669571, when administered in healthy subjects, was associated with nausea and vomiting. However, titration to higher doses improved its tolerability (data on file).

Table 4 Incidence of all-causality, treatment-related, treatment-emergent adverse events

Number (%) of subjects with AEs	PF-06669571 ($n = 10$)	Placebo ($n = 9$)
Gastrointestinal disorders	4 (4)	3 (3)
Dry mouth	2 (2)	1 (1)
Nausea	2 (2)	2 (2)
Vomiting	1 (1)	2 (2)
General disorders and administration site conditions	2 (2)	0
Ill-defined disorder	2 (2)	0
Infections and infestations	1 (1)	0
Upper respiratory tract infection	1 (1)	0
Injury, poisoning, and procedural complications	0	1 (0)
Contusion	0	1 (0)
Fall	0	1 (0)
Nervous system disorders	3 (1)	1 (0)
Dizziness	1 (1)	0
Dystonia	1 (1)	0
Headache	1 (0)	0
Presyncope	1 (0)	0
Resting tremor	0	1 (0)
Psychiatric disorders	1 (1)	0
Abnormal dreams	1 (1)	0
Renal and urinary disorders	1 (0)	0
Nocturia	1 (0)	0
Vascular disorders	1 (1)	0
Hypotension	1 (1)	0
Total	15 (12)	8 (5)

Subjects were counted only once per treatment in each row. MedDRA (version 19.0) coding dictionary applied

AE adverse event, *MedDRA* Medical Dictionary for Regulatory Activities

Following a dose titration consisting of 3 days of 1-mg and 4 days of 3-mg oral PF-06669571 QD doses, geometric mean plasma C_{max} and $AUC_{0–24}$ were 92.51 ng/mL and 1626 ng·h/mL, respectively, in subjects with Parkinson's disease. Overall, exposures observed in patients with Parkinson's disease were similar to those observed in healthy subjects. Given the long terminal half-life, the peak to trough ratio, based on median profile, is relatively narrow ($\sim$ 2-fold). Median plasma exposure of L-DOPA during the L-DOPA responsiveness test on day -1 was similar in the PF-06669571 and placebo treatment groups.

The primary endpoint was change from baseline in MDS-UPDRS Part III total motor score at pharmacodynamic T_{max} on day 7. The placebo-adjusted mean change from baseline at pharmacodynamic T_{max} (1 h) on day 7 was -4.49 (> -4.8), with a 90% 1-sided upper CI of 2.33 (therefore > 0); this result did not meet the pre-specified decision criteria of significant improvement. One subject was different from rest of the group with respect to daily L-DOPA dose (2550 mg/day), and Parkinson's disease patients with L-DOPA doses > 1500 mg have previously been reported to be unresponsive to a full D1 agonist in studies using similar methodology [11]. When the study data were analyzed excluding the data from this subject in a sensitivity analysis, the LS mean difference (1-sided 90% upper CI) was -6.72 (-0.20) on day 7 and -6.49 (-0.60) on day 1, thus the results met the pre-specified decision criteria for the primary analysis on day 7. The limited number of subjects in each group may be a contributing factor for observed variability in response. Based on the point estimates of drug effect on day 1 versus day 7, an increase in PF-06669751 exposures by $\sim$ 6-fold (day 1 vs day 7; Table 4) did not result in any additional improvement. Current evidence, therefore, suggests limited utility of PF-06669571 in treatment of Parkinson's disease-related symptoms. Further studies are required to provide conclusive evidence around the time-course of pharmacological effect of PF-06669571. This study design explored removal of L-DOPA dose limitation (daily L-DOPA dose between 300 and 1200 mg) that was included in a prior study with another partial D1R agonist (PF-06412562, NCT02006290) that utilized similar methodology. A key

learning from the current study that confirms prior findings [11] is that exclusion of subjects on high doses of L-DOPA should be strongly considered in studies using this methodology, especially for studies with limited sample sizes.

There was evidence of a reduction in HVLT-R total recall scores in the PF-06669571 group relative to placebo [LS mean difference and 80% CI: − 4.16 (− 6.72, − 1.59)], in the presence of adjunctive L-DOPA. However, there was no significant difference between PF-06669571 and placebo in HVLT-R delayed recall scores.

The reduction in HVLT-R score on a background of L-DOPA is suggestive of a deleterious effect of additive dopaminergic stimulation on verbal learning and memory, a finding that has been noted in other studies [12, 13]. However, there were no similar findings in assessments of attention (TMT-A), executive function (TMT-B), or working memory (Digit Span).

There was evidence of a reduction in AES-S scores in the PF-06669571 group compared with placebo [LS mean difference and 80% CI: 3.78 (0.59, 6.97)]. However, this result was due to a single outlier in the PF-06669571 group (change from baseline = 19). If the outlier was excluded from the analysis, the difference was not significant between the treatment group and placebo. There was no similar finding in the SHAPS endpoint, which assesses anhedonia.

PF-06669571 (1 or 3 mg QD) was safe and well tolerable for subjects with Parkinson's disease in this study. There were no deaths or SAEs reported in this study, and all treated subjects completed the study. Most AEs were considered treatment-related and none were severe. No AEs were experienced by > 2 subjects in each treatment group, and most were mild in severity. The most commonly reported AE was nausea. There were generally no consistent differences in clinically significant laboratory, vital signs, and ECG abnormalities between the active and placebo treatments.

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Compliance with Ethical Standards

Ethics approval The study was conducted in compliance with the 1964 Helsinki declaration (and its amendments) and all International Conference on Harmonization Good Clinical Practice Guidelines. All participants (or their legal representative) provided written informed consent prior to screening. The final study protocol, amendments, and informed consent documentation were reviewed and approved by the Institutional Review Boards or Ethics Committees at each participating center.

Declaration of interest RG, SD, and PS are employees of the study sponsor, Pfizer. ND was an employee of Pfizer at the time the study was conducted.

Appendix

List of Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs)

*1011 Quorum Review IRB, 1501 Fourth Ave, Ste 800, Seattle, WA 98101, UNITED STATES.

*IRB for 6 study sites.

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Exploratory Endpoints

Hopkins Verbal Learning Test-Revised (HVLT-R)

The HVLT–R™ is a word-list learning and memory test that was used in this study to assess changes in memory. It is very brief, easy to administer, and well tolerated. The test is available in 6 forms that are very similar in their psychometric properties. Each form of the HVLT-R consists of a list of 12 nouns, with 4 items drawn from each of 3 semantic categories. The specific semantic categories vary across the 6 forms.

A list was read to the respondent, who then attempted to recall as many words as possible, in any order. The examiner recorded each response verbatim, including intrusions and repetitions. This task was repeated 2 more times, for a total of 3 learning trials. After a delay interval of 20–25 min, a delayed recall trial was administered.

Learning efficiency can have been assessed by examining the learning curve over the 3 learning trials and by evaluating the sum of the scores for all 3 learning trials. Ability to access newly learned information was assessed by the number of words retained on the delayed recall trial and the percentage of words recalled from the word list.

Raw scores for each of the 3 Learning Trials were summed for the Total Recall score. The Total Recall score ranged from 0-36 while the Delayed Recall Trial score ranged from 0-12. On this assessment, higher scores indicated greater verbal learning and recall. Raw scores could have been converted to T scores by consulting the appropriate normative data tables included in the instrument manual.

Two (2) HVLT-R endpoints were evaluated: change from baseline for the raw total recall score and change from baseline for the raw delayed recall trial score. Baseline was defined as the day 0 assessment.

Apathy Evaluation Scale-Self Report (AES-S)

AES-S consists of 18 items. Each item is anchored with 4 responses: 0 to 3 (0 = Not at all, 3 = A lot). Total score ranges from 0 to 54. AES-S endpoint was the change from baseline measurement of the AES-S total score. Baseline was defined as the day 0 assessment.

Trail Making Test Parts A and B (TMT)

This test provides an assessment of executive function. This test measured the time the subject takes to connect a sequence of numbers (Trails Part A) and a sequence of alternating numbers and letters (Trails Part B). An incorrect sequence was considered an error and time limit for completion was 5 minutes.

Results for both TMT A and B are reported as the number of seconds required to complete the task. Higher scores represent greater impairment.

The TMT endpoint was a change from baseline measurement. Baseline was defined as the Day 0 assessment.

Digit Span

Digit span is an assessment of working memory and attention in which the subject was presented a series of digits and was asked to repeat them back in the same order. The other part of this assessment entailed asking the subject to repeat the series of digits backwards. In both cases, the subject was presented with an even longer list of numbers with each correct response and the assessment ended with an incorrect response. The longest series of digits that a subject could have repeated was the subject's digit span and this was recorded for both forward and backward span.

The digit span endpoint was a change from baseline measurement. Baseline was defined as the Day 0 assessment.

Snaith Hamilton Pleasure Scale (SHAPS)-Anhedonia

SHAPS consists of 14 items covering 4 domains of pleasure response (social interaction, food and drink, sensory experience, achievement and past times). Subjects were instructed to indicate the degree to which each item caused them pleasure on a 4-point scale: 0 to 3 (0 = strongly disagree, 3 = strongly agree). Total score ranges from 0 to 42.

The SHAPS endpoint was the change from baseline measurement of the SHAPS total score. Baseline was defined as the day 0 assessment.

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