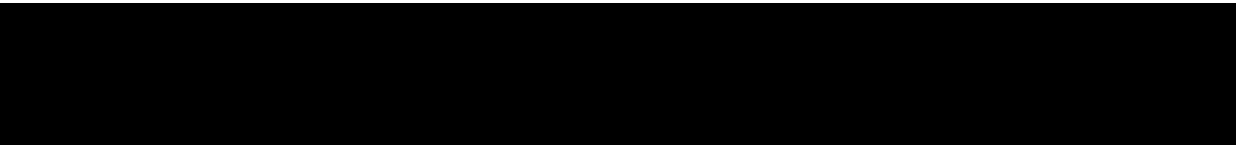




**A 15-WEEK, PHASE 2, DOUBLE BLIND, RANDOMIZED,  
PLACEBO-CONTROLLED, FLEXIBLE DOSE STUDY TO INVESTIGATE THE  
EFFICACY, SAFETY AND TOLERABILITY OF PF-06649751 IN SUBJECTS WITH  
EARLY STAGE PARKINSON'S DISEASE**

<b>Compound:</b>	PF-06649751
<b>Compound Name:</b>	Not Applicable (N/A)
<b>United States (US) Investigational New Drug (IND) Number:</b>	118647
<b>European Clinical Trials Database (EudraCT) Number:</b>	2016-001575-71
<b>Protocol Number:</b>	B7601011
<b>Phase:</b>	2



**Document History**

Document	Version Date	Summary of Changes
Amendment 1	20 July 2016	<ol style="list-style-type: none"> <li>1. Protocol Summary and Section 1.4.1: Clarification that 104 healthy volunteer subjects have participated in the completed Phase 1 studies, with 88 having received PF-06649751.</li> <li>2. Schedule of Activities Footnote #6: Clarification that FSH test at Screening is mandatory for female subjects in order to confirm non-childbearing potential, unless documented hysterectomy, bilateral oophorectomy or medically confirmed ovarian failure.</li> <li>3. Schedule of Activities Footnote #13, and Section 7.5.8: CCI [REDACTED]</li> <li>4. Section 1.3.3: Results of Study 8001294 included.</li> <li>5. Section 4.2, Exclusion Criteria #3: Fever added.</li> <li>6. Section 4.2, Exclusion Criteria #4: "Epilepsy" definition clarified with reference added.</li> <li>7. Section 4.2, Exclusion Criteria #10: History of vasculitis added.</li> <li>8. Section 4.2, Exclusion Criteria #12: History of malignancy criteria clarified.</li> <li>9. Section 5.5.1, Table 2: Clarifying footnote that the increase in dose level from Stage 1 to Stage 2 is a mandatory step at Visit 2 (from Day 8).</li> <li>10. Section 6, Section 7.2.1 and Section 7.2.9: Additional safety laboratory tests added at Screening and Visit 15 (and during the study if deemed necessary by the investigator) for monitoring of vascular inflammation.</li> <li>11. Section 7.6: CCI [REDACTED]</li> </ol>

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		<p>CCI</p> <p>12. Section 7.7: Blood volume table updated.</p> <p>13. Section 13.2: End of Trial template language included.</p> <p>14. Appendix 2: Stable low doses of benzodiazepines are permitted. The planned prescription of benzodiazepines for P.r.n. (“as needed”) use throughout the study should be discussed with the medical monitor.</p> <p>15. Minor administrative updates throughout.</p> <p>16. References updated.</p>
Original protocol	24 May 2016	Not applicable (N/A)

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## PROTOCOL SUMMARY

### Background and Rationale

In Parkinson's disease, motor dysfunction can be mitigated via pharmacologic activation of direct striatal output pathways containing dopamine-1 receptors (D1R) and/or indirect striatal output pathways containing dopamine-2 receptors (D2R). L-Dopa therapy acts through both pathways and effects an improvement in motor symptoms, which unfortunately diminishes over time.<sup>1</sup> As Parkinson's disease progresses, motor fluctuations reflect this diminished effectiveness, while dyskinesias emerge as manifestations of excessive dopaminergic stimulation. As a consequence, the clinical response to L-Dopa is gradually confined to a relentlessly narrowing therapeutic window. Agonists at the D2 and D3 receptors (D2/D3R), such as pramipexole, ropinirole, and rotigotine, are also approved for the symptomatic treatment of Parkinson's disease.<sup>2</sup> However, the maximal efficacy observed is considered inferior to L-Dopa. Efforts to develop selective D1R agonists have been ongoing for decades. Unlike D2/D3R agonists, D1R agonists may produce L-Dopa like efficacy through selective stimulation of the direct pathway. Development of a novel pharmaceutical agent that improves motor function without associated motor fluctuations or dyskinesias will provide an important new treatment option for patients with Parkinson's disease who are at increasing risk of experiencing these manifestations of the condition like the patients at early stage of the disease.

PF-06649751 is a potent and highly selective dopamine D1/D5 receptor partial agonist being evaluated for the symptomatic treatment of Parkinson's disease. PF-06649751 (0.02-0.15 mg/kg, subcutaneous administration (SC)) was tested for its ability to improve parkinsonian symptoms in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of Parkinson's disease in monkeys. Treatment with PF-06649751 dose-dependently improved both parkinsonian disability and bradykinesia scores, and this effect was maintained over three consecutive days of dosing. In monkeys primed to exhibit dyskinesias by prior chronic treatment with L-Dopa, PF-06649751 (0.1 and 0.15 mg/kg) reduced disability as effectively as an optimal dose of L-Dopa but with a longer duration of action and a lower level of dyskinesia.

A total of 104 healthy subjects (88 receiving PF-06649751) have participated in the completed single ascending dose (B7601001; n=18), multiple ascending dose (B7601002; n=77), and single dose plus trimethobenzamide hydrochloride (TMB; B7601007, n=9) Phase 1 trials.

Additionally PF-06649751 has been administered to 45 Parkinson's disease patients in one open-label multiple ascending dose study (B7601005) and 18 Parkinson's disease patients have been assigned to study treatment with PF-06649751 or placebo in one double-blind, single ascending dose study (B7601009).

The results of study B7601001, B7601002, and B7601007 and the possible risks associated with the administration of PF-06649751 are summarized in the Investigator's Brochure (IB).

This study is intended to complement other Phase 1 and 2 clinical investigations, by providing safety and efficacy experience in a population of patients with early stage Parkinson's disease.

## Study Objectives

### Primary Objective

- To evaluate the effect of PF-06649751 administered once daily on motor symptoms in subjects with early stage Parkinson's disease.

### Secondary Objectives

- To evaluate the safety and tolerability of PF-06649751 administered once daily in subjects with early stage Parkinson's disease.

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- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

## Endpoints

### Primary Endpoint (Efficacy)

- Change from baseline in the Modified Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Score Part III at Week 15.

### Safety and Tolerability

- Adverse events.
- Clinical laboratory parameters.
- Vital signs.
- Electrocardiogram (ECG) parameters.

- Columbia Suicide Severity Rating Scale (C-SSRS).
- Questionnaire for Impulsive-Compulsive Disorders in Parkinson’s Disease – Rating Scale (QUIP-RS).
- Physician Withdrawal Checklist (PWC-20).

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## Study Design

The study has a randomized, double-blind, placebo-controlled, flexible-dose design. Approximately 88 subjects from approximately 30 centers in up to 5 countries will be randomized to 2 treatment groups (PF-06649751 or placebo) in a 1:1 ratio using a central randomization system. Each subject will undergo 15 weeks of double-blind treatment (including 9 weeks of Dose Optimization Period and 6 weeks of stable dosing during the Dose Maintenance Period). During the initial up titration, subjects will gradually increase the dose of investigational product at weekly intervals, as tolerated, until Parkinsonian symptoms are optimally controlled. Investigational product will be self-administered once daily. The target dose range for PF-06649751 is 3 mg to 15 mg once daily (Stage 4 – Stage 8 in [Table 2](#)). Adjustments to the up-titration schedule are permitted during the Dose Optimization Period based on clinical judgment to mitigate adverse events or symptoms of suspected dopaminergic overstimulation.

The 15 weeks of double-blind treatment will be preceded by a 30 day screening period. There will be an additional follow-up period of 28 days following discontinuation of investigational product, for total study duration of up to 23 weeks.

## Statistical Methods

The primary endpoint is the change from baseline in the MDS-UPDRS score Part III at Week 15. The details of the statistical model will be specified in the Statistical Analysis Plan (SAP).

**SCHEDULE OF ACTIVITIES**

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the [STUDY PROCEDURES](#) and [ASSESSMENTS](#) sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the subject. **Study visit times are relative to Visit 1 (Randomization), and not relative to when the previous visit actually occurred. The indicated visit windows are only intended to mitigate scheduling conflicts for study visits.**

Visit Identifier	Screening Visit	Dose Optimization Period										Dose Maintenance Period				Follow Up Period	
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14 or Early Termination	Visit 15	Visit 16
		D -1/ RAND	D 7 +3	D 14 +3	D 21 +3	D 28 +3	D 35 +3	D 42 +3	D 49 +3	D 56 +3	D 63 ±3	D 70 ±3	D 84 ±3	D 98 ±3	D 105 -3	D 119 ±3	D 133 ±3
Protocol Activity	D -30 to -2	Wks 1 – 9									Wk 10	Wk 12	Wk 14	Wk 15	Wk 17	Wk 19	
Informed consent	X <sup>1</sup>																
Demographics <sup>2</sup>	X																
Medical history	X	X <sup>3</sup>															
Prior/Concomitant medications assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full physical and neurological examination	X										X				X		
Brief physical and neurological examination <sup>4</sup>		X						X					X			X	
Mini Mental State Examination (MMSE)	X																
UK Parkinson’s Disease Society Brain Bank Clinical Diagnostic Criteria	X																
Hoehn & Yahr Stage	X																
Height and weight, BMI <sup>5</sup>	X										X				X		

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Visit Identifier	Screening Visit	Dose Optimization Period										Dose Maintenance Period				Follow Up Period	
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5 ⌚	Visit 6	Visit 7 ⌚	Visit 8	Visit 9 ⌚	Visit 10	Visit 11 ⌚	Visit 12 ⌚	Visit 13 ⌚	Visit 14 or Early Termination	Visit 15 ⌚	Visit 16 ⌚
Protocol Activity	D -30 to -2	D -1/ RAND	D 7 +3	D 14 +3	D 21 +3	D 28 +3	D 35 +3	D 42 +3	D 49 +3	D 56 +3	D 63 ±3	D 70 ±3	D 84 ±3	D 98 ±3	D 105 -3	D 119 ±3	D 133 ±3
		Wks 1 – 9										Wk 10	Wk 12	Wk 14	Wk 15	Wk 17	Wk 19
Contraception check (Serum Pregnancy)/FSH Test <sup>6</sup>	X																
Serological Testing <sup>7</sup>	X																
Urine drug screening <sup>8</sup>	X	X															
Safety laboratory <sup>9</sup>	X	X <sup>10</sup>					X				X		X		X	X <sup>10</sup>	
CCI		█							█	█	█	█	█				█
CCI			█	█	█	█									█		
CCI			█		█	█	█				█		█		█		
ECG <sup>14</sup>	X	X	X	X	X		X		X		X		X		X	X	
Supine and standing blood pressure and heart rate	X <sup>15</sup>	X	X	X	X		X		X		X		X		X	X	
Columbia Suicidality Severity Rating Scale (C-SSRS) <sup>16</sup>	X	X	X	X	X		X		X		X		X		X	X	
Patient Health Questionnaire (PHQ-8)	X																
Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS)		X					X				X				X		
Inclusion/exclusion criteria verification	X	X															
Randomization		X															

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Visit Identifier	Screening Visit	Dose Optimization Period										Dose Maintenance Period				Follow Up Period	
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14 or Early Termination	Visit 15	Visit 16
Protocol Activity	D -30 to -2	D -1/ RAND	D 7 +3	D 14 +3	D 21 +3	D 28 +3	D 35 +3	D 42 +3	D 49 +3	D 56 +3	D 63 ±3	D 70 ±3	D 84 ±3	D 98 ±3	D 105 -3	D 119 ±3	D 133 ±3
		Wks 1 – 9										Wk 10	Wk 12	Wk 14	Wk 15	Wk 17	Wk 19
Subject training on management of investigational product and dosing diary		X			X						X						
Investigational product accountability			X	X	X		X		X		X		X		X		
Dosing compliance verification via phone <sup>17</sup>						X		X		X		X		X			
Subject investigational product dosing diary <sup>18</sup>		X	→	→	→	→	→	→	→	→	→	→	→	→	X		
Decision tree review <sup>19</sup>			X	X	X	X	X	X	X	X	X						
Dispensing of Investigational product		X	X	X	X		X		X		X		X				
Administration of Investigational product <sup>20</sup>		X <sup>20</sup>	→	→	→	→	→	→	→	→	→	→	→	→	X		
MDS-UPDRS III <sup>21</sup>	X	X			X		X		X		X		X		X		
CCI	■	■	■	■	■	■					■		■		■		
CCI		■									■				■		
		■									■				■		
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CCI		■									■				■		
		■									■				■		

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Visit Identifier	Screening Visit	Dose Optimization Period										Dose Maintenance Period				Follow Up Period	
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14 or Early Termination	Visit 15	Visit 16
Protocol Activity	D -30 to -2	D -1/ RAND	D 7 +3	D 14 +3	D 21 +3	D 28 +3	D 35 +3	D 42 +3	D 49 +3	D 56 +3	D 63 ±3	D 70 ±3	D 84 ±3	D 98 ±3	D 105 -3	D 119 ±3	D 133 ±3
		Wks 1 – 9										Wk 10	Wk 12	Wk 14	Wk 15	Wk 17	Wk 19
CCI		■									■				■		
		■									■				■		
											■				■		
Physician Withdrawal Checklist (PWC-20)																X	

Abbreviations: → = ongoing/continuous event; AE = adverse event; BMI = body mass index; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; HR = heart rate; MDS-UPDRS = Movement Disorder Society – Unified Parkinson’s Disease Rating Scale; PK = pharmacokinetics; RAND: Randomization; THC = tetrahydrocannabinol; UK = United Kingdom; Wk = week.

\* ☎ = Phone Visit (Visits 5, 7, 9, 11, 13, and 16).

1. Informed consent will be completed prior to any screening assessments and prior to initiating any treatment washout period, if applicable.
2. Current employment status will be collected as part of Demographics at Screening.
3. Medical history assessed at Visit 1 (Randomization) to confirm no change in history post screening visit, deemed relevant to study participation.
4. Brief physical will be focused on general appearance, the cardiovascular, respiratory, pulmonary, abdominal exams, as well as directed towards any subject reported symptoms. The brief neurological exam includes observation for cerebellar (intention) tremor and for no cerebellar tremors (eg, resting or positional), finger to nose, heel to shin, Romberg, gait and tandem walking, positional and gaze evoked nystagmus.
5. Height and BMI will only be assessed at Screening.
6. FSH test at Screening is mandatory for female subjects that do not have documented hysterectomy, bilateral oophorectomy or medically confirmed ovarian failure, to confirm non-childbearing potential (see Section 4.1, Inclusion Criteria #5).
7. HIV testing, Hepatitis B antigen, and Hepatitis C antibody. In the case of anti-HCV positive result, a qualitative HCV-RNA follow up test is to be performed.
8. Urine test for drugs of abuse (including THC) by central laboratory at Screening and by dipstick at site at Day -1 (Randomization).

9. Includes hematology, biochemistry, and urinalysis. Urinalysis will be performed by dipstick at site, and if positive, additional urine should be collected and sent to the central lab.
10. Refer to [Section 7.2.1](#) for additional safety laboratory tests to be completed at Screening and Visit 15, and/or as necessary throughout the study after consultation with the Medical Monitor/Sponsor per [Section 7.2.9](#).
11. CCI [REDACTED]
12. CCI [REDACTED]
13. CCI [REDACTED]
14. Triplicate ECG at all sampling time points (centrally read), except Screening. Single ECG permitted at Screening if subject meets eligibility criteria after initial measurement (refer to Exclusion Criteria #21).
15. Triplicate vital signs (HR and blood pressure) at Screening, if needed, if subject does not meet eligibility criteria after initial measurement.
16. Columbia Suicidality Severity Rating Scale (C-SSRS) “Past five years” evaluation at Screening, and Columbia Suicidality Severity Rating Scale “Since last visit” at all other time points.
17. In addition to compliance verification, subjects will be instructed on which blister card to use for following the week at each phone visit. The verification of blister card may be performed the day following the phone visits during Dose Optimization period (Visit 5 and 7).
18. Dosing diary should be started on Day 1 (first dose of investigational product) and filled in during the time course of the entire double blind treatment period.
19. At each visit, when reviewing the decision tree ([Figure 1, Section 5.5.1](#)), evaluate, if the current dose level is well tolerated and, if the degree of motor symptom control can be considered satisfactory.
20. Visits should be scheduled at approximately the same time of day throughout the study. Subjects take their morning dose at home. Subjects will document the timing of investigational product dose on study visit days via the dosing diary.
21. MDS-UPDRS Part III should be assessed approximately 2 to 4 hours following the administration of the investigational product (except at screening visit).

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## 1. INTRODUCTION

### 1.1. Indication

PF-06649751 is a D1/D5 receptor partial agonist that is being developed for the treatment of the signs and symptoms of Parkinson's disease.

### 1.2. Purpose of Study

This study will evaluate the efficacy, safety, and tolerability of PF-06649751 in subjects with early stage Parkinson's disease.

### 1.3. Background and Rationale

#### 1.3.1. Parkinson's Disease

Parkinson's disease is a neurodegenerative disease affecting over 1 million patients in the United States, 1.2 million in Europe and 6.3 million worldwide. Over 65 years of age, the prevalence of Parkinson's disease is approximately 1%, increasing to 3% for individuals in their 80s. The lifetime risk for developing Parkinson's disease may be as high as 1 in 40.<sup>3</sup> Parkinson's disease is characterized early on by the classic motor symptom triad of bradykinesia (slow and reduced amplitude of movement), rigidity (resistance to passive movement), and resting tremor. Key neuropathological features of Parkinson's disease include dopaminergic neuronal loss and regional intracellular aggregation of the protein alpha-synuclein.<sup>4</sup> Lesions in the substantia nigra result in loss of pre-synaptic dopamine-producing axon terminals in the striatum (putamen and caudate) and disruption of the physiological function of the direct and indirect basal ganglionic pathways leading to the clinical expression of Parkinson's disease.<sup>5</sup>

Currently available pharmacological treatment strategies for Parkinson's disease may be roughly grouped into approaches that: A) provide an exogenous source of a dopamine precursor (L-Dopa), B) increase the amount of dopamine in the brain (eg, by preventing degradation of endogenous dopamine [monoamine oxidase B inhibitors; MAO-Bi] or exogenous dopamine [catechol-O methyltransferase (COMT) inhibitors]), and C) are direct agonists of D2/D3 receptors (D2/D3R).

L-Dopa therapy provides increased dopamine levels in a transient and highly variable pulse and affords rapid onset improvement of motor symptoms for a limited duration.<sup>6</sup> However, chronic L-Dopa therapy is associated with significant complications. More than 40% of patients on L-Dopa experience motor fluctuations and dyskinesias after more than 3 to 5 years of therapy. These phenomena can be as troublesome as the disease itself.<sup>7</sup> The initial consistent relief of symptoms resulting from dopamine replacement is ultimately replaced by a relentlessly narrowing therapeutic window. Other pharmacologic strategies, including D2/3R agonists, do not appear to provide the same degree of symptomatic relief as patients experience with L-Dopa.

Unlike D2/D3R agonists, D1R agonists may produce L-Dopa like efficacy through selective stimulation of the direct pathway. Efforts to develop selective D1R agonists have been ongoing for decades. In small clinical studies in Parkinson's disease subjects, the selective

full D1/D5R agonists dihydrexidine,<sup>7</sup> ABT-431,<sup>8,9</sup> and CY 208 243<sup>10</sup> showed L-Dopa-like relief of parkinsonian symptoms but also induced dyskinesias comparable to those caused by L-Dopa.

In contrast to available D2/D3R agonists, D1/D5R agonists have demonstrated efficacy similar to L-Dopa in the MPTP-lesioned nonhuman primate model of Parkinson's disease (see Investigator's Brochure Section 5.1.3.2 In Vivo Pharmacodynamics). Severely lesioned MPTP-treated monkeys showed no response to D2R agonists and modest improvement with L-Dopa treatment, but showed marked improvement with D1R agonist treatment.<sup>11</sup>

### 1.3.2. PF-06649751 Mechanism of Action

PF-06649751 is a highly selective partial agonist at dopamine D1 like receptors (D1 and D5 receptors, abbreviated as D1Rs) which is being developed for the treatment of the signs and symptoms of Parkinson's disease. The compound is differentiated from other D1R agonists compounds that have been reported in the literature and tested in the clinic (eg, ABT 431 and dihydrexidine) in that PF-06649751 has a non-catechol chemical structure. PF-06649751 showed a similar binding affinity for native D1Rs in brain membranes prepared from monkey striatal tissue ( $K_i = 7$  nM). In vitro binding studies demonstrated that PF-06649751 (MW = 391.35 g/mol) displayed high binding affinity for recombinant hD1 ( $K_i = 9$  nM) and hD5 ( $K_i = 13$  nM) dopamine receptors. The binding potency of PF-06649751 for the recombinant rD1 receptor was 84 nM and ~10-fold lower than the hD1 receptor. In vitro functional testing against recombinant hD1 and hD5 receptors established that the compound is an agonist, which stimulates cAMP formation with  $EC_{50}$  values of 19 nM and 17 nM, respectively. Comparison of the cAMP response to the full agonist dopamine indicated that PF-06649751 is a partial agonist at D1Rs with intrinsic activity values of 65% and 81% for the hD1 and hD5 receptors, respectively.

The functional activity of the compound was demonstrated in vivo. In mice, PF-06649751 increased locomotor activity (LMA). Polysomnography and quantitative electroencephalography (qEEG) recordings in rats indicate that PF-06649751 approached significance to increase latency to enter rapid eye movement (REM) sleep and had no effect on overall sleep pattern, including REM and slow wave sleep (SWS). PF-06649751 also induced transient changes in qEEG. In monkeys, PF-06649751 increased eye blink rate (EBR) demonstrating that the compound was functionally active in vivo. A positron emission tomography (PET) imaging study confirmed that the compound is brain penetrant and the in vivo receptor occupancy (RO) is in agreement with the calculated RO based on in vitro binding affinity.

PF-06649751 (0.02-0.15 mg/kg, subcutaneous administration (SC)) was tested for its ability to improve parkinsonian symptoms in the MPTP model of Parkinson's disease in monkeys. Treatment with PF-06649751 dose-dependently improved parkinsonian behaviors, and this effect was maintained over three consecutive days of dosing. In monkeys primed to exhibit dyskinesias by prior chronic treatment with L-Dopa, PF-06649751 reduced disability as effectively as an optimal dose of L-Dopa but with a longer duration of action and a lower level of dyskinesia.

A predicted human plasma efficacious concentration ( $C_{\text{eff}}$ ) of PF-06649751 has been derived, based upon the experience with PF-06649751 in the MPTP-induced monkey model of Parkinson's disease. The total and unbound human  $C_{\text{eff}}$  of PF-06649751 in plasma are predicted to be 27.6 ng/mL and 1.7 ng/mL, respectively, corresponding to approximately 32% receptor occupancy.

In an evaluation of secondary (off target) pharmacology in vitro, PF-06649751 at 10  $\mu\text{M}$  did not inhibit ligand binding by more than 50% at any of the receptors, transporters, and ion channels and enzyme and uptake assays evaluated except the primary pharmacologic target, D1R. Therefore, the potential for secondary pharmacology is considered low at clinically relevant exposures.

### 1.3.3. Summary of Preclinical Toxicology

PF-06649751 was administered to rats and monkeys in oral studies up to 15 weeks in duration. PF-06649751 was negative in genetic toxicity testing. Dose-limiting toxicity consisting of persistent decreased activity (3 days) and 2 days of low (<25% total ration) food consumption was observed in an exploratory study in monkeys following a single dose (15 mg/kg); no dose-limiting toxicity has been observed in rats. The primary target organs identified in the safety pharmacology and toxicity studies were the central nervous system (monkeys and rats), reproductive system (female rats), and cardiovascular system (monkeys). Nonadverse central nervous system (CNS)-related findings associated with PF-06649751 administration included behavioral observations in monkeys, and decreased activity and inappetence in rats and monkeys. Minimal renal tubular necrosis was observed in an exploratory rat study that did not repeat in the definitive 1-month and 15-week studies. Other findings included nonadverse gastrointestinal (GI), dermal, adrenal, thyroid and hepatic effects, minor changes in clinical pathology parameters (eg, decreased red cell mass, increased cholesterol, serum electrolytes, or urine volume), and nonadverse respiratory parameter changes.

In single-dose safety pharmacology studies in monkeys, cardiovascular effects included decreased blood pressure (within 0.75 to 8.5 hours post dose [HPD]), followed by increased blood pressure during later time periods (within 9 to 20 HPD), and increased heart rate, corrected QT (QTc) interval, and cardiac contractility. Results of an in vitro hERG study and a monkey isolated heart (Langendorff) study suggested that the effects on heart rate, QTc, and contractility were not mediated by direct PF-06649751 effects on the heart, including hERG channel inhibition, as the  $\text{IC}_{50}$  in the hERG assay (64.9  $\mu\text{M}$ , 25400 ng/mL) is  $\geq 940\text{x}$  to 9700x the unbound  $C_{\text{max}}$  range in monkeys at doses where QTc interval increases were observed.

The no observed adverse effect level (NOAEL) in the 15-week monkey study of 5 mg/kg/day was associated with a combined sex mean total  $C_{\text{max}}$  and  $\text{AUC}_{24}$  of 1350 ng/mL and 11,800 ng•h/mL (78.3 ng/mL and 684 ng•h/mL, unbound), respectively. These NOAEL exposures are 4.0x and 1.8x the unbound human  $C_{\text{max}}$  (19.8 ng/mL) and  $\text{AUC}_{\text{tau}}$  (370 ng•h/mL), respectively, at a dose of 15 mg (Section 1.4.3). In the 15-week study in male and female rats, the NOAEL for males was 60 mg/kg/day and was associated with a mean total  $C_{\text{max}}$  and  $\text{AUC}_{24}$  of 7220 ng/mL and 79,700 ng•h/mL (505 ng/mL and

5580 ng•h/mL, unbound), respectively. These NOAEL exposures in males are 25x and 15x the unbound human  $C_{max}$  and  $AUC_{tau}$ , respectively, at 15 mg. An NOAEL for females could not be determined in this study. Except for the female reproductive tract changes (ovarian findings consisting of follicular cysts, decreased/absent corpus luteum, and/or interstitial cell hypertrophy), there were no other adverse effects in female rats up to the high dose of 60 mg/kg/day for 15 weeks ( $C_{max}$  9050 ng/mL,  $AUC_{24}$  77,900 ng•h/mL [634 ng/mL and 5450 ng•h/mL, unbound]). The exposures in female rats at 60 mg/kg/day are 32x and 15x the unbound human  $C_{max}$  and  $AUC_{tau}$ , respectively, at 15 mg. In a subsequent 15-week study in female rats, the NOAEL for alterations in estrous cycles and the ovary indicating impaired ovulation was 0.2 mg/kg/day ( $C_{max}$  131 ng/mL,  $AUC_{24}$  1830 ng•h/mL, [9.17 ng/mL and 128 ng•h/mL, unbound]). The exposures at the NOAEL in female rats are <1x the human exposures at 15 mg. The nonclinical safety profile of PF-06649751 is considered to be adequately characterized to support progression into human clinical trials of up to 15 weeks in duration for men and for women of non-childbearing potential.

At the end of the 26-week dosing phase in Study 8001294 (Pfizer Reference 15GR272), PF-06649751-related vascular/perivascular inflammation was noted microscopically in liver at the intermediate (20 mg/kg/day) and high (100 mg/kg/day) dose in male rats, as well as in the stomach, pancreas, or urinary bladder in males at 100 mg/kg/day. Based on these results, the preliminary NOAEL for vascular findings only following 26 weeks of administration of PF-06649751 was 5 mg/kg/day in male rats, and was 120 mg/kg/day in female rats. At the NOAEL of 5 mg/kg/day for vascular inflammation in males, the mean total plasma  $C_{max}$  was 1610 ng/mL, and  $AUC_{24}$  was 11,000 ng•h/mL. The predicted exposures of PF-06649751 for chronic dosing (beyond 15 weeks) in future clinical studies are expected to continue to maintain an approximately 2-fold AUC-related safety margin for the vascular findings based on the preliminary NOAEL of 5 mg/kg/day following 26 weeks of administration of PF-06649751 in male rats.

Detailed information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the Investigator Brochure.

## 1.4. Previous Human Clinical Experience

### 1.4.1. Clinical Studies

PF-06649751 has been evaluated in 3 completed clinical studies in 104 healthy subjects which are described in the Investigator's Brochure:

- Protocol B7601001 (n=18) was a Phase 1, first-in-human, placebo-controlled, randomized, single ascending dose study to evaluate the safety, tolerability and pharmacokinetics (PK) of PF-06649751 in healthy subjects. This study was conducted in two sequential cohorts of healthy subjects (ie, the first 3 doses given to Cohort 1, the second 3 doses given to Cohort 2), and evaluated single oral 0.25 mg, 0.75 mg, 0.75 mg fed, 1.5 mg and 2.5 mg (split over 8 hours) doses of PF-06649751.



- Protocol B7601002 (n=77) was a Phase 1, placebo controlled, randomized, multiple ascending dose trial to evaluate the safety and tolerability of PF-06649751 following multiple oral doses (with and without titration) with once daily dosing in healthy Western and Japanese subjects. This study consisted of eight cohorts of healthy subjects run sequentially in a dose escalating manner, with repeated doses of 0.15 to 5.0 mg of PF-06649751 given once daily for a total of 14, 21 or 28 days that included a titration period for doses >0.5 mg.
- Protocol B7601007 (n=9) was a Phase 1, placebo controlled, randomized, single dose study in healthy volunteers to evaluate the impact of prophylactic use of trimethobenzamide (TMB) on severity of nausea and emesis in healthy subjects. This study consisted of a single cohort of 9 healthy subjects who were administered three single doses of PF-06649751 (0.75 mg, 0.25 mg and 0.75 mg) along with TMB with at least a week long washout between each dosing.

To date, PF-06649751 has been administered to 45 Parkinson's disease patients in one open-label multiple ascending dose study:

- Protocol B7601005 was a Phase 1b, 2-period, open label, multicenter, dose escalation study of PF-06649751 in subjects with Parkinson's disease experiencing motor fluctuations and, in Cohort 5, in subjects with Parkinson's disease experiencing levodopa-induced dyskinesia. In the beginning of the study, L-Dopa was administered at one day for the evaluation of L-Dopa responsiveness. In the following, PF-06649751 was up-titrated with parallel reduction of concomitant levodopa if clinically possible based on the discretion of the investigator. The objective of the study was to evaluate the safety, tolerability and pharmacokinetics (PK) of multiple doses of PF-06649751. CCI [REDACTED] pharmacokinetics CCI [REDACTED]

Additionally, 18 Parkinson's disease patients have been assigned to study treatment with PF-06649751 or placebo in one double-blind, single ascending dose study (B7601009):

- Protocol B7601009 was a double-blind, placebo-controlled, randomized, Phase 1b, 2-cohort study to evaluate the safety, tolerability and pharmacokinetics of single ascending doses of PF-06649751 in Parkinson's disease subjects. In the first cohort of the study (n=9), subjects received single administrations of placebo and PF-06649751 0.75 mg, 1.5 mg and 3 mg. In the second cohort (n=9), subjects received single administrations of placebo and PF-06649751 3 mg, 6 mg and 9 mg. Overall, n=17 subjects were evaluated in the placebo dose group; n=6 subjects in each of the PF-06649751 0.75 mg, 1.5 mg, 6 mg and 9 mg dose groups; and n=12 subjects in the 3 mg dose groups.

In addition to the current study, one Phase 2 clinical study (B7601003) is ongoing to evaluate the efficacy, the safety and tolerability in Parkinson's disease subjects with Motor Fluctuations. The B7601003 study is a 15 week randomized, double-blind, placebo-controlled parallel group study whose dose maintenance period includes 5 week




adjunctive treatment to stable L-Dopa and 5 week down titration of L-Dopa. Approximately 200 subjects from approximately 50 centers in up to 5 countries will be randomized to 5 treatment groups (15 mg QD, 7 mg QD, 3 mg QD, 1 mg QD, or placebo). The primary endpoint is the change from baseline in daily OFF time (based on patient reported Hauser diary) at the end of the 5 week adjunctive treatment to stable L-Dopa.

#### **1.4.2. Safety**

##### B7601001

One single ascending dose study in healthy subjects (B7601001) has been completed. In study B7601001, PF-06649751 was determined to be well tolerated in healthy subjects for doses up to 0.75 mg. Mild-to-moderate instances of nausea and emesis were observed in most subjects for doses above 0.75 mg. The nausea and emesis observed after administration of a single dose of 1.5 mg (nausea in 5 of 5, and emesis in 4 of 5 subjects) precluded the ability to administer single doses of PF-06649751 above 1.5 mg. The tolerability of a split dose (with a two hour interval) was evaluated in Cohort 2. The tolerability of a split dose of 2.5 mg (nausea and vomiting in 4 of 4 subjects) precluded further titration to higher split doses. One subject was removed from Cohort 1 after a single dose of 0.25 mg due to a mild drug related angioedema of the face. No death occurred during this study. No subjects experienced a severe adverse event (AE), or a dose reduction or a temporary discontinuation due to an AE, or a serious adverse event (SAE). Sixty-seven AEs were reported (40 AEs in Cohort 1; 27 AEs in Cohort 2). In Cohort 1, 33 AEs were mild in severity, and 7 moderate AEs were reported in the PF-06649751 1.5 mg treatment group. In Cohort 2, 21 AEs were mild and 6 moderate AEs were reported in the PF-06649751 0.25-0.75-1.5 mg treatment group. All moderate AEs, except for 1 AE of abdominal pain reported in the PF-06649751 0.25-0.75-1.5 mg treatment group in Cohort 2, were considered treatment-related.

##### B7601002

One multiple ascending dose study in healthy subjects (B7601002) has been completed within the reporting period. This study was a randomized, double-blind, placebo-controlled, parallel-dose escalation, repeated dose study which evaluated the safety, tolerability and  of ascending doses of PF-06649751. Western healthy subjects were enrolled in 7 cohorts, and one cohort was conducted in Japanese healthy subjects. In study B7601002, PF-06649751 using initial titration to the target dose, was determined to be well tolerated in healthy subjects for doses up to 5 mg QD. Dose related mild-to-moderate instances of nausea and emesis were observed. A dose proportional increase in the incidence of nausea was the most frequent AE reported in this study. There was no notable difference in the incidence of nausea and vomiting between Western and Japanese subjects in the 1.5 mg QD dose group. Other AEs reported by 3 or more subjects within any dose group included gastrointestinal discomfort, abdominal pain upper, diarrhoea, and vomiting in the Gastrointestinal Disorders body system. In the Nervous System, dizziness and headache were the most common AEs and appeared to be dose related. Abnormal dreams were reported by 3 subjects receiving placebo, and 6 subjects receiving PF-06649751.

### B7601007

Nine healthy subjects participated in study B7601007, a single dose cross-over study. During study Period 1 and Period 3, 3 subjects received placebo and 6 subjects received PF-06649751 0.75 mg. During Period 2, 3 subjects received placebo and 6 subjects received PF-06649751 0.25 mg. A total of 47 all-causality AEs were reported (7 AEs in Placebo group; 28 AEs in PF-06649751 0.75 mg Period 1; 3 AEs in PF-06649751 0.25 mg; 9 AEs in PF-06649751 0.75 mg Period 3). The most frequently reported AEs were headache (4 subjects in the placebo group, 4 subjects in PF-06649751 0.75 mg Period 1 and 1 subject in Period 3), nausea (4 subjects in PF-06649751 0.75 mg Period 1 and 2 subjects in Period 3) and hot flush (1 subject in the placebo group, 3 subjects in PF-06649751 0.75 mg Period 1 and 2 subjects in Period 3); all of these AEs were considered to be treatment-related. The majority of the AEs (39/47) were mild in severity. Eight subjects reported AEs that were moderate in severity, including nausea (1 subject), vomiting (3 subjects), fatigue (1 subject), headache (1 subject), hot flush (1 subject) and orthostatic hypotension (1 subject). All moderate AEs were reported during PF-06649751 0.75 mg Period 1; they were considered to be treatment-related and resolved by end of study. Prophylactic or concomitant use of the antiemetic trimethobenzamide hydrochloride did not reduce the incidence and severity of nausea and emesis observed in the single dose first in human (FIH) study (B7601001).

### B7601005

The B7601005 included 4 completed cohorts:

- Cohort 3: 5 mg QD (n= 9 subjects).
- Cohort 4: 15 mg QD (n=11 subjects).
- Cohort 5: 15 mg QD, (n=6 subjects with levodopa-induced dyskinesia).
- Cohort 6: 25 mg QD (n=19).

Based on safety data from the multiple-ascending dose study in healthy subjects (B7601002), Cohorts 1 and 2 of the study were not conducted.

There were no deaths, n=1 serious adverse events, n=6 severe adverse events and n=11 discontinuations due to adverse events. The majority of AEs occurred during the up-titration period of PF-06649751 (Days 3 – Day 14) but the timing and dose level at which AEs occurred were variable.

Preliminary safety results from Cohort 3, Cohort 4, Cohort 5, and Cohort 6 are summarized in the following:

In **Cohort 3** (titration to 5 mg QD), 43 AEs were observed in n=9 of n=9 subjects treated with PF-06649751, all of which were mild to moderate. AEs resulting in treatment discontinuation and SAEs were not observed. The most common AEs observed in 2 or more subjects in Cohort 3 were headache in n=6 subjects (66.7%), insomnia in n=3 subjects

(33.3%), abnormal dreams in n=3 subjects (33.3%), somnolence in n=2 subjects (22.2%), and hyperhidrosis in n=2 subjects (22.2%).

In **Cohort 4** (titration to 15 mg QD), 26 AEs were observed in n=7 of n=11 subjects treated with PF-06649751 with n=2 subjects discontinued due to AEs. Most of them were mild. The most common AEs observed in 2 or more subjects in Cohort 4 were headache in n=7 subjects (63.6%), nausea in n=3 subjects (27.3%), dizziness in n=2 subjects (18.2%), and abnormal dreams in n=2 subjects (18.2%). Severe AEs were 1 event of headache at a dose level of 9 mg QD, and 1 event of nausea at a dose level of 12 mg QD.

In **Cohort 5** (titration to 15 mg QD), 27 AEs were observed in n=5 of n=6 subjects with levodopa-induced dyskinesia treated with PF-06649751 with n=2 subjects discontinued due to AEs. Most of them were mild to moderate. The most common AEs observed in 2 or more subjects in Cohort 5 were headache in n=3 subjects (50.0%), nightmare in n=2 subjects (33.3%), nausea in n=2 subjects (33.3%), dizziness in n=2 subjects (33.3%), abdominal discomfort in n=2 subjects (33.3%), anxiety in n=2 subjects (33.3%), neck pain in n=2 subjects (33.3%) and somnolence in n=2 subjects (33.3%). Severe AEs were 1 event of nightmare at a dose level of 4 mg QD.

In **Cohort 6** (titration to 25 mg QD), 63 AEs were observed in n=15 of n=19 subjects treated with PF-06649751 with n=7 subjects discontinued due to AEs. Most of them were mild to moderate. The most common AEs observed in 2 or more subjects in Cohort 6 were nausea in n=8 subjects (42.1%), headache in n=8 subjects (42.1%), dizziness in n=5 subjects (26.3%), vomiting in n=4 subjects (21.1%), abnormal dreams in n=3 subjects (15.8%), agitation in n=2 subjects (10.5%), constipation in n=2 subjects (10.5%), and nightmare in n=2 subjects (10.5%). Serious AEs were one event of event of palpitations (severe AE) not considered related to study drug by the investigator leading to discontinuation on the first day of study drug administration (Day 3) at a dose level of 1 mg. Further severe AEs were 1 event of vomiting at a dose level of 12 mg QD and 1 event of dry mouth at a dose level of 18 mg QD.

Across cohorts there were no apparent trends or clinically meaningful values for laboratory results, vital signs or ECG recordings.

In summary, multiple ascending-doses of PF-06649751 up to 25 mg QD were safe and well tolerated by subjects with Parkinson's disease.

#### B7601009

Preliminary safety results from Cohort 1 and Cohort 2 are summarized in the following:

There were no deaths, no serious adverse events, no severe adverse events and no discontinuations due to adverse events. The number of adverse events in subjects who reported at least one adverse event was 9 events in n=6 out of n=17 subjects (placebo), 1 event in n=1 out of n=6 subjects (0.75 mg), 2 events in n=2 out of n=6 subjects (1.5 mg), 15 events in n=7 out of n=12 subjects (3 mg), 14 events in n=4 out of n=6 subjects (6 mg) and 5 events in n=4 out of n=6 subjects (9 mg).

Adverse events reported more than once in any dose group included mild or moderate headache (incidence of 35.3% in the placebo group, 0 in the 0.75 mg group, 16.7% in the 1.5 mg group, 25% in the 3 mg group, 16.7% in the 6 mg group, and 50% in the 9 mg group). Mild or moderate nausea was reported with an incidence of 16.7% in the 3 mg group, 33.3% in the 6 mg group 16.7% in the 9 mg group. The incidence of vomiting (mild or moderate in severity) was 8.3% in the 3 mg group, 83.3% in the 6 mg group and 50% in the 9 mg group. Mild orthostatic hypotension was observed with an incidence of 5.9% in the placebo group, 8.3% in the 3 mg group, and 33.3% in the 6 mg group.

No clinically meaningful lab abnormalities were observed.

The maximum increase of pulse rate from baseline was slightly higher in the high dose groups, with a mean of the maximum increase of standing pulse rate being 12.4, 13.5, 10.0 in the placebo, 0.75 mg and 1.5 mg groups, and of 18.1, 18.7 and 20.8 in the 3 mg, 6 mg and 9 mg dose groups; and the mean of the maximum increase of supine pulse rate being 9.5, 14.3, 7.2 and 14.0 in the placebo, 0.75, 1.5 and 3 mg dose groups, and of 17.3 and 18.2 in the 6 mg and 9 mg dose groups. No subjects had a standing or supine pulse rate >120 bpm.

The maximum decrease from baseline in systolic or diastolic blood pressure was similar between the dose groups. N=2 (33.3%) subjects in the 1.5 mg dose group, n=1 (8.3%) in the 3 mg group, n=2 (33.3%) in the 6 mg group and n=2 (33.3%) in the 9 mg group had a standing systolic blood pressure <90 mmHg, and n=1 (5.9%) in the placebo group and n=1 (16.7%) in the 9 mg group had a standing diastolic blood pressure <50 mmHg.

There appeared to be a small dose-related increase of the QTcF interval at the 2 h, 4 h and 8 h post dose time points. At 2 hours post dose, mean changes from baseline were 2.5 msec in the placebo group, ranged from -1.0 to +3.1 msec in the 0.75, 1.5 and 3 mg groups, and were 10.6 msec in the 6 mg dose group and 11.7 in the 9 mg dose group. At 4 hours post dose, changes from baseline were -1.9 in the placebo group, ranged from 3.0 to +5.4 msec in the 0.75, 1.5 and 3 mg groups, and were 8.4 msec in the 6 mg dose group and 10.7 msec in the 9 mg dose group. At 8 hours post dose, changes from baseline were -1.1 in the placebo group, ranged from -1.6 to +2.7 msec in the 0.75, 1.5 and 3 mg groups, and were 9.0 msec in the 6 mg dose group and 6.1 msec in the 9 mg dose group. The maximum change from baseline in QTcF was higher in the 3 mg, 6 mg and 9 mg dose groups, with mean values of 14.3 msec in the placebo group, 11.3 msec, 13.9 msec, 18.1, 18.6 and 17.1 msec in the 0.75 mg, 1.5 mg, 3 mg, 6 mg and 9 mg dose groups, respectively. No subjects had QTcF values  $\geq 500$  msec, one subject in the 6 mg group had a maximum value  $\geq 450$  but <480 msec. No subject had an increase of QTcF from baseline  $\geq 60$  msec, n=1 subject in the 6 mg group had an increase of  $\geq 30$  but <60 msec.

In summary, single doses of PF-06649751 up to 9 mg were safe and well tolerated by subjects with Parkinson's disease. There were no deaths, serious adverse events, no severe adverse events and no discontinuations due to adverse events. The most common mild to moderate adverse events were headache, nausea, vomiting and orthostatic hypotension. Nausea, vomiting and orthostatic hypotension appeared to be more common in the higher

dose groups (3 mg, 6 mg and 9 mg PF-06649751). There appeared to be a small dose related increase in heart rate without consistent changes in blood pressure, except for the observations of orthostatic hypotension. There was an increase of QTcF in the higher dose groups between 2 and 8 hours post dose, but no subject had a QTcF  $\geq 500$  msec or an increase of QTcF of  $\geq 60$  msec.

To date, nausea and emesis have been identified as Adverse Drug Reactions (ADR) for PF-06649751.

### 1.4.3. Pharmacokinetics

The pharmacokinetic behavior of PF-06649751 following single doses is characterized by rapid absorption followed by bi-phasic decline in plasma concentrations. PF-06649751 reached peak concentration at approximately 1.0 to 2.0 hours following single oral doses. Both  $C_{max}$  and  $AUC_{inf}$  increased proportionally with increasing dose from 0.25 mg to 1.5 mg. Mean  $t_{1/2}$  were 21.0 to 22.4 hours. Food did not seem to alter  $T_{max}$ , however, food decreased  $AUC_{inf}$  and  $C_{max}$  by about 9% and 13%, respectively, at the 0.75 mg PF-06649751 dose. Co-administration of TMB did not have a noticeable impact on PF-06649751 exposures in healthy subjects. Increase in steady state PF-06649751 exposures following multiple oral doses appeared to be approximately dose-proportional across the B7601002 and B7601005 studies. Evaluation of PF-06649751 pharmacokinetics in healthy Japanese subjects at 1.5 mg QD dose suggests no meaningful difference between Japanese and Western subjects.

Based on preliminary data following single ascending doses in Parkinson disease (PD) patients (B7601009), peak PF-06649751 concentrations ( $C_{max}$ ) occurred at approximately 3.0 to 4.0 hours post dose. Increase in PF-06649751  $C_{max}$  and  $AUC_{last}$  values was roughly dose proportional with in the dose range of 0.75-9 mg. Exposures were observed to be in similar ranges for healthy subjects and PD patients at PF-06649751 doses of 0.75 mg and 1.5 mg.

Preliminary PF-06649751 steady state exposures in Parkinson's disease patients at different doses from an on-going study (B7601005) are presented in [Table 1](#). Final parameters will be available upon finalization of the clinical study report. PF-06649751 exposures at 5 mg QD were slightly higher than those observed in healthy subjects. At steady state, both  $AUC_{tau}$  and  $C_{max}$  increased in a roughly dose proportional manner with dose over the dose range of 5 mg to 15 mg QD. Increase in exposures from 15 mg QD to 25 mg QD was less than dose proportional. Median  $T_{max}$  was 2.0 hours for the 5 mg dose group, and approximately 4.0 hours at 15 mg and 25 mg. Based on a limited number of subjects, PF-06649751  $C_{max}$  and  $AUC_{tau}$  values appear to have higher variability at doses greater than the 5 mg dose group.

**Table 1. Steady State Exposures of PF-06649751 after Multiple Dosing in Parkinson's Disease Patients with Motor Fluctuations**

Dose	C <sub>max,ss</sub> (ng/mL)	T <sub>max</sub> (hrs)	AUC <sub>24,ss</sub> (ng*hr/ml)
5 mg QD (n=9)	118.5 (33)	2.0 (1.0-4.0)	2105 (35.0)
15 mg QD (n=7) <sup>a</sup>	325.4 (46)	4.0(2.0-12.0)	5993 (61.0)
25 mg QD (n=7)	401.6 (41)	4.03 (1.97-8.00)	7182 (52)

Values for C<sub>max,ss</sub> and AUC<sub>24,ss</sub> are presented as geometric means (%CV). Median values (range) are presented for T<sub>max</sub>

a. Values represent Cohort 4.

## 1.5. Rationale

### 1.5.1. Study Rationale

It is hypothesized that if an oral therapy were to demonstrate improvements in motor control over available therapies, but without inducing the complications of available therapies, it would represent a substantial advance in the symptomatic treatment paradigm in Parkinson's disease. This Phase 2 study will evaluate the efficacy, safety, and tolerability of PF-06649751 as a potential novel therapeutic agent in subjects with early stage Parkinson's disease. PF-06649751 is a novel D1 and D5 specific dopamine agonist and has the potential to improve motor symptoms in subjects with early Parkinson's disease. There is diversity in the therapeutic approach to this population among prescribers as well as experts in the field, with several treatment options available. The study population will include male and female subjects of non-childbearing potential diagnosed with Parkinson's disease, in the early stage of the disease, and who have no or limited history of exposure to L-Dopa and/or dopamine agonists. CCI exploratory CCI

### 1.5.2. Dose Rationale

PF-06649751 is a potent D1R agonist with terminal half-life long enough to facilitate once-daily dosing. In vitro data suggest CYP3A4 as the primary enzyme responsible for the majority of PF-06649751 metabolism. Data also indicates that overall risk of PF-06649751 to perpetrate drug interactions due to inhibition of P-glycoprotein, breast cancer resistance protein (BCRP), organic cation transporter (OCT1), and/or multidrug and toxin extrusion protein (MATE1) at the 15 mg dose level is low and clinically relevant drug-drug interactions are not anticipated (further information is available in the Investigator Brochure).

Phase 1 studies demonstrate poor tolerability at single oral doses greater than 1.5 mg in healthy subjects and titration improves tolerability at higher doses. The intent of the study is to investigate the safety, tolerability and efficacy in early Parkinson's disease patients. Due to the heterogeneity in disease severity in the patient population, a flexible dosing scheme is being implemented in the study with an aim to get each subject to his/her optimal dose for management of motor symptoms. Such a dosing paradigm would mimic the usage of PF-06649751 in a real-world clinical setting.

Subjects will be titrated to a dose that is deemed optimum by the investigator based on the subject's response with respect to motor control and tolerability. Based on all the PK, safety and tolerability data available to-date, a dose of 15 mg QD is set as the upper limit of daily dose that a subject can achieve in this study. A dose of 3 mg QD is expected to result in average concentrations similar  $C_{eff}$  values established using MPTP monkeys. Based on the observed exposures from study B7601005 (Table 1), a 15 mg QD dose is expected to provide exposures ~1.8 – 4 fold lower than the PK stopping criteria from the 15-week monkey toxicological study. The ~1.8 – 4 fold exposure window provides sufficient margin for a potential increase in PF-06649751 exposures when co-administered with weak inhibitors of CYP3A4. To prevent accidental exposure increases greater than toxicological limits, subjects on moderate or strong CYP3A4 inhibitors will be excluded from the trial until the magnitude of CYP3A4 interaction is defined within a drug-drug interaction study.

Based on previous experience in healthy subjects (study B7601002), subjects will be titrated to their optimum dose using a titration scheme presented in Section 5.5.1. Briefly, a PF-06649751 dose of 0.25 mg QD will be the starting dose in this study. This dose has been shown to be well tolerated and safe in all healthy subject Phase 1 studies, to-date. PF-06649751 doses will be increased at weekly intervals to reach the maximum allowed dose of 15 mg QD in 8 weeks. Due to the flexible nature of the study, some subjects may reach optimal dose before Visit 10. Specific instructions around up-titration and down-titrations, in case of tolerability issues, are provided in Section 5.5.1. The approximately 8 week titration scheme is similar to other dopamine agonists currently marketed for treatment of Parkinson's disease, and also allows subjects to be at stable dose for at least 6 weeks before the primary endpoint collection.

### 1.5.3. Summary of Benefit-Risk Assessment

The study is designed to assess the efficacy, safety and tolerability of PF-06649751 in subjects with early stage Parkinson's disease. Based on the clinical safety data available to-date, PF-06649751 dose levels in this study do not pose any specific risk to study participants. The study will attempt to mitigate mild-to-moderate instances of nausea, emesis and abdominal discomfort seen in prior studies in healthy subjects and subjects with Parkinson's disease by slow dose escalation, flexible dose optimization, and permitted concomitant use of anti-emetics for symptomatic treatment at the discretion of the investigator. Any potential risks will be further minimized by safety monitoring during the study and follow up for the subjects' well-being.

## 2. STUDY OBJECTIVES AND ENDPOINTS

### 2.1. Study Objectives

#### 2.1.1. Primary Objective

- To evaluate the effect of PF-06649751 administered once daily on motor symptoms in subjects with early stage Parkinson's disease.

### 2.1.2. Secondary Objectives

- To evaluate the safety and tolerability of PF-06649751 administered once daily in subjects with early stage Parkinson’s disease.

CCI [Redacted]

- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]

## 2.2. Endpoints

### 2.2.1. Primary Endpoint (Efficacy)

- Change from baseline in the Modified Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) Score Part III at Week 15.

### 2.2.2. Safety and Tolerability

- Adverse events.
- Clinical laboratory parameters.
- Vital signs.
- ECG parameters.
- Columbia Suicide Severity Rating Scale (C-SSRS).
- Questionnaire for Impulsive-Compulsive Disorders in Parkinson’s Disease – Rating Scale (QUIP-RS).
- Physician Withdrawal Checklist (PWC-20).

CCI [Redacted]

[Redacted]

- [Redacted]





During the initial up titration, subjects will gradually increase the dose of investigational product at weekly intervals, as tolerated, until Parkinsonian symptoms are optimally controlled. Investigational product will be self-administered once daily. The target dose range for PF-06649751 is 3 mg to 15 mg once daily (Stage 4 – Stage 8 in [Table 2](#)). However, a maintenance dose less than 3 mg may be selected, based on clinical response. Adjustments to the up-titration schedule are permitted during the Dose Optimization Period based on clinical judgment to mitigate adverse events or symptoms of suspected dopaminergic overstimulation. Thereafter, any dose adjustment during the Maintenance Period (after Visit 10) may only be performed after discussion with the Sponsor Medical Monitor/Study Clinician. For both the PF-06649751 and placebo treatment arms, investigational product will be discontinued at Visit 14.

### **3.1.1. Screening**

Informed consent will be completed prior to any screening assessments to initiate any treatment washout period, if applicable. All other screening assessments will occur within 30 days prior to Visit 1 (Randomization). Rescreening may be permitted after discussion with the Sponsor Medical Monitor/Study Clinician.

### **3.1.2. Double Blind Period**

Eligible subjects will enter the 15 week double blind treatment phase, consisting of:

- A 9 week Dose Optimization Period including:
  - Up titration of investigational product (PF-06649751 or placebo) administered once daily;
  - Period for stabilization after reaching an optimized dose.
- A stable treatment period (Dose Maintenance Period) for 6 weeks.

Subjects will return to the clinic each week during Visit 1 through Visit 4, and every other week thereafter during the Dose Optimization Period. Alternating phone visits will occur at every other week after Visit 4. During the Dose Maintenance Period, subjects will return to the clinic twice, at Visit 12 and Visit 14. Phone visits will be performed at Visit 11 and 13.

Each subject is planned to be up-titrated in a double-blind fashion to the clinically appropriate dose level of investigational product according to Dose optimization of Investigational Product, [Section 5.5.1](#).

Following Visit 14, treatment with investigational product will be discontinued.

### **3.1.3. Follow-up Period**

A follow-up clinic visit approximately two weeks after discontinuation of investigational product (Visit 15) will take place for the assessment of subject safety. A follow-up phone visit will occur approximately 28 days after discontinuation of investigational product (Visit 16) for a final subject safety assessment.

## **4. SUBJECT SELECTION**

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

The sponsor or designee will verify critical elements of the screening and enrollment process and provide written authorization (eg, e-mail) concurring with the investigator assessment that the subject is eligible to return for Visit 1 (Randomization) assessments. Eligibility may also be documented via telephone authorization followed by written confirmation. The key elements to be reviewed by the sponsor may include Parkinson's disease diagnosis, MDS-UPDRS Part III, medical history, concomitant medications, and select screening safety assessments including C-SSRS, PHQ-8, MMSE, labs, ECGs, and vital signs (See [Section 7.1.1](#), regarding Review of Inclusion/Exclusion Criteria).

### **4.1. Inclusion Criteria**

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

General and Administrative:

1. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.
2. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
3. Females of non-childbearing potential and/or male subjects between the ages of 45 and 80 years, inclusive.
4. Male subjects able to father children must agree to use a highly effective method of contraception throughout the study and for at least 28 days after the last dose of assigned treatment.
5. Female subjects of non-childbearing potential (ie, meet at least 1 of the following criteria):

- Have undergone a documented hysterectomy and/or bilateral oophorectomy;
- Have medically confirmed ovarian failure; or
- Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle-stimulating hormone (FSH) level confirming the post-menopausal state.

Parkinson's Diagnosis:

6. Clinical diagnosis of Parkinson's disease consistent with the United Kingdom (UK) Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria ([Appendix 4](#)).
7. Parkinson's Disease Hoehn & Yahr Stage I-III inclusive.
8. Parkinson's disease subjects deemed appropriate for treatment of motor symptoms with a MDS-UPDRS Part III score  $\geq 10$ .

Concomitant Parkinson's Disease Medications:

9. Treatment naïve or history of prior incidental treatment with dopaminergic agents (including L-Dopa and dopamine receptor agonist medications) for no more than 28 days and not within at least 7 days prior to Visit 1 (Randomization) as outlined in [Section 5.8](#), Concomitant Treatment(s), and [Appendix 2](#).
10. Willing and able to refrain from any Parkinson's disease medication not permitted by the protocol (including dopaminergic agents) throughout participation in the study as outlined in [Appendix 2](#).

Screening assessments:

11. A score of  $\geq 26$  on the Mini Mental State Examination (MMSE).
12. Body Mass Index (BMI) of 17.5 to 35 kg/m<sup>2</sup>; and a total body weight  $\geq 45$  kg.

**4.2. Exclusion Criteria**

Subjects with any of the following characteristics/conditions will not be included in the study:

Parkinson's Diagnosis:

1. History or clinical features consistent with an atypical Parkinsonian syndrome (including but not limited to Progressive Supranuclear Palsy, Multiple System Atrophy, Cortico-Basal Degeneration, etc).

2. Any Parkinson's disease-related feature or symptom that could interfere with the study conduct and results as assessed by the sponsor or Investigator.

Medical History:

3. Presence of acute or chronic clinically significant medical, including fever, or psychiatric condition or cognitive impairment or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
4. Presence or history of brain tumor, past history of hospitalization for head trauma with loss of consciousness, epilepsy (as defined by the International League Against Epilepsy),<sup>31</sup> conditions that lower seizure threshold, seizures of any etiology (including substance or drug withdrawal), or known increased risk of seizures.
5. Any significant AXIS I psychiatric disease as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition-Revised (DSM IV-TR, American Psychiatric Association, 2000) including subjects with clinically significant depression (PHQ-8 total score  $\geq 15$ ) (refer to [Section 7.1.6](#), Depression Assessment (PHQ-8)). Presence of minor depression or treated, stable depressive disorder is acceptable.
6. Subjects who have made a suicide attempt within the last 5 years. Subjects who, in the investigator's judgment, pose a significant suicide risk. Subjects who have suicidal ideation associated with actual intent and a method or plan in the past 6 months (ie, "Yes" answers on items 4 or 5 of the C-SSRS; refer to [Section 7.3](#) Assessment of Suicidal Ideation and Behavior (C-SSRS)).
7. History of clinically significant alcohol or substance dependency (other than caffeine or nicotine), as defined in DSM IV-TR, within 1 year before Screening.
8. In the opinion of the investigator (or caregiver, as applicable), has signs/symptoms suggestive of clinically significant cognitive impairment that would interfere with the ability to comply with study procedures.
9. Any condition possibly affecting drug absorption, past surgery of the gastrointestinal tract (eg, gastrectomy, colectomy), except cholecystectomy.
10. History of vasculitis.
11. History of Human Immunodeficiency Virus (HIV) infection.
12. History of malignancy other than:

- Non-metastatic basal or squamous cell carcinoma of the skin or carcinoma in situ that was surgically removed in total >1 year before screening and has not recurred.
  - Other type of malignancy which has been in remission 5 years or more before screening and has not recurred.
13. Subjects with first degree family history of unexplained sudden death, or of Long QT syndrome (LQTS).
14. Within 1 year of Screening or between Screening and Visit 1 (Randomization), any of the following: myocardial infarction; moderate or severe congestive heart failure, NYHA class III or IV; hospitalization for, or symptoms of, unstable angina; syncope due to orthostatic hypotension or unexplained syncope; known significant structural heart disease (eg, significant valvular disease, hypertrophic cardiomyopathy); or hospitalization for arrhythmia.

Concomitant Medications:

15. Currently receiving moderate or strong CYP3A4 inducers or CYP3A4 inhibitors (except for topical administration) as outlined in [Section 5.8](#) Concomitant Treatment(s), [Appendix 2](#), and [Appendix 3](#).
16. Currently receiving an antipsychotic, metoclopramide, reserpine, or amphetamine as outlined in [Section 5.8](#) Concomitant Treatment(s) and [Appendix 2](#).
17. Prohibited concomitant medications as outlined in [Section 5.8](#), Concomitant Treatment(s), and [Appendix 2](#).

Screening Assessments:

18. Pregnant female subjects; breastfeeding female subjects; females of childbearing potential (assessed at Screening); male subjects with partners currently pregnant; male subjects able to father children who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product or longer based upon the compound's half-life characteristics.
19. Screening supine blood pressure  $\geq 160$  mm Hg (systolic) or  $\geq 95$  mm Hg (diastolic), on a single measurement. If abnormal, up to 2 repeats are permitted following at least 5 minutes of rest. The screening value in that case will be the average of the 2 values closest to the normal range.
20. A decrease in systolic blood pressure (BP) of  $>20$  mmHg or in diastolic BP of  $>10$  mmHg measured 2 minutes after changing from a supine to standing position in the presence of symptoms of orthostasis. In the absence of symptoms of orthostasis a decrease in systolic blood pressure (BP) of  $>30$  mmHg or in diastolic BP of

- >15 mmHg measured 2 minutes after changing from a supine to standing position (The mean of three independent sets of vital signs, taken at least 15 minutes apart at the screening visit, will determine eligibility).
21. 12-lead ECG demonstrating QTcF >450 msec (>470 msec for females) or a QRS interval >120 msec at screening. If QTcF exceeds 450 msec (470 msec for females), or QRS exceeds 120 msec, the ECG should be repeated two more times and the average of the three values should be used to determine the subject's eligibility.
  22. Subjects with **ANY** of the following abnormalities in clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat, if deemed necessary:
    - Aspartate transaminase (AST)/ serum glutamic oxaloacetic transminase (SGOT) **or** alanine transaminase (ALT)/ serum glutamic pyruvic transminase (SGPT)  $\geq 2$  x upper limit of normal (ULN).
    - Total bilirubin  $\geq 1.5$  x ULN; subjects with a history of Gilbert's syndrome may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin is  $\leq$  ULN.
  23. A positive urine drug screen for drugs of abuse unless explained by medically indicated medication.
  24. A positive test for hepatitis B surface antigen or hepatitis C antibody (if confirmed by positive hepatitis C virus-ribonucleic acid (HCV-RNA) test).

General and Administrative:

25. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees directly involved in the conduct of the study.
26. Treatment with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study medication (whichever is longer).
27. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 56 days prior to Visit 1 (Randomization).
28. Unwilling or unable to comply with the lifestyle requirements described in [Section 4.4](#) this protocol.

### **4.3. Randomization Criteria**

Subjects will be randomized into the study provided they have satisfied all subject selection criteria. Using a central randomization system, eligible subjects will be randomized to one of two treatment groups (PF-06649751 or matching placebo) in a 1:1 ratio. Randomization blocks will be stratified by region.

### **4.4. Lifestyle Guidelines**

#### **4.4.1. Meals and Dietary Restrictions**

- Subjects will not be permitted to eat or drink grapefruit or grapefruit-related citrus fruits (eg, Seville oranges, pomelos, star fruit) from 7 days prior to the first dose of study medication until the end of double blind study medication.

#### **4.4.2. Alcohol, Caffeine, and Tobacco**

- Subjects will abstain from alcohol for at least 12 hours prior to every study visit.
- Subjects may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.
- Coffee and caffeine containing products are permitted throughout the study.
- Tobacco and tobacco containing products are permitted throughout the study.

#### **4.4.3. Activity**

- Subjects should abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests.

#### **4.4.4. Contraception – Females**

Females of childbearing potential are excluded from this study.

#### **4.4.5. Contraception – Males**

All male subjects who are able to father children and are sexually active must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and his partner from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for correct use of at least 1 of the selected methods of contraception. The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the [Schedule of Activities](#) and document such conversation in the subject's chart. In addition, the investigator or his or her designee will



instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject's partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of oral, inserted, injected, implanted or transdermal hormonal methods of contraception is allowed provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.
2. Correctly placed copper -containing intrauterine device (IUD).
3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.
4. Male sterilization with absence of sperm in the post-vasectomy ejaculate.
5. Bilateral tubal ligation / bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).
6. Female partner who meets the criteria for non-childbearing potential, as described below:

Female subjects of non-childbearing potential must meet at least one of the following criteria:

- Have undergone a documented hysterectomy and/or bilateral oophorectomy;
- Have medically confirmed ovarian failure; or
- Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle stimulating hormone (FSH) level confirming the post-menopausal state.

All other females (including females with tubal ligations) will be considered to be of childbearing potential.

All sexually active male subjects must agree to prevent potential transfer of and exposure to drug through semen to their partners by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 28 days after the last dose of investigational product.

#### **4.5. Sponsor's Qualified Medical Personnel**

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study SharePoint site.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, subject study numbers, contact information for the investigational site, and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigational site.

#### **4.6. Rater Qualifications**

Only qualified individuals who have been certified and/or trained through the Pfizer rater qualification program will be permitted to perform those evaluations for which they have been trained and/or certified. Prior to the study, the sites will be informed of the overall rater qualification methodology including the minimum qualifications and/or training requirement a rater must fulfill. Raters performing certain assessments will require certification by a vendor designated by the Sponsor prior to rating in this study.

The level of education, experience with the target population (or equivalent), and specific scale experience (or equivalent), scale-specific certification required (if applicable, eg, C-SSRS, MDS-UPDRS) will be documented and used to determine whether a rater is approved for a given assessment. Proposed raters who do not meet specific criteria but who may be qualified based on unique circumstances may be individually reviewed by the study clinical team to determine whether alternative experience or training may be equivalent to the specific criteria for a given assessment. If approval is granted, details of the relevant experience or training and the detailed rationale for judging them to be equivalent to the specified criteria will be documented in the rater tracking spreadsheet or equivalent.

All raters must be certified and/or trained on the selected study assessments as defined in the rater qualification documentation before he/she can participate in the administration of the assessments in the study. For specifically defined assessments, rater training and standardization exercises (when deemed necessary by the clinical study team) may be conducted. Each site will be provided written documentation outlining each rater's certification for specific study assessments. Recertification and/or retraining may be required at periodic intervals during the study, at the discretion of the study clinical team or designee.

The raters who administer specific study assessments may be documented in a centralized location and all site staff who administer ratings may be verified in the site study documentation during the conduct of the study.

Raters performing certain assessments will require certification by a vendor designated by the Sponsor prior to rating in this study.

## **5. STUDY TREATMENTS**

Investigational Product (IP) for the purpose of this study includes:

- PF-06649751 or placebo.

For the purposes of this study, and per International Conference on Harmonization (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

### **5.1. Allocation to Treatment**

Allocation of subjects to treatment groups will proceed through the use of an interactive response technology (IRT) system. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, the subject number and the date of birth of the subject. The site personnel will then be provided with a treatment assignment and dispensable unit (DU) or container number when drug is being supplied via the IRT system. The IRT system will provide a confirmation report containing the subject number and DU or container number assigned. The confirmation report must be stored in the site's files.

There is a 24-hour-a-day, 365-days-a-year IRT helpdesk available for any questions or issues. The study specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

### **5.2. Breaking the Blind**

Treatment assignment will be blinded to the sponsor study team, subject and investigator. At the initiation of the study, the study site will be instructed on the method for breaking the blind. The method will be either a manual or an electronic process. Blinding codes should be broken only in emergency situations for reasons of subject safety. Whenever possible, the investigator or sub-investigator will consult with a member of the study team prior to breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the case report form (CRF), and the subject is to be discontinued from the study.

### 5.3. Subject Compliance

Investigational product will be administered by the subject in the outpatient setting (each morning, daily for the duration of the treatment period). A dosing diary will be given to the subject with instructions on how to record the blister card being used and also the daily times of investigational product administration. The subject will bring all blister cards, used and un-used, back to the clinic at each visit. At each visit, a tablet count will be done by the research staff, and the subject will be questioned about any missed or extra doses taken. Site personnel will assess administration compliance based on the drug accountability of the blister packs, review of the dosing diary, and discussion with the subject. In cases where tablets are unaccounted for by the dosing diary and/or questioning of subjects, the site will consider the drug accountability to be a source for missed or additional doses. A subject will be considered compliant with the protocol at a study treatment compliance range of 80%-120%.

In cases where the subject is outside the compliance range, a protocol deviation will be captured and the site is expected to take appropriate actions depending on the reason for non-compliance (eg, if a subject did not have a valid reason for not taking investigational product, that the subject is re-educated on investigational product administration requirements and expectation to adhere to the requirements). Cases of repeated non-compliance may result in discontinuation of the subject from the study, if deemed necessary by the investigator and/or sponsor.

### 5.4. Investigational Product Supplies

#### 5.4.1. Dosage Form(s) and Packaging

Blinded PF-06649751 and its matched placebo will be provided as tablets for oral administration. PF-06649751 0.25 mg, 1 mg, 5 mg and their matching placebo will be supplied in blister cards. At each dispensing visit, subjects will receive sufficient quantity of investigational product to last until their next scheduled visit. Each blister card will be labeled according to local regulatory requirements.

#### 5.4.2. Preparation and Dispensing

The PF-06649751 0.25 mg, 1 mg, 5 mg tablets, and matching placebo are to be dispensed using a drug management system at each visit. A qualified staff member will dispense the investigational product via unique container numbers in the blister card(s) provided per the study visit schedule. The subject/caregiver are to be instructed to maintain the product in the blister cards provided throughout the course of dosing and return all blister cards, used and unused, to the site at the next study visit for accountability.

### 5.5. Administration

For investigational product administration, subjects (and caregivers, as applicable) should be instructed as follows:

- Take 3 tablets at approximately the same time each morning.

- Swallow each tablet whole, with water.
- Do not manipulate or chew the tablet prior to swallowing.
- All tablets should be taken within approximately 5 minutes.
- The tablets may be taken with or without food.
- Subjects will document the timing of investigational product administration on each day of the double-blind treatment via the subject dosing diary.

### **5.5.1. Dose Optimization of Investigational Product**

Each subject is planned to be up-titrated in a double-blind fashion to an optimal dose level of investigational product according to a flexible dose titration scheme. Reaching of the maximum allowed dose level (15 mg, Stage 8) is not mandatory; subjects may achieve a satisfactory clinical response at a lower dose level.

Modifications to the upward titration of investigational product can be made to achieve an optimized dose level. Dose escalation will continue, as tolerated, to a response level judged satisfactory by the investigator. The target dose is the dose at which the individual subject has achieved an optimal clinical balance of motor symptom control and tolerability, based on the judgment of the investigator. The target dose range for PF-06649751 is expected to be between 3 mg to 15 mg once daily.

Dose optimization is to be completed no later than Visit 10; thereafter the achieved dose level will be maintained for the remainder of the double-blind treatment period. Dose adjustments after Visit 10 may be performed only after consultation with the Sponsor Medical Monitor/Study Clinician.

The titration scheme for this study is presented in [Table 2](#).

**Table 2. Titration Scheme of PF-06649751 and Placebo**

Stage # Start Day of Dose Level <sup>a,b</sup>	PF-06649751 (QD mg)	Placebo
Stage 1/from day 1 <sup>a</sup>	0.25	P
Stage 2/from day 8 <sup>c</sup>	0.75	P
Stage 3/from day 15	1.5	P
Stage 4/from day 22	3	P
Stage 5/from day 29	5	P
Stage 6/from day 36	7	P
Stage 7/from day 43	11	P
Stage 8/from day 50	15	P

a. Subjects will initiate the first dose and subsequent dose level increases the day after the corresponding phone/clinic visit (eg, Day 1 is the day after Visit 1).

b. For subjects who will not achieve their individual optimal dose level on the day following Visit 8, dose escalation is permitted, however the final dose level increase must be completed before Visit 10.

c. The increase in dose level from Stage 1 to Stage 2 is a mandatory step at Visit 2 (from Day 8).

#### 5.5.1.1. Dose Optimization Period

- **Stage 1 (Day 1 to Day 7):** Subjects who experience intolerable adverse events during the first week of the study will need to discontinue the investigational product.
- **Stage 2 onward:** Dose level increases are permitted on a weekly basis.

At each planned visit and as necessary at unplanned visits during the Dose Optimization Period, the investigator will evaluate:

- If the current dose level is well tolerated; and
- If the degree of motor symptom control can be considered satisfactory.

Based on this evaluation and investigator discretion, a decision will be made to:

- Decrease the dose to the previous dose level to address potential tolerability findings.
- Stay at the current dose level to address potential tolerability findings, if needed for further clinical stabilization or when the individual subject has achieved an optimal balance of motor symptom control and tolerability.
- Increase the dose to the next higher dose level to evaluate if further clinical benefit can be achieved.

For subjects who have achieved an optimal balance of motor symptom control and tolerability, the investigator should consider an attempt to increase the dose to the next higher dose level in order to evaluate if further clinical benefit can be achieved.

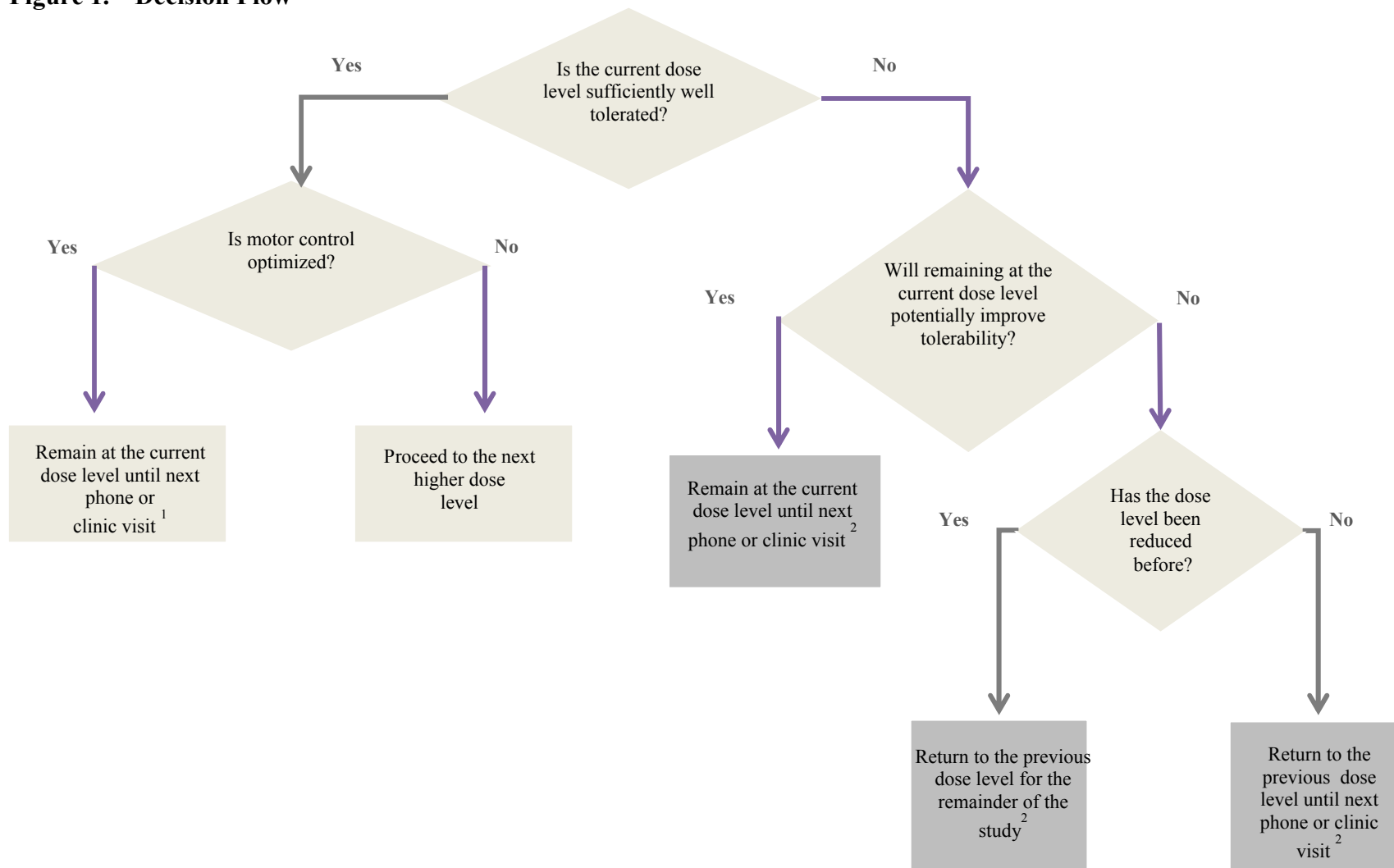
Efforts should be made to reach the minimum targeted dose of 3 mg or placebo (Stage 4). Subjects who have not reached Stage 4 by Visit 10 will stay at their current dose for the remainder of the study.

Subjects whose dose had been reduced to the previous dose level and who still do not tolerate the reduced dose level or who do not tolerate a re-challenge at the previously attempted dose level should be returned to the next lower/previous dose level and stay at this dose level for the remainder of the double-blind treatment period.

It is possible that a stable dose can be reached by or before Visit 8. However, continued dose adjustments for efficacy and tolerability may occur until Visit 10.

**Figure 1 (below)** lists the decision flow that should occur at each phone and clinic visit during the Dose Optimization Period:

**Figure 1. Decision Flow**



1. Consider proceeding to the next higher dose level to evaluate if further clinical benefit can be achieved
2. Consider discontinuation if limited tolerability persists



### 5.5.2. Dose Maintenance Period

- The maintenance dose is reached when the individual subject has achieved an optimal balance of motor symptom control and tolerability, based on clinical judgment.
- The target dose range is expected to be 3 mg to 15 mg once daily (Stage 4 – Stage 8). However, a maintenance dose less than 3 mg may be selected, based on tolerability and clinical response.
- Any dose adjustment during the Maintenance Period (after Visit 10) may only be performed after consultation with the Sponsor Medical Monitor/Study Clinician.

### 5.6. Investigational Product Storage

The investigator, or an approved designee, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements. An Investigational Product Manual will be supplied to the pharmacy prior to initiation of the study and will provide further information regarding storage conditions of the product.

Investigational product should be stored in its original container and in accordance with the label. Site staff will instruct subjects on the proper storage requirements for take home investigational products, including how to report temperature excursions. See the single reference safety document (SRSD), which for this study is the Investigator's Brochure.

However, storage conditions stated in the single reference safety document (eg, Investigator's Brochure and package insert) will be superseded by the storage conditions stated in the labeling.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the product(s) are briefly out of the temperature range described in the labeling are not considered excursions.

Site staff will instruct subjects on the proper storage requirements for take home investigational products.

### **5.7. Investigational Product Accountability**

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. Subjects will return Investigational Product to the site per the [Schedule of Activities](#). Additional details regarding the process for accountability will be provided prior to initiation of the study.

#### **5.7.1. Destruction of Investigational Product Supplies**

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

### **5.8. Concomitant Treatment(s)**

Subjects will abstain from all concomitant medications as outlined in [Appendix 2](#) and [Appendix 3](#), except for the treatment of adverse events.

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant treatment at each phone or clinic visit.

Medications taken within 60 days before the first dose of study investigational product will be documented as a prior medication. Medications taken after the first dose of study investigational product will be documented as concomitant medications.

#### **5.8.1. Medications for Parkinson's Disease**

Permitted Parkinson's disease medications:

- MAO-B inhibitors, amantadine and anticholinergic drugs are permitted. Subjects must be on a stable dose of these anti-parkinsonian medications for at least 42 days prior to Visit 1 (Randomization).

Prohibited Parkinson's disease medications:

- Prior exposure or history of treatment with L-dopa for more than 28 days; and any treatment with L-Dopa within 7 days prior to Visit 1 (Randomization).
- Prior exposure or history of treatment with dopamine receptor agonists including pramipexole, ropinirole, rotigotine and apomorphine for more than 28 days; and within 7 days prior to Visit 1 (Randomization).
- Rescue Parkinson's disease medications taken after the first dose of investigational product are not permitted.

### **5.9. Other Prohibited Concomitant Medications**

The following medications will not be permitted within 28 days prior to Visit 1 (Randomization):

- CYP3A4 inducers: the use of moderate and strong inducers of CYP3A4 is not permitted, since they may decrease the levels of the study drug. A list of potential drug inducers is provided in [Appendix 3](#).
- CYP3A4 inhibitors: the use of moderate or strong inhibitors of CYP3A4 is not permitted, since concomitant use these may lead to increased levels of the study drug. A list of potential CYP3A4 inhibitors is provided in [Appendix 3](#).

The use of marijuana is not permitted from Screening through the end of the double blind treatment period.

The following medications will not be permitted within 42 days prior to Visit 1 (Randomization):

- Amphetamines, methylphenidate or other stimulants.
- Antipsychotics, metoclopramide, or reserpine are not permitted.
- Lithium, tricyclic antidepressants, irreversible MAO-A/B inhibitor antidepressants (including moclobemide, tranlycypromine, and phenelzine).
- Antiepileptics are not permitted except if used for chronic painful conditions at steady doses (for example, gabapentin or pregabalin).

#### **5.9.1. Permitted Other Concomitant Medications**

Stable doses of other concomitant medications are permitted during the course of the study, including antihypertensives, antidepressants (other than irreversible MAO-A/B inhibitors), anticoagulants, lipid lowering agents, oral antidiabetics, thyroid replacement hormones, and antacids. For symptomatic treatment of nausea and/or emesis, the use of an anti-emetic may be considered.

Stable low dose opioids for chronic painful medical conditions may be permitted based on a consultation with the medical monitor.

The potential risk for drug-drug-interactions with PF-06649751 and primary substrates of CYP3A4 (especially those with narrow therapeutic index, vinca alkaloids), and BCRP is considered low but cannot be excluded as it has not been fully evaluated at this time. Therefore, caution is recommended when PF-06649751 is combined with BCRP (eg, rosuvastatin, methotrexate, mitoxantrone, etc.) or CYP3A substrate (eg, alfentanil, ergotamine, irinotecan, ticagrelor, simvastatin, etc.). CCI

## 6. STUDY PROCEDURES

### 6.1. Screening – Day -30 to Day -2

Subjects will be screened within 30 days prior to administration of investigational product to confirm they meet the subject selection criteria for the study. The investigator (or an appropriate delegate at the investigator site) will obtain informed consent from each subject in accordance with the procedures described in [Section 12.3](#). Informed consent may be obtained up to 60 days prior to Visit 1 (Randomization).

Rescreening may be permitted after discussion with the study Sponsor clinician or medical monitor or under the specific circumstance of HCV positive laboratory test in order to perform follow up a follow up qualitative HCV RNA test.

At any given time, the sponsor or designee will verify critical elements of the screening and enrollment process and, in cases where verification is required, will provide written authorization (eg, e-mail) concurring (or disagreeing, if necessary, dependent on outcome) with the investigator assessment that the subject is eligible for enrollment into the study. Eligibility may also be documented via telephone authorization followed by written confirmation. The key elements to be reviewed by the sponsor may include Parkinson's disease diagnosis, MDS-UPDRS scores, medical history, concomitant medications, and select screening safety assessments including labs, ECGs, and vital signs. Full instructions on the Screening Verification process will be provided as part of training. It is critical that the sponsor be provided with all requested data in a timely fashion in advance of enrollment, as will be instructed during study training.

The following procedures will be completed:

- Obtain written informed consent. For subjects needing further adjustment of concomitant medications, informed consent should be obtained prior to any adjustments and prior to the Screening visit.
- Register subject as Screened in interactive web response (IWR) system. Subjects will be assigned unique, 8-digit number, which will be retained throughout duration of study participation.

- Obtain prior medical history and demography.
- Assess prior/concomitant medications including Parkinson’s disease medications.
- Review and assess adverse events (AEs).
- Perform full physical and neurological examination.
- Perform Mini Mental State Examination (MMSE).
- Verify Parkinson’s disease diagnosis using the UK Parkinson’s Disease Society Brain Bank Clinical Diagnostic Criteria ([Appendix 4](#)).
- Perform Hoehn & Yahr Stage assessment.
- Collect height, weight, and BMI.
- Collect blood and urine specimens for the following:
  - Serum pregnancy test for all females. A negative pregnancy result (contraception check) is required before the subject may receive investigational product.
  - FSH test for female subjects that are amenorrheic for at least 12 months. This is mandatory for female subjects that do not have documented hysterectomy, bilateral oophorectomy or medically confirmed ovarian failure, to confirm non-childbearing potential (see [Section 4.1](#), Inclusion Criteria #5).
  - Serological testing (HIV, Hepatitis B antigen, and Hepatitis C antibody).
  - Urine drug screening test for drugs of abuse (including tetrahydrocannabinol (THC) to be performed at the central lab.
  - Safety laboratory tests (including additional specific tests to monitor for vascular inflammation). Urinalysis will be performed by dipstick at site, and if positive, additional urine should be collected and sent to the central lab.
- Perform standard supine 12-lead electrocardiogram (ECG). If QTcF exceeds 450 msec for males or 470 msec for females, or QRS interval exceeds 120 msec, the ECG should be repeated two more times and the average of the three values should be used to determine the subject’s eligibility.
- Perform supine and standing vitals (HR and blood pressure). If the subject does not meet the eligibility criteria for vitals (HR and blood pressure) after initial measurement, perform triplicate vital signs to determine eligibility.
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS) “Past 5 years” Evaluation.

- Perform the Patient Health Questionnaire (PHQ-8).
- Perform Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts I, II, III, and IV.
- Review Inclusion and Exclusion criteria.

To prepare for study participation, subjects will be instructed on the use of the Lifestyle Guidelines (Section 4.4) and Concomitant Medications (Section 5.8) of the protocol.

## 6.2. Study Period

For the study period described below, there is a +3 day visit window for scheduling of visits during Dose Optimization Period from Visit 2 until Visit 9 (inclusive).

From Visit 10 to Visit 16, the visit window will be  $\pm 3$  days except for Visit 14 where the visit window to be -3 days to ensure discontinuation of investigational product after 15 weeks of treatment.

If deemed necessary for the clarification of dosing decisions or further clinical assessments which cannot be completed during the phone visit an additional unplanned clinic visit may be scheduled (Section 6.4.2, Unplanned Clinic Visits).

**Study visit times are based relative to Visit 1 (Randomization), and not relative to the previous visit. The indicated visit windows are only intended to mitigate scheduling conflicts for study visits.**

For each visit, when multiple procedures are scheduled, the following chronology of events should be adhered to, where possible:

- CCI [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]

- Other procedures may be obtained between or concurrent to those listed above.

### 6.2.1. Visit 1 (Randomization)

- Assess prior/concomitant medications.
- Confirm no change in medical history since screening visit.
- Review Inclusion and Exclusion criteria.
- Instruct eligible subjects to complete the following PROs (recommended in this order, whenever possible):
  - CCI [REDACTED]
  - Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale (QUIP-RS);
    - C [REDACTED]
    - C [REDACTED]
    - [REDACTED]
    - [REDACTED]
    - [REDACTED]
  - CCI [REDACTED].
- Perform brief physical and neurological examination.
- Urine drug screening in the form of a dipstick performed at the site.
- CCI [REDACTED]
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard supine and standing vitals (HR and blood pressure).
- Collect blood and urine for safety lab tests. Screening labs must have no clinically significant findings, as judged by the investigator, in order for the subject to be randomized. Urinalysis will be performed by dipstick at site, and if positive, additional urine should be collected and sent to the central lab.

- Collect blood and urine biospecimen samples. CCI [REDACTED]
- CCI [REDACTED]
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS) “Since last evaluation”.
- Review and assess adverse events (AEs).
- CCI [REDACTED]
- Register subject as Randomized in IRT in order to obtain randomization number.
- Provide written and verbal instructions on the storage, management, and return of investigational product, and on the use of subject dosing diary to track investigational product blister cards and the daily investigational product dosing time (Sections 5.3, 5.4, 5.5, and 5.6).
- Dispense Investigational Product.
- Instruct subjects on which blister card to dose from and start of daily dosing of investigational product in accordance with the flexible dose up-titration scheme (Section 5.5.1). Subjects will begin dosing the following morning (Day 1).

#### 6.2.2. Visit 2 (Day 7)

- Assess concomitant medications.
- Review and assess adverse events (AEs).
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard supine and standing vitals (HR and blood pressure).
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS) “Since last visit”.
- Investigational Product Accountability.
- Review the dosing diary information recorded by the subject to ensure documentation of investigational product blister cards, and dosing compliance (ie, ensure daily dosing time was recorded and assess situations such as missed/additional doses).
- Evaluate and document status of dose optimization using the Decision Flow (Figure 1).



- Dispense investigational product.
- Instruct subjects which blister card to dose from and on continued daily dosing of investigational product in accordance with the flexible dose arm up-titration scheme (see [Section 5.5.1](#) Dose optimization of Investigational Product).

### 6.2.3. Visit 3 (Day 14)

- Assess concomitant medications.
- Review and assess adverse events (AEs).
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard supine and standing vitals (HR and blood pressure).
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS) “Since last visit”.
- Investigational Product Accountability.
- Review the dosing diary information recorded by the subject to ensure documentation of investigational product blister cards, and dosing compliance (ie, ensure daily dosing time was recorded and assess situations such as missed/additional doses).
- Evaluate and document the status of dose optimization using the Decision Flow ([Figure 1](#)).
- Dispense investigational product.
- Instruct subjects which blister card to dose from and on continued daily dosing of investigational product in accordance with the flexible dose arm up-titration scheme (see [Section 5.5.1](#) Dose optimization of Investigational Product).

### 6.2.4. Visit 4 (Day 21)

- Perform MDS-UPDRS Part III.
- Assess concomitant medications.
- Review and assess adverse events (AEs).
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard supine and standing vitals (HR and blood pressure).
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS) “Since last visit”.

- Retrain subjects on the storage, management, and return of investigational product, and on the use of subject dosing diary to track investigational product blister cards and the daily investigational product dosing time ([Sections 5.3, 5.4, 5.5, and 5.6](#)).
- Collect blood sample for evaluation of PF-06649751 pharmacokinetics. Document the date, time and amount of latest dose subject administered.
- Investigational Product Accountability.
- Review the dosing diary information recorded by the subject to ensure documentation of investigational product blister cards, and dosing compliance (ie, ensure daily dosing time was recorded and assess situations such as missed/additional doses).
- Evaluate and document the status of dose optimization using the Decision Flow ([Figure 1](#)).
- Dispense Investigational Product.
- Instruct subjects which blister card to dose from and on continued daily dosing of investigational product in accordance with the flexible dose arm titration scheme (see [Section 5.5.1 Dose optimization of Investigational Product](#)).

#### **6.2.5. Visit 5 (Day 28, Phone Visit)**

- Assess concomitant medications.
- Review and assess adverse events (AEs).
- Review during the phone call dosing diary information with subject to ensure documentation of investigational product blister cards, and dosing compliance (ie, ensure daily dosing time was recorded and assess situations such as missed/additional doses).
- Evaluate and document the status of dose optimization using the Decision Flow ([Figure 1](#)).
- Instruct subjects which blister card to dose from and on continued daily dosing of investigational product in accordance with the flexible dose arm titration scheme (see [Section 5.5.1 Dose optimization of Investigational Product](#)).
- Inform the subject that the verification of blister card will be performed the day following the phone visit by the site staff by text, phone or email depending on the site/subject's preference.

#### **6.2.6. Visit 6 (Day 35)**

- Perform MDS-UPDRS Part III.

- Questionnaire for Impulsive-Compulsive Disorders in Parkinson’s Disease– Rating Scale (QUIP-RS).
- Assess concomitant medications.
- Review and assess adverse events (AEs).
- Perform brief physical and neurological examination.
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard supine and standing vitals (HR and blood pressure).
- Collect blood samples for safety laboratory tests. Urinalysis will be performed by dipstick at site, and if positive, additional urine should be collected and sent to the central lab.
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS) “Since last visit”.
- Collect blood sample for evaluation of PF-06649751 pharmacokinetics. Document the date, time and amount of latest dose subject administered.
- Investigational Product Accountability.
- Review the dosing diary information recorded by the subject to ensure documentation of investigational product blister cards, and dosing compliance (ie, ensure daily dosing time was recorded and assess situations such as missed/additional doses).
- Evaluate and document the status of dose optimization using the Decision Flow (Figure 1).
- Dispense Investigational Product.
- Instruct subjects which blister card to dose from and on continued daily dosing of investigational product in accordance with the flexible dose arm titration scheme (see Section 5.5.1 Dose optimization of Investigational Product).

**6.2.7. Visit 7 (Day 42, Phone Visit)**

- Assess concomitant medications.
- Review and assess adverse events (AEs).
- Review during the phone call dosing diary information with subject to ensure documentation of investigational product blister cards, and dosing compliance (ie, ensure daily dosing time was recorded and assess situations such as missed/additional doses).

- Evaluate and document the status of dose optimization using the Decision Flow (Figure 1).
- Instruct subjects which blister card to dose from and on continued daily dosing of investigational product in accordance with the flexible dose arm titration scheme (see Section 5.5.1 Dose optimization of Investigational Product).
- Inform the subject that the verification of blister card will be performed the day following the phone visit by the site staff by text, phone or email depending on the site/subject's preference.

#### **6.2.8. Visit 8 (Day 49)**

- Perform MDS-UPDRS Part III.
- Assess concomitant medications.
- Review and assess adverse events (AEs).
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard supine and standing vitals (HR and blood pressure).
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS) "Since last visit".
- Investigational Product Accountability.
- Review the dosing diary information recorded by the subject to ensure documentation of investigational product blister cards, and dosing compliance (ie, ensure daily dosing time was recorded and assess situations such as missed/additional doses).
- Evaluate and document the status of dose optimization using the Decision Flow (Figure 1).
- Dispense Investigational Product.
- Instruct subjects which blister card to dose from and on continued daily dosing of investigational product in accordance with the flexible dose arm titration scheme (see Section 5.5.1 Dose optimization of Investigational Product).

#### **6.2.9. Visit 9 (Day 56, Phone Visit)**

- Assess concomitant medications.
- Review and assess adverse events (AEs).
- Review during the phone call dosing diary information with subject to ensure documentation of investigational product blister cards, and dosing compliance

(ie, ensure daily dosing time was recorded and assess situations such as missed/additional doses.

- Evaluate and document the status of dose optimization using the Decision Flow (Figure 1).
- Instruct subjects which blister card to dose from and on continued daily dosing of investigational product in accordance with the flexible dose arm titration scheme (see Section 5.5.1 Dose optimization of Investigational Product).
- Inform the subject that the verification of blister card will be performed the day following the phone visit by the site staff by text, phone or email depending on the site/subject's preference.

#### 6.2.10. Visit 10 (Day 63)

- Instruct subject to complete the following patient reported outcomes:
  - CCI [REDACTED]
  - Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS);
    - CCI [REDACTED]
    - [REDACTED]
    - [REDACTED]
    - [REDACTED]
    - [REDACTED]
    - [REDACTED]
  - CCI [REDACTED]
  - CCI [REDACTED]
- Assess concomitant medications.
- Review and assess adverse events (AEs).
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS) "Since last visit".
- Perform full physical and neurological examination.

- Collect weight.
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard supine and standing vitals (HR and blood pressure).
- Collect blood samples for safety laboratory tests. Urinalysis will be performed by dipstick at site, and if positive, additional urine should be collected and sent to the central lab.

- CCI [REDACTED]

- [REDACTED]

- [REDACTED]

- Retrain subjects on the storage, management, and return of investigational product, and on the use of subject dosing diary to track investigational product blister cards and the daily investigational product dosing time ([Sections 5.3, 5.4, 5.5, and 5.6](#)).
- Investigational Product Accountability.
- Review the dosing diary information recorded by the subject to ensure documentation of investigational product blister cards, and dosing compliance (ie, ensure daily dosing time was recorded and assess situations such as missed/additional doses).
- Dispense Investigational Product.
- Instruct subjects on continued daily dosing of investigational product (see [Section 5.5.2 Dose Maintenance Period](#)).

#### 6.2.11. Visit 11 (Day 70, Phone Visit)

- Assess concomitant medications.
- Review and assess adverse events (AEs).
- Review during the phone call dosing diary information with subject to ensure documentation of investigational product blister cards, and dosing compliance (ie, ensure daily dosing time was recorded and assess situations such as missed/additional doses).
- Instruct subjects on continued daily dosing of investigational product (see [Section 5.5.2 Dose Maintenance Period](#)).

#### 6.2.12. Visit 12 (Day 84)

- Perform MDS-UPDRS Part III.
- Assessment of concomitant medications.
- Review and assess adverse events (AEs).
- Perform brief physical and neurological examination.
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard supine and standing vitals (HR and blood pressure).
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS) “Since last visit”.
- CCI [REDACTED]
- Collect blood sample for evaluation of PF-06649751 pharmacokinetics. Document the date, time and amount of latest dose subject administered.
- Investigational Product Accountability.
- Review the dosing diary information recorded by the subject to ensure documentation of investigational product blister cards, and dosing compliance (ie, ensure daily dosing time was recorded and assess situations such as missed/additional doses).
- Dispense Investigational Product.
- Instruct subjects on continued daily dosing of investigational product (see [Section 5.5.2](#) Dose Maintenance Period).

#### 6.2.13. Visit 13 (Day 98, Phone Visit)

- Assess concomitant medications.
- Review and assess adverse events (AEs).
- Review during the phone call dosing diary information with subject to ensure documentation of investigational product blister cards, and dosing compliance (ie, ensure daily dosing time was recorded and assess situations such as missed/additional doses).
- Instruct subjects on continued daily dosing of PF-06649751 or placebo (see [Section 5.5.2](#) Dose Maintenance Period).

- Instruct subjects that the last dose of investigational product will be the morning of Day 105.

#### 6.2.14. Visit 14 or Early Termination Visit (Day 105)

- Instruct subject to complete the following patient reported outcomes:
  - CCI [REDACTED]
  - Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS);
  - CCI [REDACTED]
  - CCI [REDACTED]
  - CCI [REDACTED]
  - CCI [REDACTED]
  - CCI [REDACTED]
  - CCI [REDACTED]
  - CCI [REDACTED]
  - CCI [REDACTED]
- Assess concomitant medications.
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS) "Since last visit".
- Review and assess adverse events (AEs).
- Perform full physical and neurological exam.
- Collect weight.
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard supine and standing vitals (HR and blood pressure).
- Collect blood samples for safety laboratory tests. Urinalysis will be performed by dipstick at site, and if positive, additional urine should be collected and sent to the central lab.



- CCI [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- Investigational Product Accountability.
- Review the dosing diary information recorded by the subject to ensure documentation of investigational product blister cards, and dosing compliance (ie, ensure daily dosing time was recorded and assess situations such as missed/additional doses).
- Discontinuation of daily dosing of investigational product.

### 6.3. Follow Up Period

#### 6.3.1. Visit 15 – (Day 119)

- Assess concomitant medications.
- Review and assess adverse events (AEs).
- Perform brief physical and neurological exam.
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard supine and standing vitals (HR and blood pressure).
- Collect blood samples for safety laboratory tests (including additional specific tests to monitor for vascular inflammation). Urinalysis will be performed by dipstick at site, and if positive, additional urine should be collected and sent to the central lab.
- Collect blood and urine biospecimen samples.
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS) “Since last visit”.
- Perform Physician Withdrawal Checklist (PWC-20).

#### 6.3.2. Visit 16 – (Day 133, Phone Visit)

- Review and assess adverse events (AEs).

### 6.4. Unplanned Visits

Unplanned visits for adjustments of investigational product or for other purposes (eg, for safety reasons) may occur.

#### **6.4.1. Unplanned Phone Visits**

During an unplanned phone visit, the following assessments should occur (at a minimum):

- Review and assess adverse events (AEs).
- Assess concomitant medications.
- Review during the phone call dosing diary information with subject to ensure documentation of investigational product blister cards, and dosing compliance (ie, ensure daily dosing time was recorded and assess situations such as missed/additional doses).
- Instruct subjects on continued daily dosing of investigational product (see as applicable [Section 5.5.1](#) Dose optimization of Investigational Product or [5.5.2](#) Dose Maintenance Period).

#### **6.4.2. Unplanned Clinic Visits**

##### **6.4.2.1. Unplanned Clinic Visit during the Dose Optimization Period**

During an unplanned clinic visit, the following assessments should occur (at a minimum), except MDS -UPDRS Part III (which is optional):

- Review and assess adverse events (AEs).
- Assess concomitant medications.
- Perform MDS-UPDRS Part III (optional).
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard single supine and standing vitals (HR and blood pressure).
- Investigational Product Accountability.
- Review the dosing diary information recorded by the subject to ensure documentation of investigational product blister cards, and dosing compliance (ie, ensure daily dosing time was recorded and assess situations such as missed/additional doses).
- Evaluate and document the status of dose optimization using the Decision Flow ([Figure 1](#)).
- Dispense Investigational Product, if applicable.
- Instruct subjects which blister card to dose from and on continued daily dosing of investigational product in accordance with the flexible dose arm titration scheme (see [Section 5.5.1](#) Dose optimization of Investigational Product).

#### **6.4.2.2. Unplanned Clinic Visit during the Maintenance Period**

An unplanned clinic visit must occur if the sponsor is contacted during the Maintenance Period for a dose adjustment. The following assessments should occur (at a minimum), except MDS -UPDRS Part III (which is optional):

- Review and assess adverse events (AEs).
- Assess concomitant medications.
- Perform MDS-UPDRS Part III (optional).
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard single supine and standing vitals (HR and blood pressure).
- Investigational Product Accountability.
- Review the dosing diary information recorded by the subject to ensure documentation of investigational product blister cards, and dosing compliance (ie, ensure daily dosing time was recorded and assess situations such as missed/additional doses).
- Consult with the sponsor on discontinuation or dose adjustment.
- Dispense Investigational Product if authorization received from the sponsor to proceed with a dose adjustment.
- Instruct subjects on continued daily dosing of investigational product (see [Section 5.5.2](#) Dose Maintenance Period).

#### **6.5. Subject Withdrawal (Early Termination)**

Withdrawal of consent: Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Lost to follow-up: All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a

minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs).

Every effort should be made to have the subject return to the clinic for final safety assessments and to be questioned regarding their reason for withdrawal. At the early termination visit, every effort must be made to complete the assessments outlined in the [Schedule of Activities](#).

Lack of completion of all or any of the early termination procedures will not be viewed as protocol deviations so long as the subject's safety was preserved.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

## **7. ASSESSMENTS**

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that

he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

## **7.1. Eligibility**

### **7.1.1. Review of Inclusion/Exclusion Criteria**

All inclusion and exclusion criteria must be carefully reviewed and compared against the screening data for the subject. Protocol deviations related to subject eligibility are of particular concern and will be specifically monitored by the sponsor via screening verification in addition to the capture and review of protocol deviations through routine monitoring.

### **7.1.2. Medical History/Prior Medications/Procedures**

Investigators should make all reasonable efforts to obtain an accurate and complete medical history and history of prior medication use when evaluating whether a subject is eligible for the study. If the status of a subject's medical history is in doubt or information pertaining to a critical variable is conflicting, every reasonable step to secure proper documentation of correct medical status should be attempted. Documentation of the medical and medication histories over the protocol defined time periods should be available for sponsor review during the source data verification process. Questions about prior medications or eligibility should be directed to the sponsor Medical Monitor or designate.

### **7.1.3. Diagnostic Criteria for Parkinson's Disease**

Investigators must confirm and thoroughly document the diagnosis of Parkinson's disease. Parkinson's disease must be consistent with the UK Brain Bank Criteria<sup>12</sup> and will be verified by a central enrollment committee prior to enrollment. It is critically important that the investigator document the basis for confirming the diagnosis of Parkinson's disease and have this information available for sponsor verification prior to enrollment. The UK Brain Bank Criteria is supplied in [Appendix 4](#) for reference.

### **7.1.4. Mini Mental State Examination (MMSE)**

The MMSE is a brief 30 point questionnaire test that is used to assess cognition.<sup>13</sup> It is commonly used to screen for dementia. In the time span of about 10 minutes, it samples various functions, including arithmetic, memory and orientation. Scores range from 0-30. Administration and scoring guidelines will be provided to the investigator site prior to initiation of the study.

### **7.1.5. Hoehn & Yahr (HY)**

The HY is widely used to define broad categories of function in Parkinson's disease.<sup>24</sup> The HY is commonly used for describing, in broad terms, how Parkinson's symptoms progress and the relative level of disability. See Inclusion Criteria #5 ([Section 4.1](#)) for HY definition for this study.

### **7.1.6. Patient Health Questionnaire (PHQ-8)**

PHQ-8 is a self-report 8-item PRO used to assess depression and severity of depressive disorder and takes about 5 minutes to complete. The PHQ-8 consists of eight of the nine criteria on which the DSM-IV diagnosis of depressive disorders is based.<sup>28 29</sup> The scores for each item are summed to produce a total score between 0 and 24 points. A total score of 0 to 4 represents no significant depressive symptoms. A total score of 5 to 9 represents mild depressive symptoms; 10 to 14, moderate; 15 to 19, moderately severe; and 20 to 24, severe.<sup>30</sup> The PHQ-8 will be performed only at screening. Subjects with clinically significant depression, as marked by a PHQ-8 total score  $\geq 15$  are excluded per [Section 4.2](#) (Exclusion Criteria).

## **7.2. Safety**

### **7.2.1. Laboratory Tests**

The following safety laboratory tests will be performed at times defined in Study Procedures ([Section 6](#)) of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns.

Hematology <sup>f</sup>	Chemistry <sup>f</sup>	Urinalysis <sup>f</sup>	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count (w/differential) Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN/urea and Creatinine Glucose Calcium Sodium Potassium Chloride Total CO <sub>2</sub> (Bicarbonate) AST, ALT Total Bilirubin Alkaline phosphatase Uric acid Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy <sup>a</sup> Specific Gravity Urine creatinine	FSH <sup>b</sup> Urine drug screening <sup>c</sup> Human immunodeficiency virus <sup>d</sup> Hepatitis B antigen <sup>d</sup> Hepatitis C antibody <sup>d</sup> HCV-RNA test Anti-neutrophil cytoplasmic antibody panel (C-ANCA and P-ANCA) <sup>e,f</sup> Antinuclear antibody (ANA) <sup>e,f</sup> Fibrinogen <sup>e,f</sup> C-Reactive Protein (CRP) <sup>e,f</sup> Erythrocyte Sedimentation Rate (ESR) <sup>e,f</sup> Complement (C3, C4, and CH50/CH100) <sup>e,f</sup> Rheumatoid Factor <sup>e,f</sup> Immunoglobulin panel (IgG, IgA, and IgE) <sup>e,f</sup>
	Additional Tests (Needed for Hy's law)		
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT PT/INR		

a Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.  
 b At Screening only, in females who are amenorrheic for at least 12 consecutive months.  
 c At Screening and Day -1 (Randomization) only.  
 d At Screening only and in case of anti-HCV positive result, a qualitative HCV-RNA test to be performed.  
 e At Screening and Visit 15 only.  
 f Tests to be completed in the case of suspected concerning vasculitic process and after discussion with the Medical Monitor/ Sponsor Study Clinician per [Section 7.2.9](#).

- Minimum requirement for drug screening includes: cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines and amphetamines.
- Subjects may undergo random urine drug screening at the discretion of the investigator. Drug screening conducted prior to dosing must be negative for subjects to receive study medication.

### **7.2.2. Pregnancy Testing**

Females of childbearing potential are excluded from the study. All female subjects of non-childbearing potential will have a FSH test, if amenorrheic for at least 12 consecutive months. Results will be obtained prior to investigational product dosing.

Confirmation of non-childbearing potential is required before the subject may receive investigational product.

### **7.2.3. Physical Examinations**

Physical examinations must be conducted by a physician, or appropriately medically qualified person (eg, trained physician's assistant, nurse practitioner) in accordance with local (country and state) laws. A full physical examination will include head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, and neurological systems. The brief physical examination will be focused on general appearance, pulmonary, abdominal exams, the respiratory and cardiovascular systems, as well as towards subject reported symptoms.

For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Subjects must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

### **7.2.4. Neurological Examinations**

Full and brief neurological examinations should be conducted by a neurologist, a physician trained in conducting full neurological examinations as acceptable according to local (country and state) law. Brief neurological examinations may be conducted by a neurologist or physician as acceptable according to local regulation.

The complete/full neurological examination should include assessment of the cranial nerves; muscle strength, tone, abnormal movements; deep tendon reflexes; sensory exam, coordination, gait and station. Higher cortical and motor function is considered part of the complete neurological exam.

The brief neurological exam includes observation for cerebellar (intention) tremor and for non-cerebellar tremors (eg, resting or positional), finger to nose, heel to shin, Romberg, gait and tandem walking, positional and gaze evoked nystagmus. Any abnormal findings may be confirmed by consultation with a certified neurologist.

The neurological examination results will be recorded in a neurological examination case report form (CRF). All the neurological examination results must be recorded on the source documents, which will be monitored at the clinical study site. Abnormal neurological examination results deemed to be clinically significant and occurring after Day -1 (Randomization) will be captured as an AE.



### **7.2.5. Blood Pressure and Heart Rate**

Blood pressure and heart rate will be measured at times specified in the Study Procedures (Section 6) of this protocol. Additional collection times, or changes to collection times of blood pressure and heart rate will be permitted, as necessary, to ensure appropriate collection of safety data.

The same arm (preferably the dominant arm) should be used if possible throughout the study. Subjects should be instructed not to speak during measurements.

The same properly sized and calibrated blood pressure cuff will be used to measure blood pressure each time. The use of an automated device for measuring BP and heart rate is acceptable, although, when done manually, heart rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, blood pressure and heart rate should be obtained prior to the nominal time of the blood collection.

At screening, if initial vital sign measurement does not meet eligibility criteria, the subsequent two measurements will be conducted following at least 5 minutes of rest. The procedure for collecting postural or orthostatic data will be:

- Assess BP after subject is in supine position for a minimum of 5 minutes;
- Stand subject up for 2 minutes;
- Assess BP after subject is in the standing position for approximately 2 minutes.

Orthostatic hypotension is defined as a decrease of  $\geq 20$  mmHg for systolic blood pressure or  $\geq 10$  mmHg for diastolic blood pressure 2 minutes after standing from a supine position. Orthostatic hypotension may be symptomatic or asymptomatic. Symptoms of orthostatic hypotension are those that develop upon assuming the erect posture from a supine position and may include: lightheadedness, dizziness, blurred vision, weakness, fatigue, cognitive impairment, nausea, palpitations, tremulousness, headache and/or neck ache.

If a subject has symptoms suggestive of orthostasis, but not documented orthostatic hypotension, repeated measurements of supine/standing blood pressure should be obtained at the investigator's discretion. Lesser degrees of blood pressure reduction may still be considered clinically significant if the subject becomes symptomatic upon standing, especially in the presence of a significant increase in heart rate ( $\geq 30$  beats per minute (BPM)).

### **7.2.6. Electrocardiogram**

Electrocardiograms (ECGs) should be collected at times specified in the Study Procedures (Section 6) of this protocol.

All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position.

Triplicate 12-lead ECGs will be obtained approximately 2-4 minutes apart; the average of the triplicate ECG measurements collected predose on Day -1 (Randomization) will serve as each subject's baseline QTcF value. When the timing of these measurements coincides with a blood collection, the ECG should be obtained prior to the nominal time of the blood collection, blood pressure and heart rate.

To ensure safety of the subjects, a qualified individual at the investigator site will make comparisons to baseline measurements.

If the average of QTcF values from the triplicate measurements are above the threshold value ( $\geq 45$  msec from the baseline; or is  $\geq 500$  msec), then a single ECG must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If QTcF values remain  $\geq 500$  msec (or  $\geq 45$  msec from the baseline) for greater than 4 hours (or sooner at the discretion of the investigator); or QTcF intervals get progressively longer, the subject should undergo continuous ECG monitoring and sponsor should be notified. A cardiologist should be consulted if QTcF intervals do not return to less than 500 msec (or to  $< 45$  msec above the baseline) after 8 hours of monitoring (or sooner at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTcF value is prolonged, as defined above, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTcF values are in the acceptable range.

#### **7.2.7. Questionnaire for Impulsive-Compulsive Disorder in Parkinson's Disease Rating Scale (QUIP-RS)**

The Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS) is a PD-specific PRO designed to assess the severity of impulse control disorders in Parkinson's disease. The estimated timeframe for completion is approximately 5 minutes.

The QUIP-RS has 4 primary questions pertaining to commonly reported thoughts, urges/desires, and behaviors associated with impulsive-compulsive disorder, each applied to the 4 impulsive-compulsive disorders (compulsive gambling, buying, eating, and sexual behavior) and 3 related disorders (medication use, punning, and hobbyism). It uses a 5-point Likert scale (score 0–4 for each question) to gauge the frequency of behaviors, and instructs patients to answer questions based on behaviors that occurred in the preceding 4 weeks (or any 4-week period in a designated time frame). The QUIP-RS is valid and reliable as a rating scale for impulse control disorders and related disorders in Parkinson's disease, and can be used to support a diagnosis of these disorders, as well as to monitor changes in symptom severity over time.<sup>14</sup>

### **7.2.8. Physician Withdrawal Checklist (PWC-20)**

The PWC-20 is a 20-item reliable and sensitive instrument for the assessment of BZ-like discontinuation symptoms. It correlates extremely highly with the PWC-35, its parent scale ( $r=0.980$ ). Since most items are also complaints commonly reported by patients as symptoms of anxiety, it is not surprising that the PWC-20 and the Hamilton Anxiety Rating Scale (HAM-A) correlate highly ( $r=0.80$ ) with each other. Therefore, a combination of symptoms and time course, not type of symptoms alone, best differentiate between discontinuation symptoms of rebound/withdrawal and return of anxiety. Discontinuation symptoms occur early and disappear rather swiftly, depending upon speed of taper, daily medication dose, and drug elimination half-life.<sup>16</sup>

### **7.2.9. Additional Laboratory Testing for Suspected Vascular Inflammation**

During the study, if there is suspicion of the development of a concerning vasculitic process, the subject should discontinue investigational product and the investigator will contact the designated Medical Monitor/Sponsor Study Clinician immediately, and should collect the vasculitis panel of tests in addition to the other Safety Laboratory Tests (Hematology, Chemistry, and Urinalysis) before any therapy for vasculitis is initiated (refer to [Section 7.2.1](#) for the list of specific laboratory tests included).

## **7.3. Assessment of Suicidal Ideation and Behavior**

### **7.3.1. Columbia Suicide Severity Rating Scale (C-SSRS)**

The Columbia Suicide Severity Rating Scale (C-SSRS) is an interview based rating scale to systematically assess suicidal ideation and suicidal behavior.<sup>17</sup> Versions are available for “lifetime” and “since last evaluation”. The “lifetime” evaluation is done at screening, and the “since last evaluation” is done at all other time points.

The C-SSRS is to be collected at times specified in the Study Procedures ([Section 6](#)) of this protocol by an appropriately trained clinical site staff member. The C-SSRS can also be administered at any time in the study at the discretion of the investigator based on any reasonable concern.

At each suicidality assessment as per Study Procedures, subjects felt to have significant suicidal ideation with actual plan and intent or suicidal behavior, must be evaluated by a clinician/mental health professional (MHP) skilled in the evaluation of suicidality in the subjects by virtue of training or experience (eg, psychiatrist, licensed clinical psychologist) who will determine if it is safe for the subject to participate/continue in the trial. Specific criteria that indicate a need for such an assessment are:

- Suicidal ideation associated with actual intent and/or plan in the past 6 months; (a “YES” answer to C-SSRS questions 4 “some intent to act without specific plan” or 5 “specific plan and intent”).
- Previous history of suicide behaviors in the past 5 years (a “YES” answer to any of the suicidal behavior items of the C-SSRS with the behavior occurring in the past 5 years).

- In the investigators judgment a risk assessment or exclusion is warranted.

A written copy of the risk assessment should be included in the subject's clinical record (source documentation).

Other possible suicidality adverse events or other clinical observations may, based on the judgment of the investigator, also trigger a risk assessment and require a narrative.

Suicidality adverse events or other clinical observations may, based on the judgment of the investigator and clinician/MHP, also trigger a risk assessment and a narrative using information from the C-SSRS, and available information, prior to screening and baseline information, and the clinician/MHP assessment. When there is a positive response to any question on the C-SSRS, the investigator should determine whether an adverse event has occurred.

At the baseline visit (Visit 1 (Randomization)), a risk assessment will be done by qualified staff at the clinical site to determine whether it is safe for the subject to be enrolled or to continue to participate in the trial.

Subjects who respond “YES” to items 4, 5 or to any behavioral question of the C-SSRS at any time after the baseline visit (Visit 1 (Randomization)) will be assessed by clinician/MHP to determine whether it is safe for the subject to continue in the trial.

Subjects who respond “YES” to items 4, 5 or to any behavioral question of the C-SSRS on more than one occasion during a trial must have their suicidality managed appropriately by the investigator together with the clinician/MHP (or the investigator alone if the investigator is a qualified mental health professional). Depending on the specifics of the subject as assessed by the investigator and/or clinician/MHP, the subject may be discontinued from the trial.

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### 7.7. Blood Volume

The total blood sampling volume for individual subjects in this study is approximately 217 mL. The table below reflects the approximate sample volumes needed for each measured endpoint. The actual collection times of blood sampling may change, but the total blood volume collected will not increase. Additional blood samples may be taken for safety

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assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 30 consecutive days.

Sample Type	Sample Volume (mL)	Number of Sampling Times			Total Volume (mL)
		Screening	Study Period	Follow-Up	
Safety Labs	8	1	5	1	56
ANCA Testing	4	1		1	8
ANA	2	1		1	4
Fibrinogen	2.7	1		1	5.4
ESR	2	1		1	4
Complement (C3, C4, CH50/CH100)	4	1		1	8
Rheumatoid factor	2	1		1	4
Immunoglobulin panel (IgG, IgA, IgE)	3	1		1	6
HIV/Hepatitis Panel	5	1			5
CCI					
CCI					
CCI					
<b>TOTAL</b>					<b>216.4</b>

This total volume does not include discarded blood from pre-draws used to remove fluid from flushed catheters, if applicable.

## 8. ADVERSE EVENT REPORTING

### 8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

## 8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

AEs (serious and non-serious) should be recorded on the case report form (CRF) from the time the subject has taken at least 1 dose of investigational product through the subject's last visit.

## 8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;

- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

#### **8.4. Medication Errors**

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF, which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AE(s) are captured on an AE CRF page.

#### **8.5. Abnormal Test Findings**

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of protocol-stipulated dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

## 8.6. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject, or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

### 8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see the section on [Serious Adverse Event Reporting Requirements](#)).

### 8.6.2. Potential Cases of Drug-Induced Liver Injury

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to run LFTs because of clinical sign/symptom presentation in a subject, such LFT results should be handled and followed up as described below.

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values  $\geq 3$  times the upper limit of normal ( $\times$  ULN) concurrent with a total bilirubin value  $\geq 2 \times$  ULN with no evidence of hemolysis and an alkaline phosphatase value  $\leq 2 \times$  ULN or not available;
- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:
  - For subjects with preexisting AST or ALT baseline values above the normal range: AST or ALT values  $\geq 2$  times the baseline values and  $\geq 3 \times$  ULN, or  $\geq 8 \times$  ULN (whichever is smaller).

Concurrent with

- For subjects with preexisting values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least  $1 \times$  ULN **or** if the value reaches  $\geq 3 \times$  ULN (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug, and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

### 8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

### 8.8. Severity Assessment

If required on the AE CRFs, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

### 8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and nonserious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see the section on [Reporting Requirements](#)). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

### 8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).



2. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on an SAE report form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

### **8.11. Occupational Exposure**

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

### **8.12. Withdrawal Due to Adverse Events (See Also the Section on [Subject Withdrawal \(Early Termination\)](#))**

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

### **8.13. Eliciting Adverse Event Information**

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

### **8.14. Reporting Requirements**

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

#### **8.14.1. Serious Adverse Event Reporting Requirements**

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding, and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

#### **8.14.2. Non serious Adverse Event Reporting Requirements**

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

#### **8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities**

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

### **9. DATA ANALYSIS/STATISTICAL METHODS**

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be maintained by the Sponsor. This document may modify the plans outlined in the core protocol elements; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

#### **9.1. Sample Size Determination**

The sample size is based on the primary endpoint, the change from baseline in the MDS-UPDRS score Part III at Week 15. The comparisons will be of PF-06649751 against placebo, and the decision criteria for efficacy are given below:

- C1: At least 50% confident that PF-06649751 effect is 3.6 units better than placebo.
- C2: at least 95% confident that PF-06649751 effect is better than placebo effect.

Better is defined as a reduction in the MDS-UPDRS score Part III.

The sample size indicates that 34 subjects per arm will give sufficient precision for a comparison of PF-06649751 versus placebo to meet criterion C2 with observed effects of at least 3.6 units (Criterion C1). It is estimated that the probability of passing both criteria for a true effect of 5.4 units would be 81%, and the probability of passing the criteria for a true null effect (0 unit) would be 4%.

Assuming that 23% of the subjects will fail to complete the study or optimize the dose 44 subjects per arm (a total of 88 subjects) will be randomized for the study.

A conservative estimate of the between-subject standard deviation of 8.4 units has been used based on historical early Parkinson's disease trials.

## **9.2. Efficacy Analysis**

All efficacy analyses will be based on the Full Analysis Set (FAS) which is defined as all subjects who are randomized to the study, receive at least 1 dose of study medication, and have a baseline and at least one post-baseline MDS-UPDRS score Part III. Analyses may be repeated using a Per Protocol Set (PPS) as appropriate, which will exclude subjects who are major protocol deviators from the FAS.

### **9.2.1. Analysis of the Primary Endpoint**

The primary analysis will be conducted on the primary endpoint, the change from baseline in the MDS-UPDRS score Part III at Week 15, based on the FAS population. The primary analysis will utilize a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM). The response variable in the model will be the change from baseline to each post baseline visit, and the following fixed effects will be included in the model:

- Treatment (with 2 levels: PF-06649751 and placebo), a categorical factor.
- Visit, a categorical factor.
- Treatment-by-visit interaction.
- Baseline MDS-UPDRS score Part III, a continuous covariate.
- Baseline-by-visit interaction.
- Geographic region as appropriate.

An unstructured variance-covariance structure will be used to model the within-subject errors. In the unlikely event that the computational algorithm fails to converge, the following structures will be executed in the order specified (essentially in decreasing order of complexity) until convergence is achieved: heterogeneous Toeplitz, heterogeneous first-order autoregressive, autoregressive, heterogeneous compound symmetry, compound symmetry, and variance components. The first structure yielding convergence will be used as the primary analysis. The Kenward and Roger method for calculating the denominator degrees of freedom for tests of fixed effects will be used.

The efficacy comparisons for this MMRM model will be based on the treatment difference vs. placebo estimated at Week 15 using least-squares means. Their point estimates, standard errors, and two-sided 90% CIs will be reported.



#### **9.4. Safety Analysis**

Adverse events, ECGs, blood pressure, heart rate, C-SSRS, QUIP-RS, PWC-20, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. Any clinical laboratory, ECG, BP, and HR abnormalities of potential clinical concern as defined in Pfizer Data Standards will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

#### **9.5. Interim Analysis**

Up to one interim analysis will be performed when approximately 28 randomized subjects (32% total sample size) have finished their double-blind treatment period in the study, and efficacy data have been collected, databased and cleaned. The purpose of this interim analysis will be to assess study futility and to aid future development planning. If an interim analysis is performed, the study will continue whilst the analysis is being conducted.

Before any interim analysis is initiated, the details of the objectives, decision criteria, unblinding, dissemination plan and method of maintaining the study blind as per Pfizer's standard operating procedures (SOPs) will be documented and approved in an internal review committee (IRC) charter. In addition, the analysis details will be documented and approved in the statistical analysis plan (SAP) or an interim analysis SAP.

#### **9.6. Data Monitoring Committee**

Unblinded safety data of the study will be periodically reviewed by an external, independent data safety monitoring committee (eDMC).

The eDMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the charter. The recommendations made by the eDMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

### **10. QUALITY CONTROL AND QUALITY ASSURANCE**

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

## **11. DATA HANDLING AND RECORD KEEPING**

### **11.1. Case Report Forms/Electronic Data Record**

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigative site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

### **11.2. Record Retention**

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant

correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

## **12. ETHICS**

### **12.1. Institutional Review Board/Ethics Committee**

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

### **12.2. Ethical Conduct of the Study**

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

### **12.3. Subject Information and Consent**

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical code based on a numbering system provided by Pfizer in order to de-identify study subjects. The study site



will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

#### **12.4. Subject Recruitment**

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures.

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

#### **12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP**

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

### **13. DEFINITION OF END OF TRIAL**

#### **13.1. End of Trial in the United States**

Last Subject Last Visit (LSLV) is defined as the date the investigator reviews the last subject's final safety data and determines that no further evaluation is required for the subject to complete the trial.

### **13.2. End of Trial in a Member State**

End of trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of subjects have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application in the Member State. End of trial in a Member State of the European Union is defined as last subject last visit (LSLV) based on the total of randomized subjects in accordance with protocol [Section 9.1](#), Sample Size Determination. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

### **13.3. End of Trial in All Other Participating Countries**

End of trial in all other participating countries is defined as last subject last visit (LSLV).

## **14. SPONSOR DISCONTINUATION CRITERIA**

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06649751 at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 7 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

## **15. PUBLICATION OF STUDY RESULTS**

### **15.1. Communication of Results by Pfizer**

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or [www.pfizer.com](http://www.pfizer.com), and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

[www.clinicaltrials.gov](http://www.clinicaltrials.gov)

Pfizer posts clinical trial US Basic Results on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

*Primary completion* date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

### EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

[www.pfizer.com](http://www.pfizer.com)

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on [www.pfizer.com](http://www.pfizer.com) for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

### **15.2. Publications by Investigators**

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical

Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, <http://www.icmje.org/index.html#authorship>, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled [Publications by Investigators](#), the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

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## Appendix 1. Abbreviations

This is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ANA	Anti-Nuclear antibody
AST	aspartate aminotransferase
AUC	area under the curve
AUC <sub>24</sub>	area under the concentration-time curve from time 0 to 24 hours
AUC <sub>inf</sub>	area under the concentration-time curve from time 0 to infinity
AUC <sub>last</sub>	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
BCRP	breast cancer resistance protein
CCI	
BMI	body mass index
BP	blood pressure
BPM	beats per minute
BUN	blood urea nitrogen
C-ANCA	Cytoplasmic Anti-Neutrophil Cytoplasmic Antibody
C <sub>avg</sub>	average concentration
CDS	core data sheet
C <sub>eff</sub>	human plasma efficacious concentration
CI	confidence interval
CNS	central nervous system
C <sub>max</sub>	maximum (peak) observed concentration
COMT	catechol-O methyltransferase
CRF	case report form
CRP	C-Reactive Protein
CSA	clinical study agreement
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
D1R	D1 receptor
DAI	dosage and administration instructions
DaT	dopamine transporter
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dispensable unit
EBR	eye blink rate
EC	ethics committee



<b>Abbreviation</b>	<b>Term</b>
ECG	electrocardiogram
EDMC	external data monitoring committee
EDP	exposure during pregnancy
EDTA	edetic acid (ethylenediaminetetraacetic acid)
EOT	end of trial
CCI	
ESR	Erythrocyte Sedimentation Rate
CCI	
EU	European Union
EudraCT	European Clinical Trials Database
FAS	full analysis set
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FIH	first in human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HAM-A	Hamilton Anxiety Rating Scale
HCV-RNA	hepatitis C virus-ribonucleic acid
hERG	Human ether-a-go-go-related gene
HIV	human immunodeficiency virus
HPD	hours post dose
HR	heart rate
HRQL	health-related quality of life
HY	Hoehn & Yahr
IB	investigator's brochure
IC <sub>50</sub>	half maximal inhibitory concentration
ICH	International Conference on Harmonisation
ID	identification
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IVR	interactive voice response
IWR	interactive web response
L-Dopa	levodopa
LFT	liver function test
LMA	locomotor activity
LPD	local product document
LQTS	long QT syndrome

Abbreviation	Term
LSLV	last subject last visit
MAD	multiple ascending dose
MAO-B	monoamine oxidase B
MATE1	multidrug and toxin extrusion protein
CCI [REDACTED]	[REDACTED]
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
CCI [REDACTED]	[REDACTED]
MED	Minimal Efficacious Dose
MHP	mental health professional
MMRM	mixed model for repeated measures
MMSE	Mini Mental State Examination
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MTD	Maximum Tolerated Dose
N/A	not applicable
NOAEL	No observed adverse effect level
OCT1	organic cation transporter
P-ANCA	Perinuclear Anti-Neutrophil Cytoplasmic Antibody
PBMC	Peripheral Blood Mononuclear Cell
PCD	primary completion date
PD	pharmacodynamics
CCI [REDACTED]	[REDACTED]
PET	positron emission tomography
PFS	pre-filled syringe
CCI [REDACTED]	[REDACTED]
PHQ-8	Patient Health Questionnaire
CC [REDACTED]	[REDACTED]
PPS	per protocol set
PRO	patient reported outcome
PT	prothrombin time
PWC-20	Physician Withdrawal Checklist
QD	“quaque die”, once per day
QID	“quarter in die”, four times per day
qEEG	polysomnography and quantitative electroencephalography
QTcF	corrected QT (Fridericia correction)
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson’s Disease – Rating Scale
RAND	Randomization
RBC	red blood cell

<b>Abbreviation</b>	<b>Term</b>
REM	rapid eye movement
REML	restricted maximum likelihood
RNA	ribonucleic acid
RO	receptor occupancy
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCL	Supply Chain Lead
SGOT	serum glutamic oxaloacetic transminase
SGPT	serum glutamic pyruvic transminase
SIB	suicidal ideation and behavior
SOP	standard operating procedure
SPC	summary of product characteristics
SRSD	single reference safety document
SWS	slow wave sleep
T <sub>1/2</sub>	half-life
THC	tetrahydrocannabinol
TMB	trimethobenzaminde
UK	United Kingdom
ULN	upper limit of normal
US	United States
USPI	United States package insert
WBC	white blood cell

## Appendix 2. Permitted/Prohibited Concomitant Medications

Use Category	Type of Medication	Guidance
<b>Permitted</b>	Any previous, current or new medications for medical illness not listed under the prohibited medication section below.	As needed based on investigator's judgment and subject's medical needs. <sup>1</sup>
	Hypnotics, sedatives, anxiolytics	Stable low doses of benzodiazepines are permitted. The planned prescription of benzodiazepines for P.r.n. ("as needed") use throughout the study should be discussed with the medical monitor/Pfizer Clinician. For insomnia, non-benzodiazepines are permitted.
	Anticholinergics	Permitted if at a stable dose for at least 42 days prior to Visit 1 (Randomization). No dose changes should be anticipated for the duration of the study.
	MAO-B inhibitors (Parkinson's disease medication)	Permitted if at a stable dose for at least 42 days prior to Visit 1 (Randomization). No dose changes should be anticipated for the duration of the study.
	Amantadine	Permitted if at a stable dose for at least 42 days prior to Visit 1 (Randomization). No dose changes should be anticipated for the duration of the study.
<b>Prohibited</b>	L-Dopa and dopamine receptor agonist medications including pramipexole, ropinirole, rotigotine and apomorphine	Prohibited if prior exposure or history of treatment with dopaminergic agents for more than 28 days and within at least 7 days prior to Visit 1 (Randomization) and throughout the study.
	Amphetamines, methylphenidate or other stimulants	Prohibited at least 42 days prior to Visit 1 (Randomization),
	Antipsychotics or neuroleptics	Antipsychotics, metoclopramide, or reserpine are prohibited at least 42 days prior to Visit 1 (Randomization).
	Antiepileptics	Antiepileptics are prohibited at least 42 days prior to Visit 1 (Randomization), except if used for chronic painful conditions at steady doses (for example, gabapentin or pregabalin).
	Lithium, irreversible MAO-A/B inhibitor antidepressants (including moclobemide, tranylcypromine, and phenelzine)	Prohibited at least 42 days prior to Visit 1 (Randomization). Stable low dose opioids for chronic painful medical conditions may be permitted based on a consultation with the medical monitor.
	Moderate or Strong CYP3A Inhibitors and Inducers	Prohibited at least 28 days prior to Visit 1 (Randomization). Drugs that induce or inhibit the hepatic metabolizing cytochrome 3A4 enzymes.
	Marijuana	Prohibited from Screening through the end of the double blind treatment period.
	Herbal Supplements	Herbal supplements must be discontinued at least 28 days period to Visit 1 (Randomization). However, Melatonin is permitted if at a stable dose for at least 42 days prior to Visit 1 (Randomization).

1. Investigator to discuss with sponsor as needed.

### Appendix 3. Moderate or Strong CYP3A Inhibitors and Inducers

CYP 3A Inhibitors	CYP 3A Inducers
<b>HIV antivirals</b>	<b>HIV antivirals</b>
Indinavir	Efavirenz
Nelfinavir	Nevirapine
Ritonavir	Etravirine
Saquinavir	<b>Miscellaneous</b>
Boceprevir	Barbiturates
Lopinavir/ritonavir	Carbamazepine
Amprenavir	Glucocorticoids (systemic)
Atazanavir	Modafinil
Telaprevir	Oxcarbazepine
Darunavir/ritonavir	Phenobarbital
Fosamprenavir	Phenytoin
<b>Antibiotics</b>	Pioglitazone
Clarithromycin	Rifabutin
Erythromycin	Rifampin
Telithromycin	St. John's wort <sup>3</sup>
Ciprofloxacin	Troglitazone
<b>Anti-infectives</b>	Bosentan
Itraconazole	Nafcillin
Ketoconazole	Avasimibe <sup>4</sup>
Fluconazole	
Posaconazole	
Voriconazole	
<b>Anti-anginal therapy</b>	
Diltiazem	
Verapamil	
<b>Anti-cancer therapy</b>	
Crizotinib	
Imatinib	
<b>Miscellaneous</b>	
Nefazodone	
Aprepitant	
Grapefruit juice <sup>1</sup>	
Conivaptan	
Mibefradil <sup>2</sup>	

1. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (eg, high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (eg, low dose, single strength).
2. Withdrawn from the United States market.
3. The effect of St. John’s wort varies widely and is preparation-dependent.

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4. Not a marketed drug.

Reference:

U.S. Food and Drug Administration. Guidance for Industry. Drug Interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. 2012. Available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm292362.pdf>

## **Appendix 4. UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria\***

### **Step 1. Diagnosis of Parkinsonian Syndrome**

- Bradykinesia.
- At least one of the following:
  - Muscular rigidity;
  - 4-6 Hz rest tremor;
  - Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction.

### **Step 2. Exclusion criteria for Parkinson's disease**

- History of repeated strokes with stepwise progression of parkinsonian features.
- History of repeated head injury.
- History of definite encephalitis.
- Oculogyric crises.
- Neuroleptic treatment at onset of symptoms.
- More than one affected relative.
- Sustained remission.
- Strictly unilateral features after 3 years.
- Supranuclear gaze palsy.
- Cerebellar signs.
- Early severe autonomic involvement.
- Early severe dementia with disturbances of memory, language, and praxis.
- Babinski sign.
- Presence of cerebral tumor or communication hydrocephalus on imaging study.
- Negative response to large doses of levodopa in absence of malabsorption.

- MPTP exposure.

### **Step 3. supportive prospective positive criteria for Parkinson's disease**

Three or more required for diagnosis of definite Parkinson's disease in combination with step one

- Unilateral onset.
- Rest tremor present.
- Progressive disorder.
- Persistent asymmetry affecting side of onset most.
- Excellent response (70-100%) to levodopa.
- Severe levodopa-induced chorea.
- Levodopa response for 5 years or more.
- Clinical course of ten years or more.

\* Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease. A clinico-pathological study of 100 cases. *JNNP* 1992;55:181-184.