



**A 15-WEEK, PHASE 2, DOUBLE BLIND, RANDOMIZED,  
PLACEBO-CONTROLLED, DOSE RANGING STUDY TO INVESTIGATE THE  
EFFICACY, SAFETY AND TOLERABILITY OF PF-06649751 IN SUBJECTS WITH  
MOTOR FLUCTUATIONS DUE TO 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>	2015-004912-39
<b>Protocol Number:</b>	B7601003
<b>Phase:</b>	2



### Document History

Document	Version Date	Summary of Changes
Amendment 2	22 November 2016	<ol style="list-style-type: none"><li>1. Protocol Summary, Schedule Activities, Section 3.1, Section 3.1.2, Section 5.5, Section 5.5.2, and Section 5.5.3: Clarified Period A as “Primary Efficacy” and Period B as “Maintenance”.</li><li>2. Protocol Summary, Section 1.4.1, and Section 1.4.2: Clinical studies and safety data updated to include the completed Phase 1b studies (B7601005 and B7601009).</li><li>3. CCI [REDACTED]</li><li>4. CCI [REDACTED]</li><li>5. Protocol Summary, Schedule of Activities, Section 3.1 Figure 1, Section 3.1.1, and Section 6: Screening window increased from 30 days to 45 days and clarified that Screening procedures may be split between multiple days/visits for feasibility and/or subject comfort, as appropriate. Individual screening procedures should not be split between multiple days/visits (eg, all parts of the MDS-UPDRS exam to be completed on the same screening day).</li><li>6. Protocol Summary and Section 3.1: Number of countries updated to 6 and study duration updated to 25 weeks.</li><li>7. Schedule of Activities: Added line for vasculitis laboratory panel.</li><li>8. Schedule of Activities: Deleted abbreviation text related to adjunct L-Dopa Treatment.</li><li>9. Schedule of Activities: ‘(X)’ abbreviation added to denote procedure to be conducted in</li></ol>

		<p>the case of a clinic visit.</p> <p>10. Schedule of Activities and Section 1.5.1: Open Label Extension study added.</p> <p>11. CCI </p> <p>12. Schedule of Activities, Section 3.1 Figure 1, Section 3.1.2, and Section 6: During the Titration Period, the Week 2 and 3 clinic visits may be conducted as phone visits (excluding sites in Japan).</p> <p>13. Schedule of Activities, Section 3.1 Figure 1, Section 3.1.2, and Section 6: Period B, Week 11, 12, and 14 clinic visits removed.</p> <p>14. Schedule of Activities, Section 3.1 Figure 1, Section 3.1.2, and Section 6: Week 13 clinic visit to be conducted as a phone visit.</p> <p>15. Schedule of Activities and Section 6: Brief physical and neurological examination deleted at Week 3 and Week 13.</p> <p>16. Schedule of Activities and Section 6: MDS-UPDRS III deleted at Week 2, Week 3, Week 11, Week 12 and Week 13.</p> <p>17. Schedule of Activities and Section 6: OFF time diary dispensed at Screening, Day 7, 28, 35, and 70. OFF time diary collected and reviewed at Day 0 (Randomization), 21 (in case of clinic visit), 28, 35, 70, and 105. "X" for Dispense OFF time diary deleted for Week 2, Week 12 and Week 13. "X" for OFF time diary collection/review deleted for Week 3 and Week 13 visits.</p> <p>18. Schedule of Activities, Footnote 'a' and Appendix 7: Week 2 and Week 3 visits during</p>
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		<p>the Titration Period must be conducted as in clinic visits in Japan (see Appendix 7).</p> <p>19. Schedule of Activities, Footnote ‘b’ and Section 3.1.2: At the discretion of the investigator, the Week 2 and Week 3 visits may be conducted as phone visits, in which case investigational product will be dispensed by the site to secure courier and delivered to the subject following the phone visit.</p> <p>20. Schedule of Activities, Footnote ‘c’ and Section 6: The Week 10 visit (and associated procedures) may be used as screening for subjects eligible for the Open Label Extension study B7601017 (subject to availability), and the Week 15 visit may then be used as Visit 1 of the extension study. The Week 17 and Week 19 visits will not be conducted in this case.</p> <p>21. Schedule of Activities, Footnote #10, Section 6, and Section 7.2.5: Clarification that subject temperature must be assessed at Screening and Day 0 (Randomization) to confirm no symptoms of fever (see Exclusion Criteria #6).</p> <p>22. <span style="color: red;">CCI</span> [REDACTED]</p> <p>23. Schedule of Activities, Footnote #15 and Section 6: New footnote added. In addition to compliance verification, subjects will be instructed on which blister card to use for following the week at each phone visit.</p> <p>24. Schedule of Activities, Footnote #20 and Section 7.3.1: Clarification that subjects must complete the OFF time diary (Hauser diary) for three consecutive days in the week prior to each diary review visit, including Day 0 (Randomization) visit.</p>
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		<p>25. Section 1.3.3 and Section 1.5.1: Preclinical toxicology data updated.</p> <p>26. Section 1.4.3, Table 1, and Section 1.5.2: Steady state exposure data and dose rationale updated.</p> <p>27. Section 3.1: Figure 1 updated to reflect updated visit schedule and screening window of 45 days.</p> <p>28. Section 3.1.3 and Section 6.6: Clarification that all subjects (including Early Termination) who have received at least 1 dose of investigational product (except a subject who withdraws consent), will undergo a follow-up visit at least 28 calendar days, and up to 35 calendar days after the last administration of the investigational product to capture any potential adverse events and to confirm appropriate contraception usage. This may be conducted as a phone visit.</p> <p>29. Section 3.1.4, Open Label Extension Study added.</p> <p>30. Section 3.1.1: Clarification that for the final Inclusion/Exclusion criteria verification on Day 0 (Randomization) by the investigator, subjects must have <math>\geq 2.5</math> hours OFF time each day, collected over 3 consecutive days during the week prior to Day 0 (Randomization), with fewer than 4 errors or missing entries in diary data per day.</p> <p>31. Section 4.1, Inclusion Criteria #3: Male and female subjects of non-childbearing potential between 40 – 85 years are eligible.</p> <p>32. Section 4.1, Inclusion Criteria #9: L-Dopa dose must be stable at least 21 days prior to Day 0 (Randomization). Subjects on a stable dose of L-Dopa of at least 400 mg/day divided into 3 daily doses (TID) may be considered and authorized on a case-by-case basis if submitted as part of the screening</p>
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		<p>assessment to the sponsor and/or its designee for determination if the dosing regimen is considered optimized for that particular subject.</p> <p>33. Section 4.2, new Exclusion Criteria #19, Section 5.8.1 and Appendix 3: Dopamine receptor agonist medications including pramipexole, ropinirole, rotigotine, and apomorphine are prohibited at least 28 days prior to Day 0 (Randomization) through the end of the double-blind treatment period. Exclusion criteria following were renumbered sequentially.</p> <p>34. Exclusion Criteria #20: Clarification added that herbal supplements must be discontinued at least 28 days prior to Day 0 (Randomization).</p> <p>35. Section 4.4.3: Text added regarding stable rehabilitation therapy (permitted if subject's regimen remains stable over the course of the study).</p> <p>36. CCI [REDACTED]</p> <p>37. Section 5.8.1 and Appendix 3: COMT inhibitor discontinuation removed.</p> <p>38. Section 6: Added clarifying text to record missed doses or dosing errors to applicable visits: Based on blister card review and/or tablet count, any subject who is noted not to have taken at least 80% or has taken more than 120% of required doses at any scheduled visit during the study will be considered out of compliance and this must be recorded on the CRF and documented as a Medication Error on the CRF and the source documents.</p> <p>39. Section 7.1.6: Clarification that MDS-UPDRS Part III should be assessed consistently and approximately 2 to 4 hours following L-Dopa dose (except at screening).</p>
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		<p>40. Section 7.1.7: Concordance testing may be performed by investigator or qualified site staff/rater (per the Rater Qualification Guide). MDS-UPDRS Part III exam to be performed at least once while the subject is in the OFF state and at least once while the subject is in the ON state (Part III score from full screening MDS-UPDRS may be used, provided the concordance assessment is continued/completed immediately after the exam).</p> <p>41. Section 7.2.1, Footnote ‘f’: Clarification to central lab procedure. If ANCA test is positive or questionable, then quantitative Proteinase-3 Ab and Myeloperoxidase Ab tests will be performed by the central lab using existing specimen.</p> <p>42. Section 7.3.9: Oral Symbol Digit Modality Test duration changed from 120 seconds to 90 seconds for consistency with test materials.</p> <p>43. Section 7.6: Blood Volume table updated to reflect change in visit schedule.</p> <p>44. CCI [REDACTED]</p> <p>45. Minor administrative updates throughout.</p>
Amendment 1	19 July 2016	<p>1. Protocol Summary, Sections 1.4.1 and 1.4.2: Updated with completed Phase 1 study enrollment and safety data, with clarification that 104 healthy volunteer subjects have participated in the completed Phase 1 studies, with 88 having received PF-06649751.</p> <p>2. Protocol Summary, Section 2.4.1 and Section 2.4.2: Primary and Secondary endpoints measured in ON and OFF “hours”.</p> <p>3. Protocol Summary and Section 2.4.2: “Daily ON time with troublesome dyskinesia (hours)” added as a Secondary endpoint.</p>

		<p>4. Protocol Summary and Section 2.4.2: Secondary endpoints measured as change from baseline.</p> <p>5. CCI [REDACTED]</p> <p>6. CCI [REDACTED]</p> <p>7. CCI [REDACTED]</p> <p>8. 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.</p> <p>9. CCI [REDACTED]</p> <p>10. Schedule of Activities, Section 6.2.11, and Section 6.2.12: OFF time diary dispensed to subject at Day 84.</p> <p>11. Section 1.3.3: Results of Study 8001294 included.</p> <p>12. C-SSRS “Lifetime” replaced with “Lifetime/Past 12 months” throughout.</p> <p>13. Clarification that Sinemet, Menesit, Madopar, Prolopa, and EC Doparl are provided throughout as examples of common L-Dopa medications.</p> <p>14. Exclusion Criteria #2: History of intracranial surgical intervention for indications other than</p>
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		<p>Parkinson's disease added.</p> <p>15. Exclusion Criteria #6: Fever added.</p> <p>16. Exclusion Criteria #7: "Epilepsy" definition clarified with Reference #27 added.</p> <p>17. Exclusion Criteria #12: History of vasculitis added.</p> <p>18. Exclusion Criteria #14: History of malignancy criteria clarified.</p> <p>19. Section 5.8: Medications taken within 60 days before the first dose of study investigational product will be documented as a prior medication.</p> <p>20. Section 5.8.3: Specific risk of drug-drug-interactions with PF-06649751 and primary substrates of CYP3A4 and BCRP added.</p> <p>21. Section 6.1: At Screening only, urine drug screening test for drugs of abuse (including THC) are to be performed at the central lab.</p> <p>22. Section 6.1 and Section 7.1.7: MDS-UPDRS Part III must be performed at 30 minute intervals during concordance testing at Screening.</p> <p>23. Section 7: Prolactin test moved from Section 7.2 (Safety) to Section 7.8 (Other).</p> <p>24. Section 7.2.1, Section 7.2.9 and Schedule of Activities Footnote #12: Additional safety laboratory tests added at Screening and Week 17/Day 119 visits (and/or during the treatment period if deemed necessary) for monitoring of vascular inflammation.</p> <p>25. Section 7.5: Prep B2 Banked Biospecimen sample added at Day 0 (Randomization) and Week 17/Day 119.</p> <p>26. Section 7.6: Blood Volume table updated.</p>
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		<p>27. Section 7.7.2: PHQ-8 language clarified.</p> <p>28. Section 9.5: Interim Analysis language clarified.</p> <p>29. Section 13.2: End of Trial in a member state of the EU defined as LSLV.</p> <p>30. Appendix 3: 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>31. Minor administrative updates throughout.</p> <p>32. References updated.</p>
Original protocol	15 December 2015	Not applicable (N/A)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

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## PROTOCOL SUMMARY

### Background and Rationale

In Parkinson's disease, motor function can be pharmacologically rescued with activation of either or both D1R-containing direct and D2R-containing indirect striatal output pathways. Levodopa (L-Dopa) therapy acts through both pathways and provides improvement of motor symptoms for a limited duration.<sup>1</sup> As Parkinson's disease progresses, L-Dopa becomes less well tolerated as a result of motor fluctuations and dyskinesias, whereby the initial consistent relief of symptoms is ultimately diminished by a relentlessly narrowing therapeutic window. D2/D3R agonists (such as pramipexole, ropinorole, rotigotine) are 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 experiencing motor complications associated with L-Dopa use.

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 (TMB; B7601007, n=9) Phase 1 studies.

Additionally, a total of 63 Parkinson's disease subjects have participated in one open-label multiple ascending dose Phase 1b study (B7601005; n=45) and one double-blind, placebo-controlled, single ascending dose Phase 1b study (B7601009; n=18).

In addition to the current study, another Phase 2 study in Parkinson's disease subjects is ongoing: B7601011 in early Parkinson's disease subjects (88 subjects planned).

The results of study B7601001, B7601002, B7601007, B7601005, and B7601009 and the possible risks associated with the administration of PF-06649751 are summarized in the Investigator's Brochure (IB).

## Study Objectives

### Primary Objective

- To evaluate the effect on motor symptoms of PF-06649751 administered once daily as adjunctive treatment with stable doses of L-Dopa in Parkinson's disease.
- To determine the therapeutic window for motor symptom improvement of PF-06649751 administered once daily, ie, determining a dose, or a range of doses, for adequate control of motor symptoms.

### Secondary Objectives

- To evaluate the dose-response on motor symptoms of PF-06649751 administered once daily in patients with Parkinson's disease.
- To evaluate the safety and tolerability of PF-06649751 administered once daily in subjects with Parkinson's disease.
- To evaluate the effect of PF-06649751 administered once daily on dyskinesia in subjects with Parkinson's disease.

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## Endpoints

### Primary Endpoint (Efficacy)

- Change from baseline in daily OFF time (hours OFF time; based on patient reported Hauser diary) at Week 10 (Day 70; end of Period A).

### Secondary Endpoints (Efficacy; Evaluated during the entire double-blind period)

Change from baseline in:

- Daily OFF time (hours).

- Daily ON time with troublesome dyskinesia (hours).
- Daily ON time without troublesome dyskinesia (hours).
- Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III.
- MDS-UPDRS Parts I, II, IV, and total score.

**Secondary Endpoints (Safety and Tolerability)**

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

This study has a randomized, double-blind, placebo-controlled parallel group design. Approximately 198 subjects from approximately 60 centers in approximately 6 countries will be randomized to 5 treatment groups (15 mg once per day (QD), 7 mg QD, 3 mg QD, 1 mg QD, or placebo), initially in a 2:0:0:0:1 ratio of approximately 54 subjects (Cohort 1) followed by a 1:2:2:2:1 ratio of approximately total 144 (Cohort 2), using a central randomization system with randomization blocks stratified by region.

Each subject will participate in the study for approximately 25 weeks including up to a 45 day screening period, 15 week double-blind treatment period (including up to 3 week titration, 2 week dose adjustment, 5 weeks of primary efficacy with adjunctive treatment to stable L-Dopa (Period A), and 5 weeks of maintenance with adjunctive treatment to stable L-Dopa (Period B)), and an approximately 28 day follow-up period.

## Statistical Methods

The primary endpoint is the change from baseline in daily OFF time at Week 10 (end of Period A). A four parameter  $E_{\max}$  model will be primarily used to estimate the dose response for the change from baseline in daily OFF time at Week 10 (end of Period A). Bayesian estimation will be used to fit the model. The details of the statistical model, the priors and the Bayesian analysis 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 based on Day 0 (Randomization), and not based on when the previous visit actually occurred. The indicated visit windows are only intended to mitigate scheduling conflicts for study visits.**

Visit Identifier	Screening	Double Blind Treatment Period											Follow-up	
		Titration Period <sup>a,b</sup>			Dose adjustment		Period A: Primary Efficacy			Period B: Maintenance		Wk 17	Wk 19 (Phone visit)	
		Wk 1	Wk 2 <sup>a,b</sup>	Wk 3 <sup>a,b</sup>	Wk 4	Wk 5	Wk 6 (Phone visit)	Wk 8 (Phone Visit)	Wk 10 <sup>c</sup>	Wk 13 (Phone Visit)	Wk 15 <sup>c</sup>			
<b>Protocol Activity</b>	D -45 to -1 RAND	D 7 +3	D 14 +3	D 21 +3	D 28 ±3	D 35 ±3	D 42 ±3	D 56 ±3	D 70 ±3	D 91 ±3	D 105 ±3/ Early Termination	D 119 ±3	D 133 ±3	
Informed consent <sup>1</sup>	X													
Demographics	X													
Medical history	X	X <sup>2</sup>												
Contraception Check	X													
Prior/concomitant medications assessment	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	
Full physical and neurological examination	X								X					
Brief physical and neurological examination <sup>3</sup>	X													
Mini Mental State Examination (MMSE)	X													
UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria	X													
Hoehn & Yahr Stage <sup>4</sup>	X													
Height and weight, BMI	X								X <sup>5</sup>			X <sup>5</sup>		
FSH Test <sup>6</sup>	X													
Serological Testing <sup>7</sup>	X													
Urine drug screening <sup>8</sup>	X	X												
ECG <sup>9</sup>	X	X	(X)	(X)	X	X			X		X		X	

Visit Identifier	Screening	Double Blind Treatment Period												Follow-up	
		Titration Period <sup>a,b</sup>			Dose adjustment		Period A: Primary Efficacy			Period B: Maintenance		Wk 17	Wk 19 (Phone visit)		
		Wk 1	Wk 2 <sup>a,b</sup>	Wk 3 <sup>a,b</sup>	Wk 4	Wk 5	Wk 6 (Phone visit)	Wk 8 (Phone Visit)	Wk 10 <sup>c</sup>	Wk 13 (Phone Visit)	Wk 15 <sup>c</sup>	D 119 ±3	D 133 ±3		
<b>Protocol Activity</b>	D -45 to -1 RAND	D 0/ RAND	D 7 +3	D 14 +3	D 21 +3	D 28 ±3	D 35 ±3	D 42 ±3	D 56 ±3	D 70 ±3	D 91 ±3	D 105 ±3/ Early Termination	D 119 ±3	D 133 ±3	
Supine and standing blood pressure and pulse rate	X <sup>10</sup>	X <sup>10</sup>	X	(X)	(X)	X	X			X		X	X		
Columbia Suicidality Severity Rating Scale (C-SSRS) <sup>11</sup>	X	X	X	(X)	(X)	X	X			X		X	X		
Safety laboratory	X <sup>12</sup>	X		(X)		X	X			X		X	X <sup>12</sup>		
Vasculitis laboratory panel	X	X											X		
<b>CCI</b>		X											X <sup>13</sup>		
Prolactin laboratory <sup>14</sup>		X				X				X		X			
Patient Health Questionnaire-8 (PHQ-8)	X														
Inclusion/exclusion criteria verification	X	X													
Randomization		X													
Dispensing of Investigational Product		X	X	X	X	X	X			X					
Investigational Product accountability			X	X	X	X	X			X					
Investigational Product and L-Dopa dosing documentation		X	X	(X)	(X)	X	X			X					
Dosing compliance verification via phone <sup>15</sup>			X	X	X										
PF-06649751 (or placebo) administration <sup>16</sup>		X <sup>17</sup>	→	→	→	→	→	→	→	→	→	→	→	→	
Adjunct L-Dopa (open-label)	→	→	→	→	→	→	→	→	→	→	→	→	→	→	
Blood sample for PF-06649751 concentration <sup>18</sup>							X			X					
ON/OFF time concordance testing and OFF time diary training <sup>19</sup>	X														
OFF time diary training video	X						X								
Dispense OFF time diary	X					X	X			X					
OFF time diary collection/review <sup>20</sup>		X			(X)	X	X			X					
MDS-UPDRS III <sup>21</sup>	X	X	X			X	X			X					
MDS-UPDRS I,II,IV	X	X				X	X			X					
<b>CCI</b>		X					X			X					
Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale (QUIP-RS)		X					X			X					

Visit Identifier	Screening	Double Blind Treatment Period										Period B: Maintenance		Follow-up	
		Titration Period <sup>a,b</sup>			Dose adjustment		Period A: Primary Efficacy			Wk 13 (Phone Visit)	Wk 15 <sup>c</sup>	Wk 17	Wk 19 (Phone visit)		
		Wk 1	Wk 2 <sup>a,b</sup>	Wk 3 <sup>a,b</sup>	Wk 4	Wk 5	Wk 6 (Phone visit)	Wk 8 (Phone Visit)	Wk 10 <sup>c</sup>	Wk 13 (Phone Visit)	Wk 15 <sup>c</sup>	Wk 17	Wk 19 (Phone visit)		
Protocol Activity	D -45 to -1 RAND	D 0/ +3	D 7 +3	D 14 +3	D 21 +3	D 28 ±3	D 35 ±3	D 42 ±3	D 56 ±3	D 70 ±3	D 91 ±3	D 105 ±3/ Early Termination	D 119 ±3	D 133 ±3	
CCI	X						X			X		X			
CCI	X						X			X		X			
CCI	X						X			X		X			
CCI	X						X			X		X			
Physician Withdrawal Checklist (PWC-20)															
CCI	X						X			X		X		X	
CCI	X						X			X		X			
CCI															
CCI	X						X			X		X			
CCI	X						X			X		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; CCI = [redacted]; THC = tetrahydrocannabinol; UK = United Kingdom; (X) = procedure to be conducted only in the case of a clinic visit

- a. Refer to the Appendix 7 (Japan-specific Appendix) for additional observation visits to be conducted during the Titration Period. The Week 2 and Week 3 visits must be conducted as clinic visits in Japan.
- b. At the discretion of the investigator and per local regulation, the Week 2 and Week 3 visits may be conducted as phone visits, in which case investigational product will be dispensed by the site to secure courier, and subsequently delivered to the subject following the phone visit. Investigational product will not be dispensed if the protocol specified phone visit has not been performed. Details of the courier process will be included in the study site reference guide. The Week 10 visit may be used as the Screening visit for subjects eligible for the Open Label Extension study, B7601017 (subject to availability), and the Week 15 visit may subsequently be used as Visit 1 (Baseline) of the open label extension study.
1. Informed consent may be obtained up to 60 days prior to Day 0 (Randomization). All other screening procedures should take place within D -45 to D -1. The Screening procedures may be split between multiple days/visits for feasibility and/or subject comfort, however individual procedures should not be split between multiple days/visits.
2. Medical history assessed at Day 0 (Randomization) to confirm no change in history post screening visit.

3. 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 non-cerebellar tremors (eg, resting or positional), finger to nose, heel to shin, Romberg, gait and tandem walking, positional and gaze evoked nystagmus. Full physical and neurological examination may be performed at the investigator's discretion.
4. Assessed while subject is ON.
5. Weight only assessed at Week 10 visit and Week 17 follow-up visit.
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 #3).
7. Hepatitis B antigen, Hepatitis C antibody, and HIV testing.
8. Urine test for drugs of abuse (including THC).
9. Triplicate ECG at all time points.
10. Triplicate vitals (HR and blood pressure) at Screening. Vitals should be collected first while the subject is in the supine position and then in the standing position. Subject temperature must also be assessed at Screening and Day 0 (Randomization) to confirm no symptoms of fever (see Exclusion Criteria #6).
11. Columbia Suicidality Severity Rating Scale (C-SSRS) "Lifetime/Past 12 months" evaluation at Screening, and Columbia Suicidality Severity Rating Scale "Since last evaluation" at all other time points.
12. Refer to [Section 7.2.1](#) for additional safety laboratory tests (blood and urine) to be completed at Screening and Week 17 follow-up visits, and/or as necessary throughout the study after consultation with the Medical Monitor/Sponsor per [Section 7.2.9](#).  
CCI [REDACTED]
14. Prolactin results may be shared with the blinded study team after database release.
15. 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.
16. 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 PF-06649751 or placebo dose on study visit days.
17. First dose will be administered the morning of Day 1.  
CCI [REDACTED]
19. Diary training and concordance testing will be conducted during the screening visit, as detailed in [Section 7.1.7](#).
20. Subjects will complete an OFF time diary (Hauser diary) for three consecutive days in the week prior to Day 0 (Randomization) Visit and each diary review visit (except the Day 28 visit, in which the OFF time diary will be completed between Day 14 and Day 21 and brought the next clinic visit).
21. UPDRS Part III should be assessed consistently and approximately 2 to 4 hours following L-Dopa dose (except at Screening).

## **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 up to 4 different doses of PF-06649751 in subjects with Parkinson's disease as adjunctive therapy to L-Dopa.

### **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 or 6.3 million worldwide. In people 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; MAO-B] or exogenous dopamine [catechol-O methyltransferase (COMT) inhibitors]), and C) are direct agonists of 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 induces 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.

In Parkinson's disease, motor function can be pharmacologically rescued with activation of either or both D1R-containing direct and D2R-containing indirect striatal output pathways. Although D2/D3R agonists (such as pramipexole, ropinorole, rotigotine) are approved for the symptomatic treatment of Parkinson's disease,<sup>6</sup> the maximal efficacy observed is considered inferior to 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 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lesioned nonhuman primate model of Parkinson's disease (see Investigators Brochure Section 5.1.3.2, In Vivo Pharmacodynamics). Severely lesioned MPTP-treated monkeys showed no response to D2 agonists and modest improvement with L-Dopa treatment, but showed marked improvement with D1 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 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 moderate 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 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<sub>50</sub> 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 has 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. In MPTP treated monkeys, an animal model of Parkinson's disease, PF-06649751 with or without L-Dopa reversed parkinsonian disabilities with a reduced propensity to induce dyskinesia when compared to L-Dopa. Finally, 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. The predicted human plasma efficacious concentration ( $C_{eff}$ ) of PF-06649751 is defined as a target threshold concentration above which efficacy is expected. The total and unbound human  $C_{eff}$  of PF-06649751 in plasma are predicted to be 27.6 ng/mL and 1.7 ng/mL, respectively,

corresponding to 32% receptor occupancy. The  $C_{\text{eff}}$  value is derived from the exposure response relationship established through the 1 methyl 4 phenyl 1,2,3,6 tetrahydropyridine (MPTP) induced monkey model of Parkinson's disease.

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, enzymes, and ion channels evaluated except the primary pharmacologic target, D1R. Therefore, the potential for secondary pharmacology is considered low at clinically relevant exposures.

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

### **1.3.3. Summary of Preclinical Toxicology**

The primary target organs identified in the PF-06649751 safety pharmacology and toxicity studies up to 26 or 39 weeks in duration in rats or monkeys, respectively, were the central nervous system (monkeys and rats), vascular system (male rats), reproductive system (female rats), and cardiovascular system (monkeys). Other findings included nonadverse gastrointestinal, adrenal, thyroid, pituitary, and hepatic effects, minor effects on clinical pathology parameters (eg, decreased red cell mass, increased cholesterol, serum electrolytes, or urine volume), and nonadverse respiratory parameter changes. Exacerbation of artificial light-induced retinal atrophy present in albino female rats in a 26-week toxicity study was considered an adverse effect relevant only to nonpigmented animals and, because of the protection afforded by uveal pigment in the eye of nonalbino animals, not expected to be an adverse finding relevant to humans administered PF-06649751 in clinical studies.

#### **Central Nervous System (CNS)**

Adverse CNS observations have been limited to the 1-month monkey toxicity study. At the high dose in this study, 1 female administered 7.5 mg/kg/day was euthanized on Day 1 due to self-injury (persistent biting and chewing at the tip of the tail, first noted ~ 5.5 hours post-dose (HPD)). The plasma concentration in this animal was 1310 ng/mL (76.0 ng/mL unbound) at 7 HPD, which is 3.8x compared with the unbound human  $C_{\text{max}}$  (19.8 ng/mL) at a dose of 15 mg. Nonadverse CNS-related clinical observations were noted after single or repeated doses in monkeys and included chewing action, teeth grinding, cage manipulation/licking, locomotory stereotypy, excessive repetitive behavior/grooming, self-injurious behavior, auto-erotic behavior ( $\geq 0.15$  mg/kg/day), cage biting, excessive scratching, jerky movements ( $\geq 0.75$  mg/kg/day), head pressing, decreased activity, skin picking ( $\geq 2.5$  mg/kg/day), yawning (7.5 mg/kg/day). Persistent decreased activity associated with low to no food consumption in monkeys following a single dose of 15 mg/kg was considered dose limiting for repeat-dose studies. In the 1-month toxicity study in monkeys, an isolated observation of clonic activity of short duration (~10 seconds of activity at ~7.5 HPD) occurred in 1 male at 2.5 mg/kg/day. However, in the 15-week monkey study, electroencephalography (EEG) evaluation results indicated no test article-related effects on EEG parameters, and this single episode of clonic activity was not reproducible across a wide exposure range in a large number of animals, including 15- or 39-week studies at doses up to 6 mg/kg/day in monkeys.

### **Vascular System**

In the 26-week rat toxicity study only, adverse degenerative vascular/perivascular inflammation was noted in the liver as well as in the stomach, pancreas, or urinary bladder of male rats. There was minimal disruption of the vascular integrity and no associated degenerative effects in adjacent tissues or correlating functional effects in organ systems. Overall the microscopic features were consistent with test article-related exacerbation of spontaneous polyarteritis. No vascular lesions were observed in the organs of any recovery phase animals, indicating complete recovery. No similar vascular findings were observed in female rats in the 26-week study, or in male or female rats in the completed studies up to 15 weeks, at doses up to 60 mg/kg/day. In addition, there was no evidence of vascular or perivascular inflammation in any tissue in monkey studies following up to 39 weeks of dosing. These data suggest a later onset (ie, beyond 15 weeks of dosing) for the PF-06649751-induced vascular findings observed in male rats, and suggest a potential for PF-06649751 to induce arterial lesions in rats with chronic dosing similar to rodent-specific findings reported for the D1 receptor (D1R) agonist fenoldopam. Fenoldopam has a well-documented history of inducing vascular injury in rats with effects consisting largely of arteriolar hemorrhage as well as degeneration and necrosis in rats administered 24-hour continuous intravenous infusion.<sup>33</sup> These lesions are morphologically identical to the lesions produced in rats following an infusion of dopamine, and mechanistic data suggest the injury involves activation of the D1R.<sup>34</sup> Despite reproducibility of acute vascular injury in rats, arterial lesions have not been observed in mice or dogs, and there are no reports of similar lesions being observed in humans treated with fenoldopam, including safety data reported after long term dosing in clinical studies following oral administration.<sup>35</sup> While potential for PF-06649751 to induce arterial lesions in humans cannot be ruled out with all certainty, the historical observations for fenoldopam and nonclinical data with PF-06649751 suggest that the rat is uniquely sensitive to this endpoint following administration of D1R agonists, and there is low likelihood for this finding to occur in human subjects administered PF-06649751.

At the NOAEL of 5 mg/kg/day for this finding in male rats in the 26 week study, the unbound margins were 5.7 and 2.1x, respectively, the unbound human exposures ( $C_{max}$  19.8 ng/mL,  $AUC_{tau}$  366 ng•h/mL) at a dose of 15 mg.

### **Reproductive System**

In the 15- and 26-week rat studies, several PF-06649751-related microscopic findings in the ovary, and secondary changes in the ovary, mammary gland, or cervix, collectively indicated a recent reduction in ovarian function, and were considered adverse at doses  $\geq 0.7$  mg/kg/day. There were no necrotic or degenerative effects noted microscopically in the reproductive organs, and these findings are similar to those that begin to occur naturally with reproductive senescence in aging rats. At the NOAEL of 0.2 mg/kg/day, the exposures in female rats were  $< 1x$  the unbound human exposures at a dose of 15 mg. In the 26-week study in rats, similar PF-06649751-related ovarian findings were present but not considered adverse given the nondegenerative nature and natural reproductive senescence occurring in all female groups. These findings were attributed to PF-06649751-related persistent estrus that was

characterized by daily vaginal cytology in a 15-week study, and in a 4-week investigative study in female rats that included recovery and an assessment of reproductive hormones. In the 4-week study, persistent estrus was associated microscopically with estrous cycle asynchrony; both returned to normal during the recovery phase. Hormone concentrations for animals with persistent estrus induced by PF-06649751 were similar to other animals in the same stage of estrus.

These findings in rats are not considered a risk for women of non-childbearing potential, based on the lack of necrotic or degenerative findings at the microscopic level, but are of potential concern for women of childbearing potential based on the anticipated adverse effect on reproductive function. However, findings are specific to rat studies with PF-06649751 as there were no reproductive organ findings in monkeys in studies up to 39 weeks of dosing. In the 39-week toxicity study, sexually mature female monkeys with a stable menses baseline were used and menstrual cycle frequency was monitored. There was no effect of PF-06649751 on menstrual cycles or in any reproductive organ at the end of 39 weeks of dosing at any dose ( $\leq 6$  mg/kg/day). At the dose of 6 mg/kg/day (NOAEL) in sexually mature female monkeys, the  $AUC_{24}$  was 14,100 ng•h/mL, which is 2.2x the unbound human  $AUC_{\tau}$  of 366 ng•h/mL at a dose of 15 mg.

### **Cardiovascular System**

Cardiovascular findings in single dose safety pharmacology studies in monkeys included decreased blood pressure (within 0.75 to 8.5 HPD), followed by increased blood pressure during later time periods (within 9 to 20 HPD), and increased heart rate, QTc interval, and cardiac contractility. Results of an in vitro hERG study and a monkey isolated heart (Langendorff Model) study suggested that the effects on heart rate, QTc, and contractility were indirect (ie, not mediated by direct PF-06649751 effects on the heart). The  $IC_{50}$  for PF-06649751 in the hERG assay (64.9  $\mu$ M, 25400 ng/mL) is  $\geq 940$ x to 9700x the unbound  $C_{\max}$  range in monkeys at doses where QTc interval increases were observed. PF-06649751 had no effects on heart rate, QT interval, or left ventricular pressure in the cynomolgus monkey isolated heart (Langendorff model) at concentrations up to 1  $\mu$ M (391 ng/mL), or 15x to 49x the unbound  $C_{\max}$  in monkeys at doses (0.6 to 2.5 mg/kg) where increased contractility was observed in vivo.

Exposure margins from the NOAELs from the chronic toxicity studies in monkeys and male rats to the human exposure at 15 mg are similar. The NOAEL in the 39-week chronic monkey study was the highest administered dose of 6 mg/kg/day, and was associated with a combined sex mean total  $C_{\max}$  and  $AUC_{24}$  of 1370 ng/mL and 14,100 ng•h/mL (79.5 ng/mL and 818 ng•h/mL, unbound), respectively. These values are 4x and 2.2x the unbound human  $C_{\max}$  (19.8 ng/mL) and  $AUC_{\tau}$  (366 ng•h/mL) at a dose of 15 mg. In male rats, the NOAEL in the 26-week study was 5 mg/kg/day, based upon adverse vascular/perivascular inflammation noted in males at  $\geq 20$  mg/kg/day, and was associated with a  $C_{\max}$  and  $AUC_{24}$  of 1610 ng/mL and 11,000 ng•h/mL (113 ng/mL and 770 ng•h/mL, unbound). These values are 5.7x and 2.1x the unbound human  $C_{\max}$  and  $AUC_{\tau}$  at a dose of 15 mg. In female rats, adverse test article-related microscopic findings in the eyes (exacerbation of light induced retinal atrophy) were present at all doses ( $\geq 1$  mg/kg/day), therefore the NOAEL in female

rats was undetermined. However, this eye finding was considered an adverse effect relevant only to nonpigmented animals and, as per expert consultation, not a likely finding or potential risk expected in humans.

The nonclinical safety profile of PF-06649751 is considered to be adequately characterized to support progression into human clinical studies of 6 months or longer dosing duration for men and for women of non-childbearing potential. Detailed information for this compound may be found in the Single Reference Safety Document (SRS), 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 (FIH), 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 study 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.

PF-06649751 has been evaluated in 2 completed clinical studies in 63 Parkinson's disease patients which are described in the Investigator's Brochure:

- Protocol B7601005 (n=45) 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 Day 1 for the evaluation of L-Dopa responsiveness. In the following

days, 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. Within the study, pharmacokinetics of PF-06649751 in Parkinson's disease patients was evaluated on Days 7, 13 and 22. Continued dosing of PF-06649751 up to 25 mg QD for up to 3 weeks were safe and well tolerated by subjects with Parkinson's disease, with no new safety findings.

- Protocol B7601009 (n=18) was a Phase 1b, double blind, placebo controlled, randomized, 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.

#### **1.4.2. Safety**

##### B7601001

One single ascending dose study in healthy subjects (B7601001) has been completed. In this study, 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 PK 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

B7601005 was a Phase 1b, 2-period, open label, multi-center, dose escalation study of PF-06649751 in subjects with Parkinson's disease experiencing motor fluctuations and, in one of the cohorts, subjects with Parkinson's disease experiencing levodopa induced dyskinesia (LID). In Period 1 of the study, L-Dopa and placebo were administered for the evaluation of L-Dopa responsiveness. During Period 2, PF-06649751 was administered for the evaluation of the safety, tolerability and pharmacokinetics of PF-06649751. The B7601005 study 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. Multiple ascending doses of PF-06649751 up to 25 mg QD were safe and well tolerated by subjects with Parkinson's disease, with no new safety findings.

There were no deaths reported in the study. There was 1 SAE, 6 severe AEs, and 11 permanent discontinuations due to AEs. The majority of AEs occurred during the up titration period of PF-06649751 (Period 2, Days 3-24 and follow-up) but the timing and dose level at which AEs occurred were variable. The most common AE reported in all PF-06649751 treatment groups were headache, nausea, abnormal dreams, dizziness and vomiting. The gastrointestinal disorders appeared to be dose-driven as there were more nausea and vomiting in the 15 mg QD (including LID) and 25 mg QD doses compared with the 5 mg QD dose. Most AEs in all PF-06649751 treatment groups appeared related to pace and increment of up-titration rather than maximum exposure and were generally self-limited.

Across cohorts there were no apparent trends or clinically significant changes in vital signs, ECG, physical findings, laboratory values and the Parkinson's disease diary.

#### B7601009

B7601009 (n=18) was a Phase 1b, double-blind, placebo-controlled, randomized, study to evaluate the safety, tolerability and pharmacokinetics of single ascending doses of PF-06649751 in Parkinson's disease subjects. Single doses of PF-06649751 0.75 mg, 1.5 mg, 3 mg, 6 mg, 9 mg were evaluated in the study.

Two (2) sequential cohorts were planned and were to be conducted over 3 treatment periods. Study drug or placebo was administered once during each of 3 treatment periods, with an at least 7 day study drug wash out phase between treatment periods.

Single doses of PF-06649751 up to 9 mg were safe and well tolerated by subjects with Parkinson's disease. There were no deaths, SAEs, severe AEs, discontinuations due to AEs, dose reductions or temporary discontinuation due to AEs. The most common mild to moderate AEs were headache, nausea, and vomiting. Nausea and vomiting appeared to be more common in the higher dose groups (PF-06649751 3 mg, PF-06649751 6 mg and PF-06649751 9 mg treatment groups).

There were no notable findings in clinical laboratory. There appeared to be a small dose-related increase in heart rate without consistent changes in blood pressure (BP), except for the observations of orthostatic hypotension.

There was an increase of mean QTcF values in the higher dose groups (PF-06649751 6 mg and PF-06649751 9 mg) between 2 and 8 hours post dose, but no subject had a QTcF  $\geq 500$  msec or an increase of QTcF  $\geq 60$  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 oral 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 modestly 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.

Increases in steady state PF-06649751 exposures following multiple oral doses appeared to be approximately dose-proportional across the B7601002 and B7601005 studies. Consistent with the observed half-life, approximately 2-fold accumulation in exposures was observed following once daily dosing. Approximately 0.2% of the dose was excreted un-changed in urine at steady state. Evaluation of PF-06649751 pharmacokinetics in healthy Japanese subjects at 1.5 mg QD dose suggest no meaningful difference between Japanese and Western subjects.

Steady state PF-06649751 exposures in Parkinson's disease patients at different doses from (study B7601005) are presented in Table 1. Average steady state PF-06649751 exposures in healthy subjects (B7601002) were approximately 65% of the values observed in Parkinson's disease patients (B7601005). However, with limited number of subjects in B7601002 (N=5) and differences in the tolerability profile across populations, these differences are considered preliminary.

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

Dose	$C_{max,ss}$ (ng/mL)	$T_{max}$ (hrs)	$AUC_{24,ss}$ (ng*hr/mL)
5 mg once daily (n=9)	118.5 (33)	2.0 (1.0-4.0)	2105 (35)
15 mg once daily (n=7)	325.4 (46)	4.0(2.0-12.0)	5993 (61)
25 mg once daily (n=7)	401.6 (41)	4.03 (1.97-8.0)	7182 (52)

Values for  $C_{max,ss}$  and  $AUC_{24,ss}$  are presented as geometric means (%CV). Median values (range) are presented for  $T_{max}$ .

### 1.4.4. Additional Information

Detailed information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the Investigator's Brochure of PF-06649751, and the prescribing information for L-Dopa (for example, Sinemet, Menesit, Madopar, Prolopa, or EC Dopar).

## **1.5. Rationale**

### **1.5.1. Study Rationale**

This study will evaluate the efficacy, safety, and tolerability of PF-06649751 as a potential novel therapeutic agent in subjects with Parkinson's disease.

PF-06649751 is a novel D1 and D5 specific dopamine partial agonist and has the potential to reduce OFF time in subjects with moderate to advanced Parkinson's disease who are experiencing significant OFF time despite their current dopaminergic therapy. Following an initial titration phase, which is intended to mitigate potential dopaminergic adverse events such as nausea and vomiting, fixed doses of PF-06649751 will be evaluated as adjunctive treatment with L-Dopa. The overall doses of PF-06649751 selected for this study were influenced by the aim to identify not only a minimally-effective dose but also characterize the maximum efficacious dose.

The study was initially limited to a maximum 15 week treatment period due to the available toxicological coverage. Subsequently, the nonclinical safety profile of PF-06649751 is considered to be adequately characterized to support progression into human clinical studies of 6 months or longer dosing duration for men and for women of non-childbearing potential.

Subjects who complete through Week 15 of the B7601003 study will have the option to enroll in an open label extension study (B7601017). If the pre-specified Inclusion/Exclusion criteria are met at Week 10 (screening), the subject may exit the current B7601003 study at Week 15 for continued treatment and follow-up under the extension study (B7601017), provided they remain eligible. Subjects not directly entering study B7601017 at Week 15 must complete the Week 17 and Week 19 Follow-up visits and must rescreen under the B7601017 protocol.

Based on reports of other dopaminergic drugs, the peak effect on OFF time has been observed after approximately 8 weeks of treatment.

The study population will include male subjects and female subjects of non-childbearing potential diagnosed with Parkinson's disease who experience motor fluctuations.

### **1.5.2. Dose Rationale**

PF-06649751 doses for this study are selected based on evidence of pharmacological activity from preclinical data and clinical studies in Parkinson's disease subjects. Based on experiments in MPTP monkeys, the human  $C_{\text{eff}}$  was established at 27.6 ng/mL. Based on the human Phase 1 pharmacokinetic data, a dose of 3 mg QD is expected to produce total plasma concentrations of PF-06649751 of at least 27.6 ng/mL, across the entire dosing interval, in Parkinson's disease subjects. Based on observed MDS-UPDRS Part III data from B7601009 and B7601005, a dose of 1 mg QD is likely to be a no- or minimal effect dose to evaluate the lower part of the dose-response curve. The top dose of 15 mg is chosen to establish safety and efficacy at a dose that is at the top part of the dose-response curve. The 7 mg QD dose will provide safety, tolerability and efficacy data at a dose lower than 15 mg dose to establish maximum efficacious dose with adequate safety in case of safety/tolerability issues at 15 mg

PF-06649751 dose group. The overall doses of PF-06649751 selected for this study were influenced by the aim to identify not only a minimally-effective dose but also characterize the maximum efficacious dose with adequate safety using the limited tablet strengths available (ie, 1 mg and 5 mg) as efficiently as possible without exceeding more than three tablets per dose. The selected dose range of 1 mg – 15 mg PF-06649751 QD is wide enough to facilitate appropriate dose selection for Phase 3 studies.

Even though MDS-UPDRS Part III scores from Phase 1b studies are used to drive dose selection, it should be noted that the primary endpoint for the current study is OFF time and not MDS-UPDRS Part III. Moreover, due to the uncontrolled, open-label study design, data from B7601005 may be subject to bias. These shortcomings in dose selection are addressed in the study design in order to achieve the primary aim of the study (establish dose response with OFF time).

- Confirm OFF time reduction at 15 mg dose (only) at the first interim analysis before initiating the dose ranging part of the study (see [DATA ANALYSIS/STATISTICAL METHODS](#)).
- Uncertainty in Phase 1b data is addressed by including doses (1 mg and 7 mg) bracketing the current preclinical estimate (~3 mg).

Based on the observed exposures from the 15 mg cohort in study B7601005, the top dose of 15 mg QD dose is expected to provide exposure ~2-3 fold lower than the stopping criteria from 15 week monkey toxicological study. Given the CYP3A4 mediated metabolism of PF-06649751, this provides a margin to allow for a possible increase in exposure of PF-06649751 when used together with weak inhibitors of CYP3A4. Patients receiving moderate to strong CYP3A4 inhibitors will be excluded from the study until further elucidation of the exact interaction magnitude in a drug-drug interaction study.

Therefore, based on the objectives to identify a minimum efficacious dose, maximum efficacious dose and evaluate dose-response, the following four PF-06649751 doses are proposed for the study along with a placebo: 1 mg QD, 3 mg QD, 7 mg QD and 15 mg QD PF-06649751.

### **1.5.3. Summary of Benefit-Risk Assessment**

The study is designed to assess the efficacy, safety, tolerability, and pharmacokinetics of PF-06649751 in subjects with Parkinson's disease. Based on the clinical safety data available to-date, PF-06649751 doses 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. 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. Primary Objective

- To evaluate the effect on motor symptoms of PF-06649751 administered once daily as adjunctive treatment with stable doses of L-Dopa in Parkinson's disease.
- To determine the therapeutic window for motor symptom improvement of PF-06649751 administered once daily, ie, determining a dose, or a range of doses, for adequate control of motor symptoms.

### 2.2. Secondary Objectives

- To evaluate the dose-response on motor symptoms of PF-06649751 administered once daily in subjects with Parkinson's disease.
- To evaluate the safety and tolerability of PF-06649751 administered once daily in subjects with Parkinson's disease.
- To evaluate the effect of PF-06649751 administered once daily on dyskinesia in subjects with Parkinson's disease.

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### 2.4. Endpoints

#### 2.4.1. Primary Endpoint (Efficacy)

- Change from baseline in daily OFF time (hours OFF time; based on patient reported Hauser diary) at Week 10 (Day 70; end of Period A).

#### 2.4.2. Secondary Endpoints (Efficacy; Evaluated during the entire double-blind period)

Change from baseline in:

- Daily OFF time (hours).
- Daily ON time with troublesome dyskinesia (hours).
- Daily ON time without troublesome dyskinesia (hours).

- MDS - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III.
- MDS-UPDRS Parts I, II, IV, and total score.

**2.4.2.1. Secondary Endpoints (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).

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### 3. STUDY DESIGN

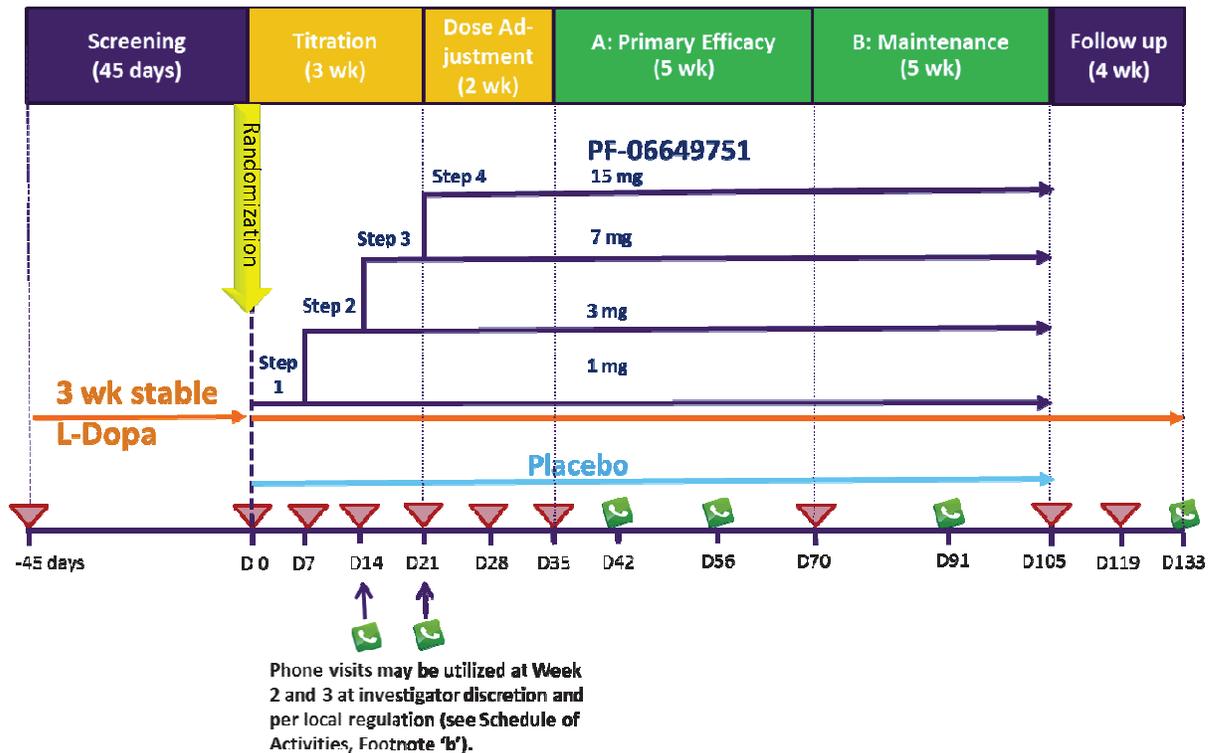
#### 3.1. Study Overview

The study has a randomized, double-blind, placebo-controlled parallel group design. Approximately 198 subjects from approximately 60 centers in approximately 6 countries will be randomized to 5 treatment groups (15 mg QD, 7 mg QD, 3 mg QD, 1 mg QD, or placebo), initially in a 2:0:0:0:1 ratio of approximately 54 subjects (Cohort 1) followed by a 1:2:2:2:1 ratio of approximately 144 subjects (Cohort 2), using a central randomization system with randomization blocks stratified by region.

Each subject will participate in the study for approximately 25 weeks including up to a 45 day screening period, 15 week double-blind treatment period (comprising up to a 3 week titration, 2 week dose adjustment, 5 weeks of primary efficacy with adjunctive treatment to stable L-Dopa (Period A), and 5 weeks of maintenance with adjunctive treatment to stable L-Dopa (Period B)), and an approximately 28 day follow-up period.

The study design is illustrated in the figure below. For details on the dosing during the titration phase, see Section 5.5.1, **Titration of PF-06649751**.

Figure 1. Study Schematic



### 3.1.1. Screening

Screening evaluation will occur within 45 days prior to Day 0 (Randomization). Rescreening may be permitted after discussion with the study medical monitor. Screening procedures may split between multiple days/visits for feasibility and/or subject comfort; however individual procedures should not be split between multiple days/visits.

Subjects will document their symptoms (ON, OFF, ON with/without dyskinesia, ON with non-troublesome dyskinesia, ON with troublesome dyskinesia) in a patient diary (see Section 7.3.1 [OFF Time Diary \(Hauser Diary\)](#)).

- For Screening ON/OFF time concordance testing (see Section 7.1.7, [Concordance Testing and OFF Time Diary Training](#)), the subject must have at least 75% concordance with investigator (or qualified site staff/rater).
- For the final Inclusion/Exclusion criteria verification on Day 0 (Randomization) by the investigator, subjects must have  $\geq 2.5$  hours OFF time each day, collected over 3 consecutive days during the week prior to Day 0 (Randomization), with fewer than 4 errors or missing entries in diary data per day.

### 3.1.2. Double Blind Period

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

- Up to 3 week titration of PF-06649751 or placebo administered once daily to the randomized target dose ([Section 5.5.1](#)).
- 2 week stabilization period for dose adjustment after reaching the target dose with possible return to previous dose level after completion of the titration period. For subjects with intolerable adverse events, adjunct L-Dopa dose may subsequently be reduced after consultation with the Medical Monitor (see Section 5.5.1 [Titration of PF-06649751](#)).
- Period A (Primary Efficacy): a 5 week period of PF-06649751 or placebo administered once daily adjunctive to stable doses of L-Dopa ([Section 5.5.2](#)).
- Period B (Maintenance): a 5 week maintenance period of PF-06649751 or placebo administered once daily adjunctive to stable doses of L-Dopa ([Section 5.5.3](#)).

Subjects will return to the clinic at the end of Weeks 1, 2, 3, 4, 5, 10, 15, and 17. Weeks 2 and 3 may be conducted as phone visits, at the discretion of the investigator.

All other visits will be conducted as phone visits; as per Section 6.5 ([Unplanned Visits](#)), the investigator has the discretion to conduct an unplanned clinic visit if warranted for subject safety. For guidance on concomitant medications for Parkinson's disease and other disorders please see Section 5.8, [Concomitant Treatment\(s\)](#).

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

A follow up visit two weeks after discontinuation of PF-06649751 or placebo will take place at Week 17 for subject safety. A follow up phone visit will occur approximately 28 days after discontinuation of PF-06649751 or placebo at Week 19 for subject safety assessment. For all subjects who have received at least 1 dose of investigational product (except a subject who withdraws consent), follow-up contact will be completed at least 28 calendar days, and up to 35 calendar days after the last administration of the investigational product.

### **3.1.4. Open Label Extension Study**

Subjects who complete through Week 15 of the B7601003 study will have the option to enroll in an open label extension study (B7601017). If all specified Inclusion/Exclusion criteria are met at Week 10/Screening Visit (B7601017), the subject may exit the current B7601003 study at Week 15/Baseline Visit (B7601017) for continued treatment and follow-up under the open label extension study (B7601017), provided they remain eligible.

Subjects not directly entering study B7601017 at Week 15 must complete the Week 17 and Week 19 Follow-up visits as required per protocol.

## **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. Unless otherwise specified, the following Inclusion and Exclusion Criteria are referring to the Screening Visit.

### **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, including dosing and Parkinson's disease diaries.
3. Females of non-childbearing potential and/or male subjects between the ages of 40 and 85 years, inclusive. Male subjects able to father children must agree to use

one (1) highly effective method of contraception throughout the study and for at least 28 days after the last dose of assigned treatment.

Female subjects who are not of childbearing potential (ie, who 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.

All other female subjects (including females with tubal ligations) will be considered to be of childbearing potential and are not eligible for participation.

Diagnosis:

4. Clinical diagnosis of Parkinson's disease consistent with the United Kingdom (UK) Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria.<sup>12</sup> (See [Appendix 6](#) for detailed criteria).
5. Parkinson's disease Hoehn & Yahr Stage less than or equal to III while the subject is ON.
6. Currently responding to L-Dopa therapy.
7. Total duration of  $\geq 2.5$  hours OFF time each day, based on the OFF time diary (Hauser diary) collected over 3 consecutive days during the screening period (with fewer than 4 errors or missing entries in diary data per day) and at least 75% concordance with investigator (or qualified site staff/rater) for Screening ON/OFF time concordance testing (see [Concordance Testing and OFF Time Diary Training](#)).
8. Subjects must be able to recognize their "wearing off" symptoms and confirm that they usually improve after their next dose of Parkinson's disease medication.
9. On a stable dose of L-Dopa of at least 400 mg total daily dose for at least 21 days prior to Day 0 (Randomization), in conjunction with a dopa-decarboxylase inhibitor (eg, L-Dopa/carbidopa or L-Dopa/benserazide) divided in at least 4 doses per day. Subjects on a stable dose of L-Dopa of at least 400 mg/day divided into 3 daily doses (TID) may be considered and authorized on a case-by-case basis if submitted as part of the screening assessment to the sponsor and/or its designee for determination if the dosing regimen is considered optimized for that particular subject. No subject on TID

dosing will be considered eligible for Randomization without this additional eligibility assessment. Please refer to [Section 7.1.8](#) for details.

10. Willing and able to refrain from any Parkinson's disease medication not permitted by the protocol throughout participation in the study.

Screening assessments:

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

#### **4.2. Exclusion Criteria**

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

Diagnosis:

1. History or clinical features consistent with an atypical Parkinsonian syndrome.
2. History of intracranial surgical intervention for Parkinson's disease or other indications (pallidotomy, thalamotomy, deep brain stimulation, etc).
3. A score of 4 on item 4.2 Functional Impact of Dyskinesias of MDS-UPDRS Part IV (motor complications) at Screening.
4. Psychotic symptoms related to Parkinson's disease requiring treatment with an antipsychotic medication within 6 months prior to Screening.
5. 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:

6. Severe acute or chronic medical, including fever, psychiatric condition, 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.
7. 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>27</sup> or conditions that lower seizure threshold, seizures of any etiology (including substance or drug withdrawal), or known increased risk of seizures.
8. A 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) that in the opinion of the investigator could interfere with study participation or poses a risk to the subject. Presence of minor depression or treated, stable depressive disorder is acceptable.
9. History of clinically significant alcohol or substance dependency (other than caffeine or nicotine), as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), within 1 year before Screening.
  10. 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.
  11. Any condition possibly affecting drug absorption, past surgery of the gastrointestinal tract (eg, gastrectomy, colectomy), except cholecystectomy.
  12. History of vasculitis.
  13. History of Human Immunodeficiency Virus (HIV) infection.
  14. 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.
  15. Subjects with first degree family history of unexplained sudden death, or of Long QT syndrome (LQTS).

Concomitant Medications:

16. Currently receiving an antipsychotic, metoclopramide, reserpine, or amphetamine.
17. Currently receiving moderate or strong CYP3A4 inducers or CYP3A4 inhibitors (except for topical administration).
18. Previous implantation of apomorphine pump, or surgery for intraduodenal use of Duodopa<sup>®</sup>.
19. Dopamine receptor agonist medications including pramipexole, ropinirole, rotigotine and apomorphine must be discontinued at least 28 days prior to Day 0 (Randomization).
20. Herbal supplements must be discontinued at least 28 days prior to Day 0 (Randomization).

21. Prohibited concomitant medications as outlined in Section 5.8, [Concomitant Treatment\(s\)](#), and [Appendix 3](#).

Screening assessments:

22. Females of childbearing potential (assessed at Screening); Pregnant female subjects; breastfeeding female subjects; male subjects with partners currently pregnant; male subjects able to father children who are unwilling or unable to use one (1) 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.
23. Suicidal ideation associated with actual intent and/or plan in the past year; (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 10 years (a "YES" answer to any of the suicidal behavior items of the C-SSRS with the behavior occurring in the past 10 years).
24. Subjects with Clinically significant depression: PHQ-8 total score  $\geq 15$ .
25. 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.
26. 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).
27. 12-lead ECG (average of triplicate measures) demonstrating QTcF  $>450$  msec ( $>470$  msec for females) or a QRS interval  $>120$  msec at Screening.
28. 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 aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT) **or** alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT)  $\geq 2x$  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.

29. A positive test for hepatitis B surface antigen or hepatitis C antibody.
30. A positive urine drug screen for drugs of abuse unless explained by medically indicated medication.

General and Administrative:

31. 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.
32. Participation in other studies involving investigational drug(s), or treatment with any 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).
33. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 56 days prior to Day 0 (Randomization).
34. Unwilling or unable to comply with the lifestyle requirements described in [Section 4.4](#) of 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 5 treatment groups (15 mg QD, 7 mg QD, 3 mg QD, 1 mg QD, or placebo), initially in a 2:0:0:0:1 ratio (Cohort 1) followed by a 1:2:2:2:1 ratio (Cohort 2). Randomization blocks will be stratified by region.

If following an interim analysis a decision is made to stop enrollment in one or more dose groups, the randomization schedule will be adjusted to reflect the number of treatment groups.

### 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 Investigational Product until the end of double blind study medication.

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

- Subjects should abstain from alcohol for at least 12 hours prior to every study visit.
- Subjects may undergo an alcohol breath 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.
- Stable rehabilitation therapy is permitted if regimen remains stable during the course of the study.

#### **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 and at risk for causing a pregnancy 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/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 or 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 postvasectomy ejaculate.
5. For a female partner, 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.

#### **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 contact list located in the team 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**

For specific rating assessments, only qualified raters will be allowed to evaluate and/or rate subjects in this study. The list of relevant study rating assessments and the minimum qualifications a rater must meet for each assessment will be outlined in the “Rater Qualification Guide” provided to each participating site. The level of experience with the target population (or equivalent), and specific scale experience (or equivalent), certification required (if applicable) will be listed 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 Guide before he/she can participate in the administration of the assessments in the study. For specifically defined assessments, rater training and standardization exercises may be conducted, and written & signed documentation will be provided by the site for each rater’s certification. In return each site will be provided written documentation outlining each rater’s certification for specific study assessments. Recertification may be required at periodic intervals during the study. 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. 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.

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

#### **5. STUDY TREATMENTS**

Investigational Product 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**

All subjects will be on L-Dopa treatment (for example, Sinemet, Menesit, Madopar, Prolopa, or EC Doparl).

For PF-06649751 or placebo, allocation of subjects to treatment groups will proceed through the use of an interactive web response (IWR) technology 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 IWR system. The IWR 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 IWR helpdesk available for any questions or issues. The study specific IWR reference manual (ie, B7601003 Impala Quick Reference Guide) will provide the contact information and further details on the use of the IWR system.

Note: The IWR is the source of the subject number. The IWR system will provide the subject number at the end of the first IWR subject transaction.

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

L-Dopa treatment is open-label and not blinded.

For PF-06649751 or placebo, treatment assignment will be sponsor, subject, and investigator blinded. At the initiation of the study, the study site will be instructed on the method for breaking the blind. The method will be either through the IRT system or a call center. Blinding codes should be broken only in emergency situations for reasons of subject safety. Whenever possible, the investigator or subinvestigator consults 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**

L-Dopa will be administered daily by the subject or caregiver at dose and frequency prescribed or as instructed by the investigator. A subject will be considered compliant with the protocol at a study treatment compliance range of 80%-120%.

PF-06649751 or placebo will be administered by the subject or caregiver in the outpatient setting (each morning, daily for the duration of the treatment period). 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 medication, 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 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. The 1 mg, 5 mg, and their matching placebos will be supplied in weekly blister cards. At each dispensing visit, subjects will receive sufficient quantity of investigational product (IP) 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 1 mg, 5 mg, and its matched placebo should 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 provided, in quantities appropriate for the study visit schedule. The subject/caregiver should be instructed to maintain the product in the blister cards provided throughout the course of dosing and return the blister cards to the site at the next study visit.

## **5.5. Administration**

For L-dopa, subjects should be instructed to take the L-dopa in accordance with instructions provided in the product labelling information, at a dose and frequency per the instructions of the investigator and in consideration of the administration instructions provided in the instructions in Section 5.5.1 ([Titration of PF-06649751](#)); Section 5.5.2 ([Period A: Primary Efficacy](#)) and Section 5.5.3 ([Period B: Maintenance](#)).

For PF-06649751 or placebo, 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 3 tablets should be taken within approximately 5 minutes.
- The tablets may be taken with or without food.
- If L-Dopa is taken in the morning, the PF-06649751 or placebo tablets may be taken before or after the morning dose of L-Dopa.

- Subjects will document the timing of PF-06649751 or placebo dose on study visit days.

### 5.5.1. Titration of PF-06649751

Each subject is planned to be up-titrated in a double-blind fashion to the assigned target dose level of PF-06649751 or placebo according to the following titration scheme:

**Table 2. Proposed Titration Schemes for PF-06649751 and Placebo Doses**

Week/ Start Day of Dose Level	Treatment Group				
	Placebo	1 mg	3 mg	7 mg	15 mg
Week 1 / from Day 1	P	1 mg	1 mg	1 mg	1 mg
Week 2/ from Day 8	P	1 mg	3 mg	3 mg	3 mg
Week 3 / from Day 15	P	1 mg	3 mg	7 mg	7 mg
Weeks 4-15 / from Day 22	P	1 mg	3 mg	7 mg	15 mg

**Titration (Week 1 to Week 3):** No modifications to the upward titration of Study Medication can be made. Subjects who experience intolerable adverse events during titration will need to be discontinued from the study.

**Post Week 3 (Week 4 to Week 5):** For subjects who experience unacceptable new adverse events after having achieved the target dose (after Day 21) and deemed related to the dose increase, the dose of investigational product can be changed to the previous dose level (Week 3 dose level). This results in a dose reduction from 15 mg/day to 7 mg/day for the highest dose group, and no change in dose for the other dose groups in a blinded fashion. Only one dose modification of investigational product is permitted.

**L-Dopa Adjustment for Unacceptable Dopaminergic Side Effects (Week 1 to Week 15):** In the case of unacceptable dopaminergic side effects and following discussion with the Medical Monitor, the dose of L-Dopa may be reduced between Day 1 and Day 105 visit.

### 5.5.2. Period A: Primary Efficacy

During Period A, subjects will be administered double blind study medication once daily (up to 4 different dose levels of investigational product) as adjunctive treatment to a stable dose of open-label L-Dopa.

### 5.5.3. Period B: Maintenance

After the Week 10 Visit (primary endpoint collection), subjects will enter Period B. During Period B, double-blind treatment with investigational product will continue as adjunctive treatment to a stable dose of open label L-Dopa.

## **5.6. Investigational Product Storage**

The investigator, or an approved representative, 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 taking home investigational products, including how to report temperature excursions. See the single reference safety document (SRSD) for this study, the Investigator's Brochure for PF-06649751.

Storage conditions stated in the Investigator's Brochure 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.

## **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 3](#) and [Appendix 4](#) except for:

- The treatment of adverse events.
- [Rescue Medication](#), as described in Section 5.9.
- All concomitant medications 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 medication at each clinic and telephone 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:

- Subjects must be on a stable dose of L-Dopa of at least 400 mg total daily dose for at least 21 days prior to Randomization, in conjunction with a dopa-decarboxylase inhibitor (eg, L-Dopa/carbidopa or L-Dopa/benserazide) divided into at least 4 doses per day. Subjects on a stable dose of L-Dopa of at least 400 mg/day divided into 3 daily doses (TID) may be considered and authorized on a case-by-case basis if submitted as part of the screening assessment to the sponsor and/or its designee for determination if the dosing regimen is considered optimized for that particular subject.
- MAO-B inhibitors or COMT inhibitors, amantadine, and anticholinergics are permitted but should remain at stable dose from 42 days prior to Day 0 (Randomization) through the end of the double blind treatment period.

Prohibited Parkinson's disease medications:

- Dopamine receptor agonist medications including pramipexole, ropinirole, rotigotine and apomorphine are prohibited for at least 28 days prior to Randomization and through the end of the double blind treatment period.

- Istradefylline and zonisamide are prohibited 42 days prior to Randomization and through the end of the double blind treatment period.
- The use of inhaled L-Dopa is prohibited from Screening through the end of the double blind treatment period.
- Subjects with prior implantation of apomorphine pump, or surgery for intraduodenal use of Duodopa<sup>®</sup> are not eligible.

### **5.8.2. Prohibited Other Concomitant Medications**

The following medications will not be permitted within 28 days prior to Randomization:

- CYP3A4 inducers: the use of moderate and strong inducers of CYP3A4 is not permitted, since they may decrease the levels of PF-06649751. A list of potential drug inducers is provided in [Appendix 4](#).
- CYP3A4 inhibitors: the use of moderate or strong inhibitors of CYP3A4 is not permitted throughout the study since concomitant use these may lead to increased levels of PF-06649751. A list of potential CYP3A4 inhibitors is provided in [Appendix 4](#).
- 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 Randomization:

- The use of amphetamines, methylphenidate or other stimulants.
- Antipsychotics (except stable low dose quetiapine), metoclopramide, or reserpine are not permitted.
- Lithium, MAO-A/B inhibitor antidepressants (including moclobemide, tranylecypromine, and phenelzine); stable low dose opioids for chronic painful medical conditions may be permitted based on a consultation with the medical monitor.
- Antiepileptics are not permitted except if used for chronic painful conditions at steady doses (for example, gabapentin or pregabalin).

### **5.8.3. Permitted Concomitant Medications**

Subjects will use background L-Dopa (for example, Sinemet, Menesit, Madopar, Prolopa, or EC Dopar) provided in the local commercial packaging throughout the study. Subjects should remain on the same formulation of L-Dopa from Screening through the duration of the study. The daily L-dopa dose should not change from 21 days prior to Day 0 (Randomization) through the end of the study. In the case of unacceptable dopaminergic side

effects, and only following discussion with the Medical Monitor, the dose of L-Dopa may be reduced between the Day 1 and Day 105 visit.

Stable doses of concomitant medications for treatment of medical conditions are permitted during the course of the study, including antihypertensives, antidepressants (other than MAO inhibitors), anticoagulants, lipid lowering agents, oral antidiabetics, thyroid replacement hormones, and antacids.

The potential risk for drug-drug-interactions with PF-06649751 and primary substrates of CYP3A4 (especially those with a narrow therapeutic index; eg, vinca alkaloids), and BCRP is considered to be 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 substrates (eg, alfentanil, ergotamine, irinotecan, ticagrelor, simvastatin, etc.). Further information on potential drug-drug-interactions and data available to date can be found in Section 5.2.7 Pharmacokinetic-Drug Interactions of the Investigator's Brochure.

### **5.9. Rescue Medication**

Rescue medication is permitted in the form of L-Dopa. The dose and dose frequency can be defined using investigator discretion based on patients' needs. Rescue L-Dopa may be administered if needed in between study visits based on a phone consultation and the discretion of the investigator.

## **6. STUDY PROCEDURES**

### **6.1. Screening: Day -45 to Day -1**

Subjects will be screened within 45 days prior to Day 0 (Randomization) 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, [Subject Information and Consent](#). The informed consent may be obtained up to 60 days prior to Day 0 (Randomization).

The Screening procedures may be split between multiple days/visits for feasibility and/or subject comfort, however individual procedures should not be split between multiple days/visits.

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.

- Collect Demographics.
- Obtain prior medical history, medication history including current medications, and demography.
- Contraception Check.
- Assessment of prior/concomitant medications.
- Collect height, weight, and BMI.
- Perform full physical and neurological examination.
- Perform Mini Mental State Examination (MMSE).
- Confirm clinical diagnosis of Parkinson's disease using the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria ([Appendix 6](#)).
- Perform Hoehn & Yahr Stage assessment while subject is ON.
- Collect blood and urine specimens for the following:
  - Safety laboratory tests (including specific tests for monitoring of vascular inflammation);
  - Serological testing (HIV testing, Hepatitis B antigen, and Hepatitis C antibody);
  - Urine drug screening test for drugs of abuse (including tetrahydrocannabinol (THC) performed at the central lab;
  - FSH test for females who are amenorrheic for at least 12 consecutive 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 #3).
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard triplicate supine and standing vitals (heart rate (HR) and blood pressure) and assess subject temperature to confirm no symptoms of fever.
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS) "Lifetime/Past 12 months" Evaluation.
- Perform the Patient Health Questionnaire-8 (PHQ-8).

- Perform Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts I, II, III, and IV (all parts to be completed on the same screening day).
- Train subject on OFF time recognition and OFF time diary (Hauser diary) with use of training video, and test concordance. Concordance testing includes at least one MDS-UPDRS Part III in the OFF state and one MDS-UPDRS Part III in the ON state (Part III score from full screening MDS-UPDRS may be used to fulfill one of these two exams, if the concordance assessment is continued/completed immediately after exam) which must be performed by the investigator (or qualified site staff/rater). At least 75% concordance with investigator (or qualified site staff/rater) for Screening ON/OFF time is required for eligibility (see [Section 7.1.7](#)).
- Dispense OFF time diary, review instructions including requirement to complete diary for 3 consecutive days in the week prior to Day 0 (Randomization).
- Instruct subjects on adjunct stable L-Dopa (open-label) administration.
- Review and assess adverse events (AEs).
- Review Inclusion and Exclusion criteria.

To prepare for study participation, subjects will be instructed on the use Section 4.4 and Section 5.8, [Lifestyle Guidelines](#) and [Concomitant Treatment\(s\)](#).

## 6.2. Study Period

For the study period described below, there is a +3 day visit window for scheduling of visits during Weeks 1, 2, and 3.

For Weeks 4-19, the visit window for scheduling visits will be  $\pm 3$  days.

**Study visit times are relative to Day 0 (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, and efforts should be made to return the subject to the correct timelines.**

For each visit, the following chronology of events should be adhered to, where possible:

- Patient Reported Outcome scales (ie, [CCI](#), [QUIP-RS](#), [CCI](#)): obtain prior to UPDRS.
- UPDRS Assessment: obtain prior to ECGs.
- ECGs: obtain prior to blood pressure and heart rate.
- Blood pressure/pulse rate: obtain prior to safety laboratory tests.

- Safety laboratory tests: obtain prior to pharmacokinetic (PK) blood.
- Pharmacokinetic blood specimens.
- Other procedures may be obtained before or after those listed above.

### 6.2.1. Randomization: Day 0

- Assessment of prior/concomitant medications.
- Review changes in medical history since screening visit.
- Review Inclusion and Exclusion criteria.
- Perform brief physical and neurological examination.
- 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 dosed with PF-06649751 or placebo.
- Urine drug screening in the form of a dipstick performed at the site.
- CCI [REDACTED]
- Collect Prolactin laboratory sample.
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard single supine and standing vitals (HR and blood pressure) and assess subject temperature to confirm no symptoms of fever.
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS) “Since last evaluation”.
- Collect and review OFF time diary while subject is present; confirm subject eligibility for OFF time has been met.
- Perform MDS-UPDRS I, II, III, and IV.
- CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]

- CCI [REDACTED].
- CCI [REDACTED].
- Perform Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS).
- Perform Oral Symbol Digit Modality Test (SDMT).
- Perform Modified Clinical Global Impression - Severity (MCGI-S).
- CCI [REDACTED].
- Review and assess adverse events (AEs).
- Register subject as Randomized in IWR system in order to obtain randomization number.
- Dispense Investigational Product. Subjects will begin PF-06649751 or placebo dosing the following morning (Day 1).
- Instruct subjects on continued daily dosing of PF-06649751 or placebo in accordance with randomized dose arm up-titration scheme (see [Table 2](#), Section 5.5.1, [Titration of PF-06649751](#)) and instruct subjects on proper dosing documentation.
- Instruct subjects on continued adjunct stable L-Dopa (open-label) administration.

#### 6.2.2. Dosing: Day 1 through Day 105

- Continued once daily dosing of PF-06649751 or placebo in accordance with randomized dose arm up-titration scheme (see [Table 2](#), Section 5.5.1, [Titration of PF-06649751](#)).
- Continued adjunct stable open-label L-Dopa administration (through Period B).

#### 6.2.3. Titration Period: Day 7

- Dosing compliance verification (Investigational product accountability and documentation) while subject is present to confirm reasons for missed/additional doses. **Based on blister card review and/or tablet count, any subject who is noted not to have taken at least 80% or has taken more than 120% of required doses at any scheduled visit during the study will be considered out of compliance and this must be recorded on the CRF and documented as a Medication Error on the CRF and the source documents.**
- Review and assess adverse events (AEs).
- Assessment of concomitant medications.

- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS) “Since last evaluation”.
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard single supine and standing vitals (HR and blood pressure).
- Perform MDS-UPDRS Part III.
- Dispense OFF time diary, review instructions including requirement to wait until the next phone visit before completion of the diary.
- Dispense Investigational Product. Next immediate dose level of PF-06649751 or placebo will be taken the next morning.
- Instruct subjects on continued daily dosing of PF-06649751 or placebo in accordance with randomized dose arm up-titration scheme (see [Table 2](#), Section 5.5.1, [Titration of PF-06649751](#)).
- Instruct subjects on continued adjunct stable L-Dopa (open-label) administration.

#### 6.2.4. Titration Period: Day 14

In the case of a phone visit:

- Dosing compliance verification via phone to confirm reasons for missed/additional doses. **Based on blister card review and/or tablet count, any subject who is noted not to have taken at least 80% or has taken more than 120% of required doses at any scheduled visit during the study will be considered out of compliance and this must be recorded on the CRF and documented as a Medication Error on the CRF and the source documents.**
- Review and assess adverse events (AEs).
- Assessment of concomitant medications.
- Instruct subjects on continued daily dosing of PF-06649751 or placebo in accordance with randomized dose arm up-titration scheme (see [Table 2](#), Section 5.5.1, [Titration of PF-06649751](#)).
- Instruct subjects on continued adjunct stable L-Dopa (open-label) administration.
- 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, and remind subjects to bring used blister cards to the next clinic visit.

- Review OFF time diary instructions including requirement to complete diary for 3 consecutive days during the following week.
- Dispense Investigational Product. Next immediate dose level of PF-06649751 or placebo will be taken the next morning following secure courier delivery.

In the case of a clinic visit:

- Dosing compliance verification (Investigational product accountability and documentation) while subject is present to confirm reasons for missed/additional doses. **Based on blister card review and/or tablet count, any subject who is noted not to have taken at least 80% or has taken more than 120% of required doses at any scheduled visit during the study will be considered out of compliance and this must be recorded on the CRF and documented as a Medication Error on the CRF and the source documents.**
- Review and assess adverse events (AEs).
- Assessment of concomitant medications.
- Collect blood and urine for safety lab tests.
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard single supine and standing vitals (HR and blood pressure).
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS) “Since last evaluation”.
- Dispense Investigational Product. Next immediate dose level of PF-06649751 or placebo will be taken on the next morning.
- Instruct subjects on continued daily dosing of PF-06649751 or placebo in accordance with randomized dose arm up-titration scheme (see [Table 2](#), Section 5.5.1, [Titration of PF-06649751](#)).
- Instruct subjects on continued adjunct stable L-Dopa (open-label) administration.
- Review OFF time diary instructions including requirement to complete diary for 3 consecutive days during the following week.

### 6.2.5. Titration Period: Day 21

In the case of a phone visit:

- Dosing compliance verification via phone to confirm reasons for missed/additional doses. **Based on blister card review and/or tablet count, any subject who is noted not to have taken at least 80% or has taken more than 120% of required doses at any scheduled visit during the study will be considered out of compliance and this must be recorded on the CRF and documented as a Medication Error on the CRF and the source documents.**
- Review and assess adverse events (AEs).
- Assessment of concomitant medications.
- Instruct subjects on continued daily dosing of PF-06649751 or placebo in accordance with randomized dose arm up-titration scheme (see [Table 2](#), Section 5.5.1, [Titration of PF-06649751](#)).
- Instruct subjects on continued adjunct stable L-Dopa (open-label) administration.
- 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, and remind subjects to bring all used blister cards to the next clinic visit.
- Confirm the completion of the OFF time diary for 3 consecutive days during the past week and remind the subject to bring the completed diary to the next clinic visit.
- Dispense Investigational Product. Next immediate dose level of PF-06649751 or placebo will be taken the next morning following secure courier delivery.

In the case of a clinic visit:

- Dosing compliance verification (Investigational product accountability and documentation) while subject is present to confirm reasons for missed/additional doses. **Based on blister card review and/or tablet count, any subject who is noted not to have taken at least 80% or has taken more than 120% of required doses at any scheduled visit during the study will be considered out of compliance and this must be recorded on the CRF and documented as a Medication Error on the CRF and the source documents.**
- Collect and review OFF time diary while subject is present.
- Review and assess adverse events (AEs).
- Assessment of concomitant medications.

- Collect blood and urine for safety lab tests.
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard single supine and standing vitals (HR and blood pressure).
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS) “Since last evaluation”.
- Dispense Investigational Product. Next immediate dose level will be taken the next morning.
- Instruct subjects on continued daily dosing of PF-06649751 or placebo in accordance with randomized dose arm up-titration scheme (see [Table 2](#), Section 5.5.1, [Titration of PF-06649751](#)).
- Instruct subjects on continued adjunct stable L-Dopa (open-label) administration.

#### 6.2.6. Dose Adjustment: Day 28

- Dosing compliance verification (Investigational product accountability and documentation) while subject is present to confirm reasons for missed/additional doses. **Based on blister card review and/or tablet count, any subject who is noted not to have taken at least 80% or has taken more than 120% of required doses at any scheduled visit during the study will be considered out of compliance and this must be recorded on the CRF and documented as a Medication Error on the CRF and the source documents.**
- Collect and review OFF time diary while subject is present (if first clinic visit since Day 7).
- Review and assess adverse events (AEs).
- Assessment of concomitant medications.
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard single supine and standing vitals (HR and blood pressure).
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS) “Since last evaluation”.
- Perform MDS-UPDRS Part III.
- Dispense Investigational Product.

- Instruct subjects on continued daily dosing of PF-06649751 or placebo in accordance with randomized dose arm up-titration scheme (see [Table 2](#), Section 5.5.1, [Titration of PF-06649751](#)).
- Instruct subjects on continued adjunct stable L-Dopa (open-label) administration.
- Dispense OFF time diary, review instructions including requirement to complete diary for 3 consecutive days during the following week.

#### 6.2.7. Dose Adjustment: Day 35

- Dosing compliance verification (Investigational product accountability and documentation) while subject is present to confirm reasons for missed/additional doses. **Based on blister card review and/or tablet count, any subject who is noted not to have taken at least 80% or has taken more than 120% of required doses at any scheduled visit during the study will be considered out of compliance and this must be recorded on the CRF and documented as a Medication Error on the CRF and the source documents.**
- Collect and review OFF time diary while subject is present.
- Review and assess adverse events (AEs).
- Assessment of concomitant medications.
- Perform brief physical and neurological examination.
- Collect blood and urine for safety lab tests.
- Collect Prolactin laboratory sample.
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard single supine and standing vitals (HR and blood pressure).
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS) “Since last evaluation”.
- CCI [REDACTED]
- Perform MDS-UPDRS Parts I, II, III, and IV.
- CCI [REDACTED]
- CCI [REDACTED]

- CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]
- Perform Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS).
- CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]).
- Dispense Investigational Product.
- Instruct subjects on continued daily dosing of PF-06649751 or placebo in accordance with randomized dose arm up-titration scheme (see [Table 2](#), Section 5.5.1, [Titration of PF-06649751](#)).
- Instruct subjects on continued adjunct stable L-Dopa (open-label) administration.
- Dispense OFF time diary, re-watch instructional training video and review instructions including requirement to complete diary for 3 consecutive days during Week 10.

#### 6.2.8. Period A: Day 42 (Phone Visit)

- Dosing compliance verification via phone to confirm reasons for missed/additional doses. **Based on blister card review and/or tablet count, any subject who is noted not to have taken at least 80% or has taken more than 120% of required doses at any scheduled visit during the study will be considered out of compliance and this must be recorded on the CRF and documented as a Medication Error on the CRF and the source documents.**
- Review and assess adverse events (AEs).
- Assessment of concomitant medications.
- Instruct subjects on continued daily dosing of PF-06649751 or placebo in accordance with randomized dose arm up-titration scheme (see [Table 2](#), Section 5.5.1, [Titration of PF-06649751](#)).

- Instruct subjects on continued adjunct stable L-Dopa (open-label) administration.

#### 6.2.9. Period A: Day 56 (Phone Visit)

- Dosing compliance verification via phone to confirm reasons for missed/additional doses. **Based on blister card review and/or tablet count, any subject who is noted not to have taken at least 80% or has taken more than 120% of required doses at any scheduled visit during the study will be considered out of compliance and this must be recorded on the CRF and documented as a Medication Error on the CRF and the source documents.**
- Review and assess adverse events (AEs).
- Assessment of concomitant medications.
- Instruct subjects on continued daily dosing of PF-06649751 or placebo in accordance with randomized dose arm up-titration scheme (see [Table 2](#), Section 5.5.1, [Titration of PF-06649751](#)).
- Instruct subjects on continued adjunct stable L-Dopa (open-label) administration.
- Review OFF time diary instructions including requirement to complete OFF time diary for 3 consecutive days during Week 10.

#### 6.2.10. Period A: Day 70 (Procedures may be used as screening for eligible and consenting subjects for the open label extension study)

- Dosing compliance verification (Investigational product accountability and documentation) while subject is present to confirm reasons for missed/additional doses. **Based on blister card review and/or tablet count, any subject who is noted not to have taken at least 80% or has taken more than 120% of required doses at any scheduled visit during the study will be considered out of compliance and this must be recorded on the CRF and documented as a Medication Error on the CRF and the source documents.**
- Collect and review OFF time diary while subject is present.
- Review and assess adverse events (AEs).
- Assessment of concomitant medications.
- Perform full physical and neurological examination.
- Collect weight.
- Collect blood and urine for safety lab tests.
- Collect Prolactin laboratory sample.

- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard single supine and standing vitals (HR and blood pressure).
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS) “Since last evaluation”.
- PK blood sample collection for PF-06649751 concentration. The time of sample collection and the date and time of the most recent dose of study medication prior to PK sampling should be recorded in the source documentation.
- Perform MDS-UPDRS Parts I, II, III, and IV.
- CCI [REDACTED].
- Perform Questionnaire for Impulsive-Compulsive Disorders in Parkinson’s Disease – Rating Scale (QUIP-RS).
- CCI [REDACTED].
- Dispense Investigational Product.
- Dispense OFF time diary and review instructions including requirement to complete diary for 3 consecutive days during Week 15.
- Instruct subject on continued daily dosing of PF-06649751 or placebo in accordance with randomized dose arm up-titration scheme (see [Table 2](#), Section 5.5.1, [Titration of PF-06649751](#)).
- Instruct subjects on continued adjunct stable L-Dopa (open-label) administration.

- Instruct subject to begin simultaneous adjunct down-titration of stable L-Dopa dose (refer to Section 5.5.3, [Period B:](#) ).

#### 6.2.11. Period B: Day 91 (Phone Visit)

- Dosing compliance verification via phone to confirm reasons for missed/additional doses. **Based on blister card review and/or tablet count, any subject who is noted not to have taken at least 80% or has taken more than 120% of required doses at any scheduled visit during the study will be considered out of compliance and this must be recorded on the CRF and documented as a Medication Error on the CRF and the source documents.**
- Review and assess adverse events (AEs).
- Assessment of concomitant medications.
- Instruct subject on continued daily dosing of PF-06649751 or placebo in accordance with randomized dose arm up-titration scheme (see [Table 2](#), Section 5.5.1, [Titration of PF-06649751](#)).
- Instruct subjects on continued adjunct stable L-Dopa (open-label) administration.
- Review OFF time diary instructions including requirement to complete diary for 3 consecutive days during Week 15.

#### 6.2.12. Period B: Day 105 (Procedures may be used as Visit 1 for eligible and consenting subjects for the open label extension study)

- Dosing compliance verification (Investigational product accountability and documentation) while subject is present to confirm reasons for missed/additional doses. **Based on blister card review and/or tablet count, any subject who is noted not to have taken at least 80% or has taken more than 120% of required doses at any scheduled visit during the study will be considered out of compliance and this must be recorded on the CRF and documented as a Medication Error on the CRF and the source documents.**
- Collect and review OFF time diary while subject is present.
- Review and assess adverse events (AEs).
- Assessment of concomitant medications.
- Perform full physical and neurological examination.
- Collect blood and urine for safety lab tests.
- Collect Prolactin laboratory sample.

- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard single supine and standing vitals (HR and blood pressure).
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS) “Since last evaluation”.
- PK blood sample collection for PF-06649751 concentration. The time of sample collection and the date and time of the most recent dose of study medication prior to PK sampling should be recorded in the source documentation.
- Perform MDS-UPDRS Parts I, II, III, and IV.
- CCI [REDACTED]
- Perform Questionnaire for Impulsive-Compulsive Disorders in Parkinson’s Disease – Rating Scale (QUIP-RS).
- CCI [REDACTED]
- Perform Physician Withdrawal Checklist (PWC-20).

**6.3. Follow-up Visit: Day 119**

- Review and assess adverse events (AEs).
- Assessment of concomitant medications.
- Perform brief physical and neurological examination.
- Collect weight.

- Collect blood and urine for safety lab tests (including specific tests for monitoring of vascular inflammation).
- CCI [REDACTED]
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard single supine and standing vitals (HR and blood pressure).
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS) “Since last evaluation”.
- Perform Physician Withdrawal Checklist (PWC-20).

#### **6.4. Follow-up Visit: Day 133 (Phone Visit)**

- Review and assess adverse events (AEs).

#### **6.5. Unplanned Visits**

During an unplanned site visit for adjustments of PF-06649751, placebo, L-dopa or other purposes, the following assessments should occur at a minimum:

- Review and assess adverse events (AEs).
- Assessment of concomitant medications.
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard single supine and standing vitals (HR and blood pressure).
- Dosing compliance verification (Investigational product accountability and documentation) while subject is present to confirm reasons for missed/additional doses.
- Dispense Investigational Product, if appropriate.
- If appropriate, instruct subject on continued daily dosing of PF-06649751 or placebo in accordance with randomized dose arm up-titration scheme (see [Table 2](#), Section 5.5.1, [Titration of PF-06649751](#)).

Additional procedures are at the discretion of the investigator to ensure subject safety.

## 6.6. Subject Withdrawal

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).

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.

It may be appropriate for the subject to return to the clinic for final safety assessments and to be questioned regarding their reason for withdrawal. At the early withdrawal visit, every effort must be made to complete the assessments as specified in the Early Termination Visit.

- Full physical and neurological examination, if there is a new or open AE or clinically significant abnormal physical finding from the last visit;
- Assessment of concomitant medications;
- Single supine and standing blood pressure and pulse rate measurements;
- Triplicate 12-lead ECG measurement;
- Columbia Suicidality Severity Rating Scale (C-SSRS) "Since last evaluation";
- Blood and urine specimens for safety laboratory;

- Blood sample for pharmacokinetic analysis;
- Review OFF time diary since dosing was stopped;
- MDS-UPDRS Part I, II, III, and IV;
- CCI [REDACTED];
- CCI [REDACTED];
- CCI [REDACTED];
- CCI [REDACTED];
- Perform Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS).
- CCI [REDACTED];
- Physician Withdrawal Checklist (PWC-20);
- CCI [REDACTED];

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.

For all subjects (including Early Termination) who have received at least 1 dose of investigational product (except a subject who withdraws consent), follow-up contact will be completed at least 28 calendar days, and up to 35 calendar days after the last administration of the investigational product to capture any potential adverse events (see the Time Period for Collecting AE/SAE Information section) and to confirm appropriate contraception usage (see the Contraception section). Contact with the subject may be done via a phone call.

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. If not otherwise specified, the baseline will be Day 0 (Randomization).

### **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 may be specifically monitored by the sponsor via a [Screening Verification Process](#) (Section 7.1.8).

#### **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. Alcohol and tobacco use history will be documented at the screening visit and subjects will be asked about their lifetime consumption. 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 (UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria)**

Investigators should confirm and thoroughly document the diagnosis of Parkinson's disease. Parkinson's disease must be consistent with Brain Bank Criteria.<sup>12</sup> Patients should be currently responding to L-Dopa. 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 with reference to [Appendix 6](#).

#### **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>14</sup> The HY is commonly used for describing, in broad terms, how Parkinson's disease symptoms progress and the relative level of disability. See [Inclusion Criteria #5](#) for HY definition for this study.

### **7.1.6. Unified Parkinson's Disease Rating Scale (MDS-UPDRS)**

The total MDS-UPDRS score is the most common method of evaluating the severity of Parkinson's disease across behaviors, activities of daily living, motor abilities, and other complications of Parkinson's disease.<sup>15</sup> The MDS-UPDRS focuses primarily on measuring impairments associated with Parkinson's disease, with subsections organized according to motor and non-motor aspects of the disease.

The MDS-UPDRS includes components assessed by the study investigator as well as sections completed by the subject.

Part I assesses non-motor experiences of daily living and is comprised of two components:

- Part IA contains 6 questions that are assessed by the investigator and focuses on complex behaviors.
- Part IB contains 7 questions that are part of the Patient Questionnaire completed by the subject.

Part II assesses motor experiences of daily living. There are an additional 13 questions that are also part of the Patient Questionnaire completed by the subject.

Part III assesses the motor signs of Parkinson's disease and is administered by the investigator.

Part IV assesses motor complications, dyskinesias, and motor fluctuations using historical and objective information. The investigator will complete this assessment once a subject has started Parkinson's disease medication.

Although not required, every effort should be made to have the same individual perform the ratings for an individual subject throughout the course of the study. MDS-UPDRS Part III should be assessed consistently and approximately 2 to 4 hours following L-Dopa dose (except at screening). At screening, a baseline MDS-UPDRS Part III should be performed prior to concordance testing.

### **7.1.7. Concordance Testing and OFF Time Diary Training**

At the Screening and Week 5 visits, subjects will be instructed to watch a training video on the completion of the OFF time diary (Hauser diary).

At the Screening visit, subjects and investigators (or qualified site staff/rater as per the Rater Qualification Guide) will then complete concordance testing over 2 hours consisting of

4 consecutive assessments at time-matched intervals (assessment at baseline followed by further assessments every 30 minutes). Subjects may complete other assessments (eg, questionnaires) during concordance testing, but should not engage in physical examinations (including ECGs, vitals, etc.) which could affect the outcome of the ON- and OFF-state assessment during concordance testing. The concordance testing should be started at a time point when it is expected that the subject's status will switch from OFF to ON, or from ON to OFF within the assessment period. The Part III score from full screening MDS-UPDRS may be utilized as the first concordance testing assessment, provided further concordance testing is initiated immediately following this exam.

During the concordance testing, the subject and the investigator (or qualified site staff/rater) will complete the OFF time diary at the end of each 30 minute interval separately and independently. Over the course of the testing, the investigator (or qualified site staff/rater) will complete at least *one* MDS-UPDRS Part III while the subject is in the OFF state and at least *one* MDS-UPDRS Part III while the subject is in the ON state (Part III score from full screening MDS-UPDRS may be used to fulfill one of these two exams, if the concordance assessment continued/completed immediately after exam). Investigators and qualified site staff/raters may also refer to vendor instructions for further details and examples. At a minimum, the rater must:

- Withhold their ON/OFF determinations from the subject for the duration of the concordance testing.
- Conduct four exams of which a minimum of two must be MDS-UPDRS Part III exams (one in OFF state, and one in ON state; Part III score from full screening MDS-UPDRS acceptable, if the concordance assessment is continued/completed immediately after exam). For the intervals of concordance testing in which MDS-UPDRS Part III is not conducted, the investigator (or qualified site staff/rater) may assess ON/OFF status using an exam of their choosing.

Subjects must experience ON- and OFF-state during the concordance testing; subjects may take their regular antiparkinsonian medication during the concordance testing. Dyskinesia (troublesome or non-troublesome) is not to be considered in concordance testing.

At the end of the 2 hour concordance testing, if the concordance criterion is not met or if the subject's status does not switch between OFF and ON or ON and OFF, concordance testing may be extended to 4 hours. If after this first session the concordance criterion is still not met, the concordance testing may be repeated one more time within the screening period.

Successful completion of the concordance testing requires a) at least 75% concordance in ON/OFF status between subject and investigator (or qualified site staff/rater; ratings must be concordant at 3 or more out of 4 post-baseline assessments, or 6 out of 8, respectively) AND b) at least one concordant ON period AND one concordant OFF period.

### **7.1.8. Screening Verification Process**

The sponsor or designee may verify critical elements of the screening and enrollment process and, in cases where verification is required, will provide written authorization (eg, e-mail) concurring with the investigator assessment that the subject is eligible to return for Day 0 (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 scores, concordance testing results, 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 study training. It is critical that the sponsor be provided with all requested data in a timely fashion in advance of the planned Day 0 (Randomization) visit, as will be instructed during study training.

The sponsor may waive the requirement for screening verification at any given time if the site has demonstrated consistent compliance with the eligibility requirements. In such cases, written notification will be provided indicating to the site that screening verification process has been waived. However, such information will continue to be evaluated as part of the general study monitoring process. The sponsor reserves the right to reinstate the screening verification process that had been previously waived, if deemed necessary, to ensure quality standards regarding subject eligibility.

For any potential subject on TID dosing of L-Dopa at Screening, the site must submit the rationale for this dosing and its optimized regimen during screening verification, and retain as part of the subject's source documentation. The sponsor and/or its designated representative will review and validate eligibility or non-eligibility of this criterion.

## **7.2. Safety**

### **7.2.1. Laboratory Tests**

The following safety laboratory tests will be performed at times defined in the [STUDY PROCEDURES](#) section of this protocol. Day 0 (Randomization) labs will be used as baseline. 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. Please refer to [Appendix 2](#) for criteria for safety laboratory values of potential clinical concern.

Hematology <sup>f</sup>	Chemistry <sup>f</sup>	Urinalysis <sup>f</sup>	Other <sup>f</sup>
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> Anti-neutrophil cytoplasmic antibody panel (C-ANCA and P-ANCA) <sup>e,f</sup> Qualitative 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 0 only.

d At Screening only

e At Screening and Week 17/Day 119 visits 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](#). If anti-neutrophil cytoplasmic antibody (ANCA) is positive or questionable, then quantitative Proteinase-3 Ab and Myeloperoxidase Ab tests will be performed by the central lab using existing specimen.

- 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 Investigational Product.

### **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 PF-06649751 or placebo dosing.

Confirmation of non-childbearing potential is required before the subject may receive PF-06649751 or placebo.

### **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 or 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 0 will be captured as an AE.

### **7.2.5. Vital Signs (Blood Pressure, Pulse Rate, and Temperature)**

Blood pressure and pulse rate will be measured at times specified in the [STUDY PROCEDURES](#) section of this protocol. Subject temperature must also be assessed at Screening and Day 0 (Randomization) to confirm no symptoms of fever (see Exclusion Criteria #6). Additional collection times, or changes to collection times of blood pressure and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

The same arm (preferably the dominant arm) will be used 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 pulse rate is acceptable, although, when done manually, pulse 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 pulse 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. 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 pulse rate ( $\geq 30$  beats per minute (BPM)).

### **7.2.6. Electrocardiogram**

Electrocardiograms (ECGs) should be collected at times specified in the [STUDY PROCEDURES](#) section 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 on Day 0 will serve as each subject's baseline QTcF value.

To ensure safety of the subjects, a qualified individual at the investigator site will make comparisons to baseline measurements. If either of the QTcF values from these repeated ECGs remains 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 the average of QTcF values from the triplicate measurements remains 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. 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 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 Disorders in Parkinson's Disease – Rating Scale (QUIP-RS)**

The Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS) is a brief, patient reported outcome measure designed to assess the severity of symptoms of ICDs and related behaviors reported to occur in Parkinson's disease.

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 subjects 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>20</sup>

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

The PWC-20 is a physician-completed, 20-item reliable and sensitive instrument for the assessment of benzodiazepine 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. Efficacy Measures**

### **7.3.1. OFF Time Diary (Hauser Diary)**

In patient diaries, “OFF” time is defined as a period when medication has worn off and is no longer providing benefit with regard to mobility, slowness, and stiffness. During this period, Parkinson’s disease patients experience relatively poor overall function with worsening of tremor, rigidity, balance, or bradykinesia. “ON” time is defined as the time when medication is providing benefit with regard to mobility, slowness, and stiffness. “ON” time can be classified as associated with or without troublesome dyskinesia that interfere with activities of daily living. It has been demonstrated that “OFF” time and “ON” time with troublesome dyskinesia are generally considered by patients to be “bad time” with regard to motor function, whereas “ON” time without dyskinesia and on time with non-troublesome dyskinesia are generally considered to be “good time”.<sup>17</sup>

Currently, available diaries are designed to record patient motor state for half hour intervals. These diaries are a way for patients to assess their own health status without clinician bias or interpretation. Diaries are especially useful in understanding symptoms’ temporal dynamics, including triggers that exacerbate symptoms. They also help individuals to evaluate the impact of their treatment.<sup>18</sup>

For the purposes of this study, a paper Hauser diary will be utilized. Entries are made on the days noted in the [STUDY PROCEDURES](#) section of the protocol. Training on the diary will be provided to sites and subjects. Subjects will complete the diary for three consecutive days in the week prior to each visit (except Day 28 visit) as indicated in the [STUDY PROCEDURES](#) section, including three consecutive days during the week prior to Day 0 (Randomization).

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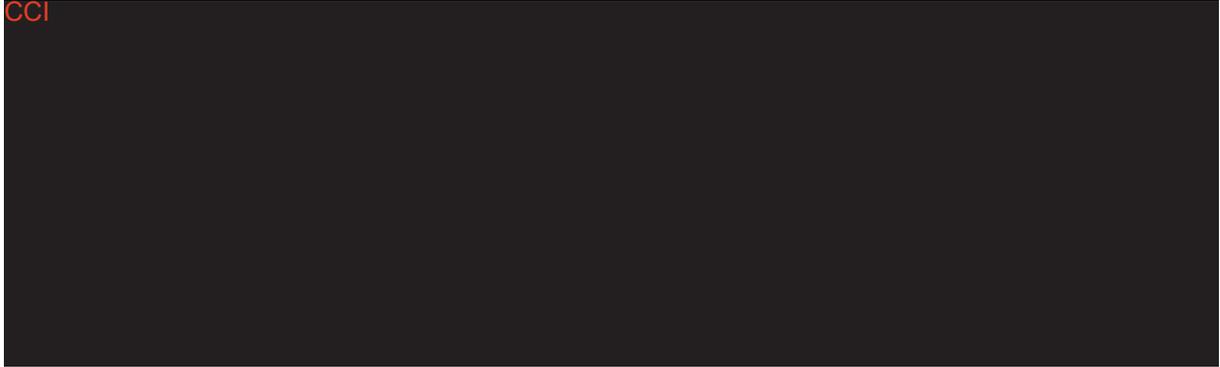
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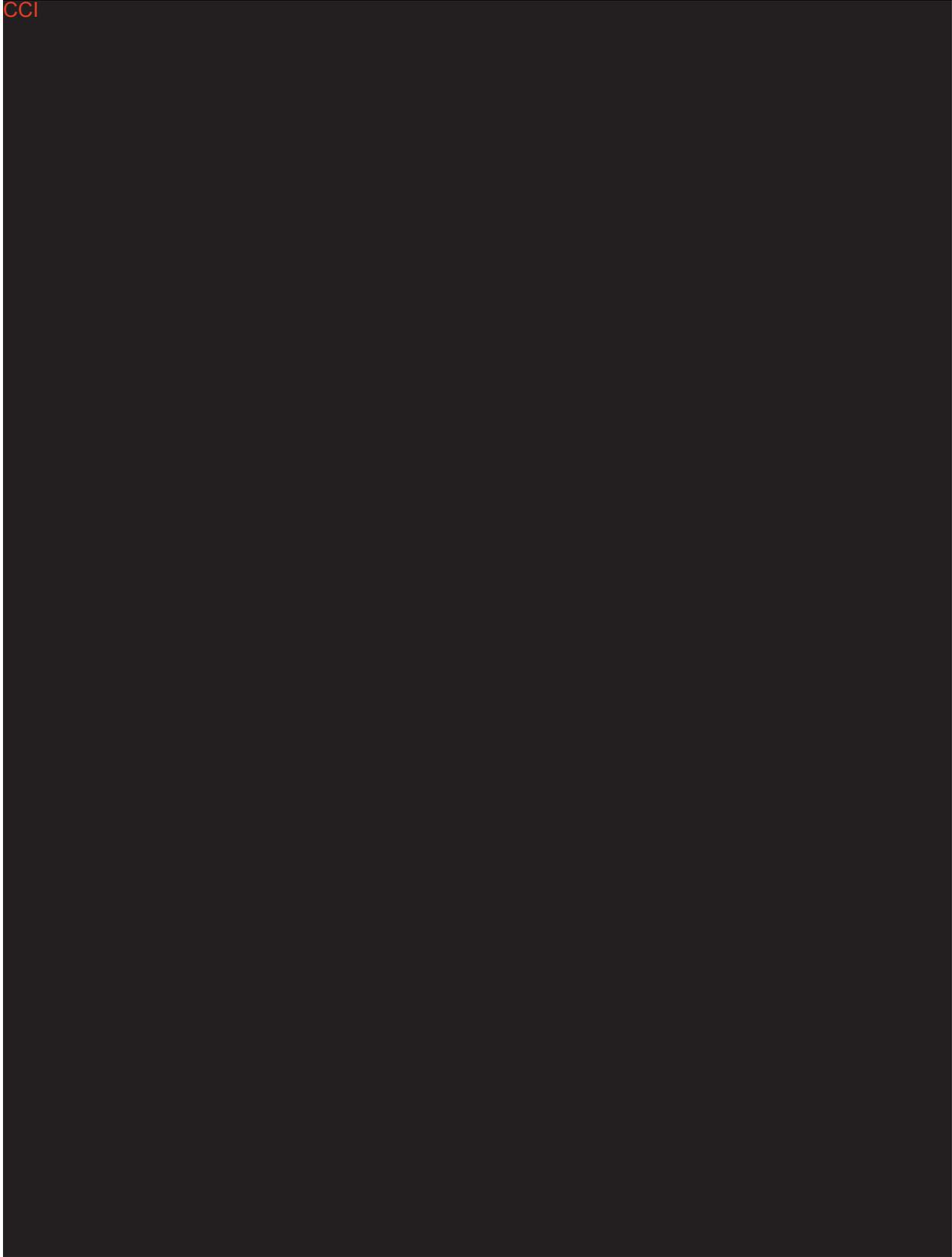
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### **7.6. Blood Volume**

The total blood sampling volume for individual subjects in this study is approximately 205 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

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	7	1	6	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
Prolactin	1		4		4
HIV/Hepatitis Panel	4	1			4
CCI	6		3		18
CCI	4		1		4
CCI	10		1	1	20
CCI	30		1	1	60
<b>TOTAL</b>					<b>205.4</b>

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

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

### **7.7.1. 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>25</sup> Versions are available for “lifetime/Past 12 months” and “since last evaluation”. The “lifetime/Past 12 months” evaluation is done at screening, and the “since last evaluation” is done at all other time points.

The C-SSRS should be collected at times specified in the [STUDY PROCEDURES](#) section 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 study. Specific criteria that indicate a need for such an assessment are:

- Suicidal ideation associated with actual intent and/or plan in the past year; (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 10 years (a “YES” answer to any of the suicidal behavior items of the C-SSRS with the behavior occurring in the past 10 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 visits (Screening, Day 0, or both), 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 study.

Subjects who respond “YES” to items 4, 5 or to any behavioral question of the C-SSRS at any time after the baseline visit (Screening or Day 0 (Randomization)) will be assessed by clinician/MHP to determine whether it is safe for the subject to continue in the study.

Subjects who respond “YES” to items 4, 5 or to any behavioral question of the C-SSRS on more than one occasion during a study 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 study.

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

PHQ-8 is a self-report 8-item questionnaire used to assess depression and takes about 3-5 minutes to complete. The PHQ-8 will be performed only at screening. The following criterion indicates a need for risk assessment by mental health professional (MHP):

- PHQ-8 total score  $\geq 15$ .

The risk assessment involves an evaluation by a clinician/MHP skilled in the evaluation of suicidality in the subjects by virtue of training or experience (eg, psychiatrist, licensed clinical psychologist). A written copy of the risk assessment should be included in the subject's clinical record (source documentation) and include whether it was determined it was safe for the subject to be enrolled.

## **7.8. Other**

### **7.8.1. Prolactin Test**

A blood sample of approximately 1 mL for Prolactin will be collected at Day 0 (Randomization), Week 5, Week 10, and Week 15 visits in a standard red top or SST tube. Detailed collection, processing, storage, and shipment instructions are provided in the central laboratory manual. Results will not be reported to investigators and will remain blinded until the end of the study.

## **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**

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 liver function test (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 non-serious); 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. Subject Withdrawal**

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. Nonserious 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 a pair-wise comparison of a dose of the PF-06649751 against placebo and is based on the primary endpoint, the change from Baseline to Week 10 (end of Period A) in the daily OFF time. The decision criteria for efficacy are given as below, which will be based on a Bayesian interpretation of the results:

- C1: Point estimate of PF-06649751 vs. placebo effect  $\geq 1.5$  hours, and
- C2: 95% confident of PF-06649751 vs. placebo effect  $\geq 0$ .

Better is defined as a reduction in the daily OFF time.

The sample size indicates that 32 evaluable subjects per arm will give sufficient precision for a comparison of an active dose versus placebo to meet criterion C2 with observed effects of  $\geq 1.5$  hours (Criterion C1). It's estimated that the probability of passing both criteria for a true effect of 2.25 hours would be 85%, and the probability of passing the criteria for a true null effect (0 hour) would be 2%.

Accounting for a 10% rate of non-evaluable subjects as well as dropouts before the stable dose period (ie, by 5 weeks post dose), 36 subjects per arm and an approximate total of

198 subjects (54 in Cohort 1 and 144 in Cohort 2) are expected to be randomized for the study. Depending on actual enrollment, additional subjects may be randomized in the same treatment ratio, but there will be no more than 260 subjects in total.

The calculations were based on an estimate of the variability obtained from a meta-analysis of the historical Parkinson's disease trials. This provided an estimate of the between subject standard deviation of 2.9 hours in change from baseline in daily OFF time. The meta-analysis also provided an informative prior for placebo effect, which will be included in the Bayesian data analysis.

## 9.2. Efficacy Analysis

The dataset used in the efficacy analyses will be the Full Analysis Set (FAS), consisting of all subjects who receive at least 1 post-dose efficacy measurement. Analyses may be repeated using a Per Protocol Set (PPS) as appropriate, which will exclude subjects who are major protocol deviators and subjects whose dosing compliance is less than 80%.

### 9.2.1. Analysis of the Primary Endpoint

The primary endpoint is the change from baseline in daily OFF time at Week 10 (end of Period A). A four parameter  $E_{max}$  model will be primarily used to estimate the dose response for the change from baseline in daily OFF time at Week 10 (end of Period A). The model is as follows:

$$y = E_0 + \frac{E_{max} \cdot D^\lambda}{ED_{50}^\lambda + D^\lambda}; \text{ where,}$$

- $y$  is the change from baseline in daily OFF time;
- $D$  is the PF-06649751 dose in mg;
- $E_0$  is the placebo response;
- $E_{max}$  is the additive increase over placebo in the response of PF-06649751 at a theoretically infinite dose;
- $ED_{50}$  is the PF-06649751 dose in mg that provides an effect of  $E_0 + E_{max}/2$ ;
- $\lambda$  is the Hill parameter and measures the steepness of the dose response curve.

Bayesian estimation will be used to fit the model. An informative prior distribution will be used for the placebo response derived from the meta-analysis of historical Parkinson's disease trials. Weak empirically-based prior distributions will be specified for the other model parameters, which were obtained from a meta-analysis of many dose response studies.<sup>26</sup> The details of the priors and the Bayesian analysis will be specified in the SAP.

The efficacy comparisons will be based on the treatment difference vs. placebo estimated at Week 10. Their point estimates and two-sided 90% credible intervals from the fitted model will be reported.

An acceptable range of a true effect for an MED will be evaluated from the  $E_{\max}$  model, and is defined as the lowest PF-06649751 efficacious dose that

- is within the range of tested doses in the study,
- has a lower dose that is not efficacious, and
- has placebo-corrected effect between 1.5 and 2 hours.

If the  $E_{\max}$  model is deemed to be inappropriate for the data, the pairwise comparison of the active doses vs. placebo based on an analysis of a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) will be primarily utilized for efficacy. In such case, the response variable will be the change from baseline to each post baseline visit, and the model will include the following fixed effects:

- treatment (with 5 levels: PF-06649751 1 mg QD, 3 mg QD, 7 mg QD, 15 mg QD, and placebo), a categorical factor;
- visit, a categorical factor;
- treatment-by-visit interaction;
- baseline daily OFF time, 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.

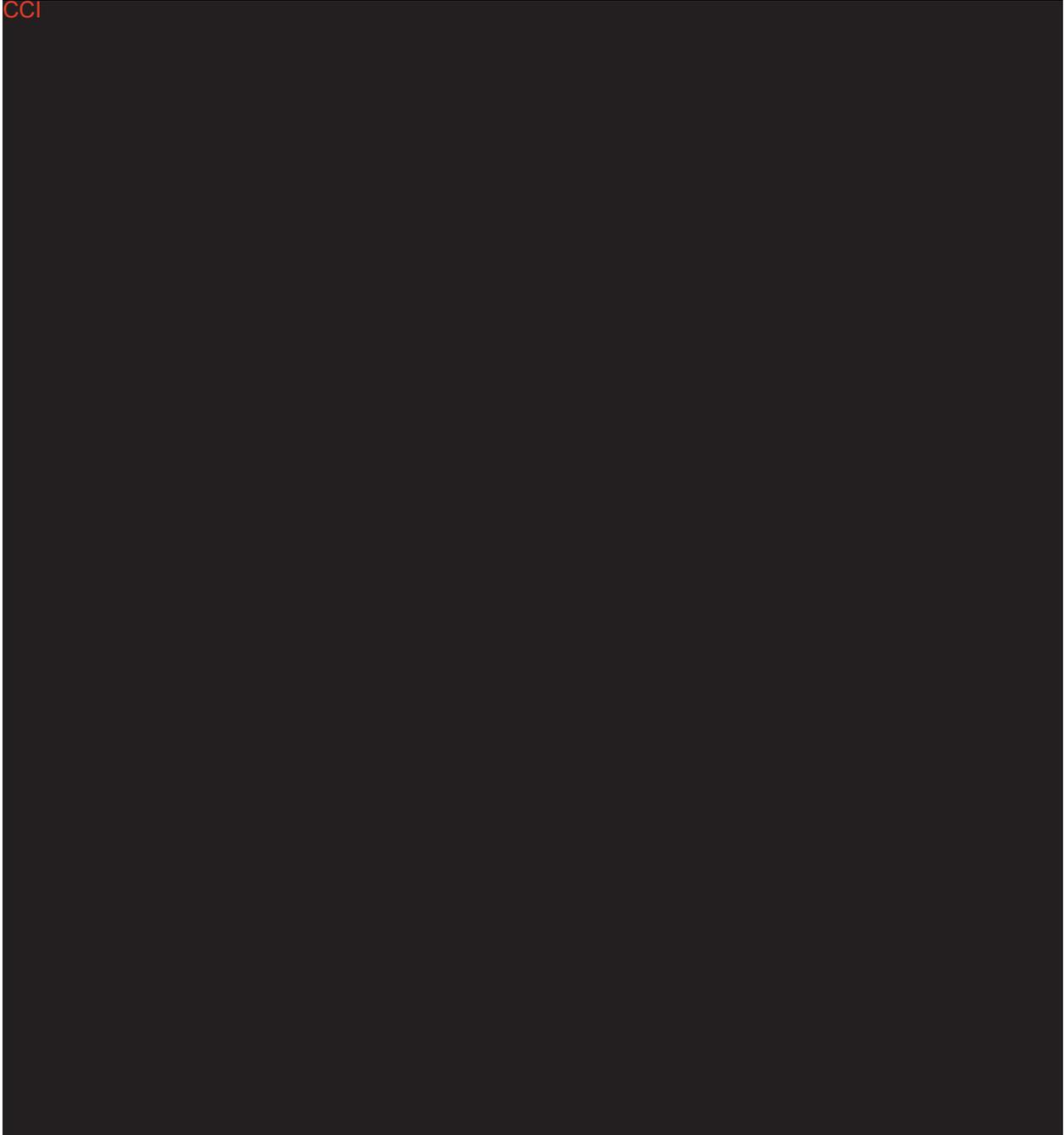
The efficacy comparisons for this MMRM model will be based on the treatment difference vs. placebo estimated at Week 10 using least-squares means for each PF-06649751 dose. Their point estimates, standard errors, and two-sided 90% CIs will be reported. It will also be conducted within a Bayesian framework utilizing informative placebo prior. The details of the prior and the Bayesian analysis will be specified in the SAP.

All secondary and sensitivity analyses for the primary endpoint will be detailed in the SAP.

### 9.2.2. Analysis of Secondary <sup>CCI</sup> ██████████ Endpoints

All secondary endpoint analyses will be detailed in the SAP.

CCI



### 9.4. Safety Analysis

The safety analysis set will include all patients who received at least one dose of PF-06649751 or placebo.

Adverse events, ECGs, blood pressure, pulse 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 AEs, ECGs, blood pressure, pulse rate, C-SSRS, QUIP-RS, PWC-20 and safety laboratory data 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 two interim analyses may be performed when approximately 27% and 80% subjects are randomized and have the opportunity to complete through Period A of the study. The first interim analysis will be conducted when Cohort 1 (approximately 54 subjects in a 2:1 ratio of 15 mg QD and placebo groups respectively) is completed through Period A and efficacy data have been collected, databased and cleaned. A second interim analysis may be undertaken when approximately 104 subjects complete through Period A of Cohort 2 (1:2:2:2:1 in 15 mg QD, 7 mg QD, 3 mg QD, 1 mg QD, and placebo respectively) and efficacy data have been collected, databased and cleaned. The purpose of these interim analyses 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 blinded 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 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 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. For this study, the End of trial in EU Member States is defined as Last Subject Last Visit (LSLV) based on the total of randomized subjects in accordance with protocol [Section 9.1](#). 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.

#### **13.2. 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
ANCA	Anti-Neutrophil cytoplasmic 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
CCI	
BID	“bis in die”, twice per day
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>	predicted human plasma efficacious concentration
CI	confidence interval
CNS	central nervous system
COMT	catechol-O methyltransferase
C <sub>max</sub>	maximum (peak) observed concentration
CRF	case report form
CRP	C-Reactive Protein
CSA	clinical study agreement
C-SSRS	Columbia Suicidality Severity Rating Scale
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
D1R	D1 receptor
DAI	dosage and administration instructions
DNA	deoxyribonucleic acid
DU	dispensable unit
EBR	eye blink rate
EC	ethics committee
ECG	electrocardiogram
EDMC	external data monitoring committee

<b>Abbreviation</b>	<b>Term</b>
EDP	exposure during pregnancy
EDTA	edetic acid (ethylenediaminetetraacetic acid)
EEG	electroencephalogram
EOT	End of Trial
ESR	Erythrocyte Sedimentation Rate
CCI	
EU	European Union
EudraCT	European Clinical Trials Database
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
hERG	Human ether-a-go-go-related gene
HIV	human immunodeficiency virus
HPD	hours post-dose
HRQL	health-related quality of life
HR	heart rate
HY	Hoehn and 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
IWR	interactive web response
K <sub>2</sub> EDTA	dipotassium ethylene diamine tetraacetic acid
L-Dopa	levodopa
LFT	liver function test
LID	levodopa-induced dyskinesia
LMA	locomotor activity
LQTS	Long QT Syndrome
LSLV	last subject last visit
MAD	Multiple ascending dose
MAO-B	monoamine oxidase B
MCH	Mean corpuscular hemoglobin

<b>Abbreviation</b>	<b>Term</b>
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MED	Minimal Efficacious Dose
MDS-UPDRS	Movement Disorder Society-Universal Parkinson's Disease Rating Scale
CCI	[REDACTED]
CCI	[REDACTED]
MHP	Mental health professional
MMSE	Mini Mental State Examination
MPTP	1 methyl 4 phenyl 1,2,3,6 tetrahydropyridine
MTD	maximum tolerated dose
NDA	new drug application
NOAEL	No observed adverse effect level
NRS	numerical rating scale
P-ANCA	Perinuclear Anti-Neutrophil Cytoplasmic Antibody
PBMC	Peripheral Blood Mononuclear Cell
PBGT	Patient Best Guess at Treatment
PCD	primary completion date
PD	pharmacodynamics
PD AID	Parkinson's Disease Activities, Interference, and Dependence
CCI	[REDACTED]
PET	positron emission tomography
CCI	[REDACTED]
PT	prothrombin time
PWC-20	Physician Withdrawal Checklist
QD	"quaque die", once per day
QID	"quater in die", four times per day
QTcF	corrected QT (Fridericia correction)
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease
RBC	red blood cell
REM	rapid eye movement
RNA	ribonucleic acid
RO	receptor occupancy
SAD	Single Ascending Dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCL	Supply Chain Lead
CCI	[REDACTED]

<b>Abbreviation</b>	<b>Term</b>
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
TID	“ter in die”, three times per day
T <sub>max</sub>	time to reach maximum concentration
TMB	trimethobenzamide
UK	United Kingdom
ULN	upper limit of normal
US	United States
USPI	United States package insert
WBC	white blood cell

## Appendix 2. Criteria for Safety Values of Potential Clinical Concern

### Hematology

Hemoglobin	<0.8 times the lower limit of the reference range
Hematocrit	<0.8 times the lower limit of the reference range
RBC Count	<0.8 times the lower limit of the reference range
MCV	<0.9 or >1.1 times the limits of the reference range
MCH	<0.9 or >1.1 times the limits of the reference range
MCHC	<0.9 or >1.1 times the limits of the reference range
Platelets	<0.5 or >1.75 times the limits of the reference range
Total Neutrophils (Abs)	<0.8 or >1.2 times the limits of the reference range
Eosinophils (Abs)	>1.2 times the upper limit of the reference range
Basophils (Abs)	>1.2 times the upper limit of the reference range
Lymphocytes (Abs)	<0.8 or >1.2 times the limits of the reference range
Monocytes (Abs)	>1.2 times the upper limit of the reference range

### Chemistry

Total bilirubin	>1.5 times the upper limit of the reference range
Direct bilirubin	>1.5 times the upper limit of the reference range
Indirect bilirubin	>1.5 times the upper limit of the reference range
AST	>3 times upper limit of the reference range
ALT	>3 times upper limit of the reference range
Alk Phosphatase	>3 times upper limit of the reference range
Creatinine	>1.3 times upper limit of the reference range
BUN	>1.3 times upper limit of the reference range
Glucose	<0.6 or >1.5 times the limits of the reference range
Uric acid	>1.2 times upper limit of the reference range
Sodium	<0.95 or >1.05 times the limits of the reference range
Potassium	<0.9 or >1.1 times the limits of the reference range
Chloride	<0.9 or >1.1 times the limits of the reference range
Bicarbonate	<0.9 or >1.1 times the limits of the reference range
Calcium	<0.9 or >1.1 times the limits of the reference range
Albumin	<0.8 or >1.2 times the limits of the reference range
Total protein	<0.8 or >1.2 times the limits of the reference range
Creatine Kinase	>2.0 times upper limit of the reference range

### Urinalysis

Urine WBC	≥20/HPF
Urine RBC	≥20/HPF
Urobilinogen	≥1
Urine Bilirubin	≥1

**Vital Signs**

Pulse Rate	Supine/Sitting: <40 or >120 bpm    Standing: <40 or >140 bpm
Blood Pressure	Systolic $\geq 30$ mm Hg change from baseline in same posture Systolic <90 mm Hg Diastolic $\geq 20$ mm Hg change from baseline in same posture Diastolic <50 mm Hg

**Electrocardiogram**

PR interval	$\geq 300$ msec; $\geq 25\%$ increase when baseline >200 msec Increase $\geq 50\%$ when baseline $\leq 200$ msec
QRS interval	$\geq 140$ msec; $\geq 50\%$ increase from baseline
QTc interval	$\geq 500$ msec

### Appendix 3. 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-benzodiazepine hypnotics are permitted.
	Monoaminoxidase B (MAO-B) inhibitors	Permitted if at a stable dose for at least 42 days prior to Randomization. No dose changes should be anticipated for the duration of the study.
	Catechol O methyltransferase (COMT) inhibitors	Permitted if at a stable dose for at least 42 days prior to Randomization.
	Antidepressants except MAO-A/B inhibitor antidepressants	Permitted if subject is taking a stable dose at least 42 days prior to Randomization.
	Anticholinergics	Permitted if at a stable dose for at least 42 days prior to 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 Randomization. No dose changes should be anticipated for the duration of the study.
<b>Prohibited</b>	Dopamine receptor agonist medications including pramipexole, ropinirole, rotigotine and apomorphine	Prohibited for at least 28 days prior to Randomization and through the end of the double blind treatment period.
	Istradefylline and zonisamide	Prohibited for at least 42 days prior to Randomization and through the end of the double blind treatment period.
	Inhaled L-Dopa, intraduodenal use of Duodopa®	Not permitted.
	Antipsychotics or neuroleptics	Antipsychotics (except stable low dose quetiapine), metoclopramide, or reserpine are not permitted.
	Antiepileptics	Antiepileptics are prohibited except if used for chronic painful conditions at steady doses (for example, gabapentin or pregabalin).
	Lithium, MAO-A/B inhibitor antidepressants (including moclobemide, tranylcypromine, and phenelzine)	Prohibited for at least 42 days prior to Randomization and throughout the study. 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	Drugs that induce or inhibit the hepatic metabolizing cytochrome 3A4 enzymes; CYP3A inducers or inhibitors are prohibited from at least 28 days prior to Randomization
	Marijuana	Prohibited from Screening through the end of the double blind treatment period.

1. Investigator to discuss with sponsor as needed.

#### Appendix 4. 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.

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 5. Country-Specific Appendix – Applicable to France Only**

The following supplementary text should be read in conjunction with the B7601003 protocol:

- Prior to enrollment of any subjects, the investigator and any sub-investigators will complete the Pfizer-provided Good Clinical Practice training course (“Pfizer GCP Training”) or training deemed equivalent by Pfizer. Any investigators who later join the Study will complete the Pfizer GCP Training or equivalent before performing Study-related duties. For studies of applicable duration, the investigator and sub-investigators will complete Pfizer GCP Training or equivalent every three years during the term of the Study, or more often if there are significant changes to the ICH GCP guidelines or course materials.
- No subjects or third-party payers will be charged for investigational product.
- The investigator(s) will notify Pfizer or its service provider immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its service provider to prepare the study site for the inspection and will allow Pfizer or its service provider (if not prohibited by law) to be present during the inspection. The study site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its service provider. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its service provider with an opportunity to review and comment on responses to any such findings.

## **Appendix 6. UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria**

### **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.

## Appendix 7. Country-Specific Appendix - Japan

### Schedule of Activities and Study Procedures (Section 6)

For sites in Japan, the Week 2 (Day 14) and Week 3 (Day 21) visits during the Titration Period must be conducted as site (in-clinic) visits. Additionally, two phone visits are required a day after both the Day 0 (Randomization) Visit (Day 1) and Week 1 Visit (Day 7 [+3 day window]) and two additional study site visits are required a day after both Week 2 Visit (Day 14 [+3 day window]) and Week 3 Visit (21 [+3 day window]). Phone visits can optionally be conducted as site visits (eg, for logistical reasons). Subjects should be offered an optional overnight stay at the study site prior to a site visit. Study drug administration on both site visits (day after Week 2 Visit and Week 3 Visit) should occur at the study site. For phone visits, the phone calls should take place approximately 4 hours post-dose. During site visits, the study procedures are to be performed approximately 4 hours post-dose. Afterwards, subjects may be discharged at investigator's discretion if no safety concerns are identified. These visits (Day 1, Day 8, Day 15, and Day 22) are to be conducted in addition to the protocol [Schedule of Activities/Study Procedures \(Section 6\)](#).

Protocol Activity	Japan Specific Visits (including additional observation visits)					
	Rand. Visit	Wk 1 Observation Visit	Wk 2	Wk 2 Observation Visit	Wk 3	Wk 3 Observation Visit
	Day 1 (phone visit or optional site visit)	Day 8 (phone visit or optional site visit)	Day 14 (site visit)	Day 15 (site visit)	Day 21 (site visit)	Day 22 (site visit)
Concomitant medications assessment	X	X	X	X	X	X
AE assessment	X	X	X	X	X	X
Triplicate ECG			X	X	X	X
Supine and standing blood pressure and pulse rate			X	X	X	X
Columbia Suicidality Severity Rating Scale (C-SSRS)			X		X	
Safety Laboratory			X		X	
Dispensing of Investigational Product			X		X	
Investigational Product accountability			X		X	
Investigational Product and L-Dopa dosing documentation			X		X	
PF-06649751 (or placebo) administration	X	→	→	→	→	→
Adjunct L-Dopa (open-label)	→	→	→	→	→	→

### Day 1 and Day 8

- Assessment of concomitant medications.
- Review and assess adverse events (AEs).
- PF-06649751 or placebo administration in accordance with randomized dose arm up-titration scheme (see [Table 2](#), Section 5.5.1, [Titration of PF-06649751](#)).
- Instruct subjects on continued adjunct stable L-Dopa (open-label) administration.

### Day 14

- Dosing compliance verification to confirm reasons for missed/additional doses. **Based on blister card review and/or capsule count, any subject who is noted not to have taken at least 80% or has taken more than 120% of required doses at any scheduled visit during the study will be considered out of compliance and this must be recorded on the CRF and documented as a Medication Error on the CRF and the source documents.**
- Assessment of concomitant medications.
- Review and assess adverse events (AEs).
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard single supine and standing vitals (HR and blood pressure).
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS) “Since last evaluation”.
- Collect blood and urine for safety lab tests.
- Dispense Investigational Product. Next dose level of PF-06649751 or placebo will be taken on the morning of Day 15.
- PF-06649751 or placebo administration in accordance with randomized dose arm up-titration scheme (see [Table 2](#), Section 5.5.1, [Titration of PF-06649751](#)).
- Instruct subjects on continued adjunct stable L-Dopa (open-label) administration.

### Day 15

- Assessment of concomitant medications.
- Review and assess adverse events (AEs).

- Perform standard supine triplicate 12-lead electrocardiogram (ECG), approximately 4 hours post-dose.
- Perform standard single supine and standing vitals (HR and blood pressure), approximately 4 hours post-dose.
- PF-06649751 or placebo administration in accordance with randomized dose arm up-titration scheme (see [Table 2](#), Section 5.5.1, [Titration of PF-06649751](#)).
- Instruct subjects on continued adjunct stable L-Dopa (open-label) administration.

### Day 21

- Dosing compliance verification to confirm reasons for missed/additional doses. **Based on blister card review and/or capsule count, any subject who is noted not to have taken at least 80% or has taken more than 120% of required doses at any scheduled visit during the study will be considered out of compliance and this must be recorded on the CRF and documented as a Medication Error on the CRF and the source documents.**
- Assessment of concomitant medications.
- Review and assess adverse events (AEs).
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard single supine and standing vitals (HR and blood pressure), if clinic visit.
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS) “Since last evaluation”.
- Collect blood and urine for safety lab tests.
- Dispense Investigational Product. Next dose level of PF-06649751 or placebo will be taken on the morning of Day 22.
- PF-06649751 or placebo administration in accordance with randomized dose arm up-titration scheme (see [Table 2](#), Section 5.5.1, [Titration of PF-06649751](#)).
- Instruct subjects on continued adjunct stable L-Dopa (open-label) administration.

### Day 22

- Assessment of concomitant medications.
- Review and assess adverse events (AEs).

- Perform standard supine triplicate 12-lead electrocardiogram (ECG), approximately 4 hours post-dose.
- Perform standard single supine and standing vitals (HR and blood pressure), approximately 4 hours post-dose.
- PF-06649751 or placebo administration in accordance with randomized dose arm up-titration scheme (see [Table 2](#), Section 5.5.1, [Titration of PF-06649751](#)).
- Instruct subjects on continued adjunct stable L-Dopa (open-label) administration.

**Reason(s) for Additional Visits (Day 1, Day 8, Day 15, and Day 22) in Japan:**

The titration scheme implemented in the study ([Section 5.5.1](#)) results in patients randomized into PF-06649751 7 mg QD and 15 mg QD dose groups to be administered with 7 mg and 15 mg dose of PF-06649751 for the first time on Day 15 and Day 22. These doses have not been previously evaluated for safety and tolerability in Parkinson's disease patients of Japanese origin, to-date.

Based on all the available data, 5 mg QD and 15 mg QD PF-06649751 doses have been demonstrated to be safe and well tolerated in PD patients of non-Japanese origin (Study B7601005). PF-06649751 dose of 1.5 mg QD has been evaluated in healthy subjects of Japanese origin in Study B7601002. Safety, tolerability and exposures at this dose (1.5 mg QD) were similar to those in non-Japanese healthy subjects. Moreover, PF-06649751 doses up to 5 mg QD were found to be safe and tolerable in healthy non-Japanese subjects. Generally, tolerability at 5 mg QD in Parkinson's disease patients was better than healthy subjects. More information on safety, tolerability of PF-06649751 across different doses/studies can be found in the Investigator's Brochure.

During titration up to target doses, Parkinson's disease patients progressively step through PF-06649751 1 mg QD and 3 mg QD before being dosed with 7 mg QD followed by 15 mg QD. It is expected that the first two PF-06649751 dose levels (1 mg QD and 3 mg QD) during the titration period will be well tolerated in Japanese PD patients based on acceptable safety and tolerability observed at 1.5 mg QD (in healthy subjects; Study B7601002) and also better tolerability in PD study patients (Study B7601005) compared to healthy subjects.

Thus, phone visits with safety assessments (approximately 4 hours post dose) the day patients are dosed with PF-06649751 1 mg QD/Placebo and 3 mg QD/Placebo will help ensure Japanese patient safety and tolerability during the study.

Additional study site visits with safety assessments (approximately 4 hours post dose) on the day patients are dosed with PF-06649751 7 mg QD/Placebo and 15 mg QD/Placebo will help assure Japanese patient safety and well-being during the study.

CCI



PF-06649751  
B7601003

Final Protocol Amendment 2, 22 November 2016

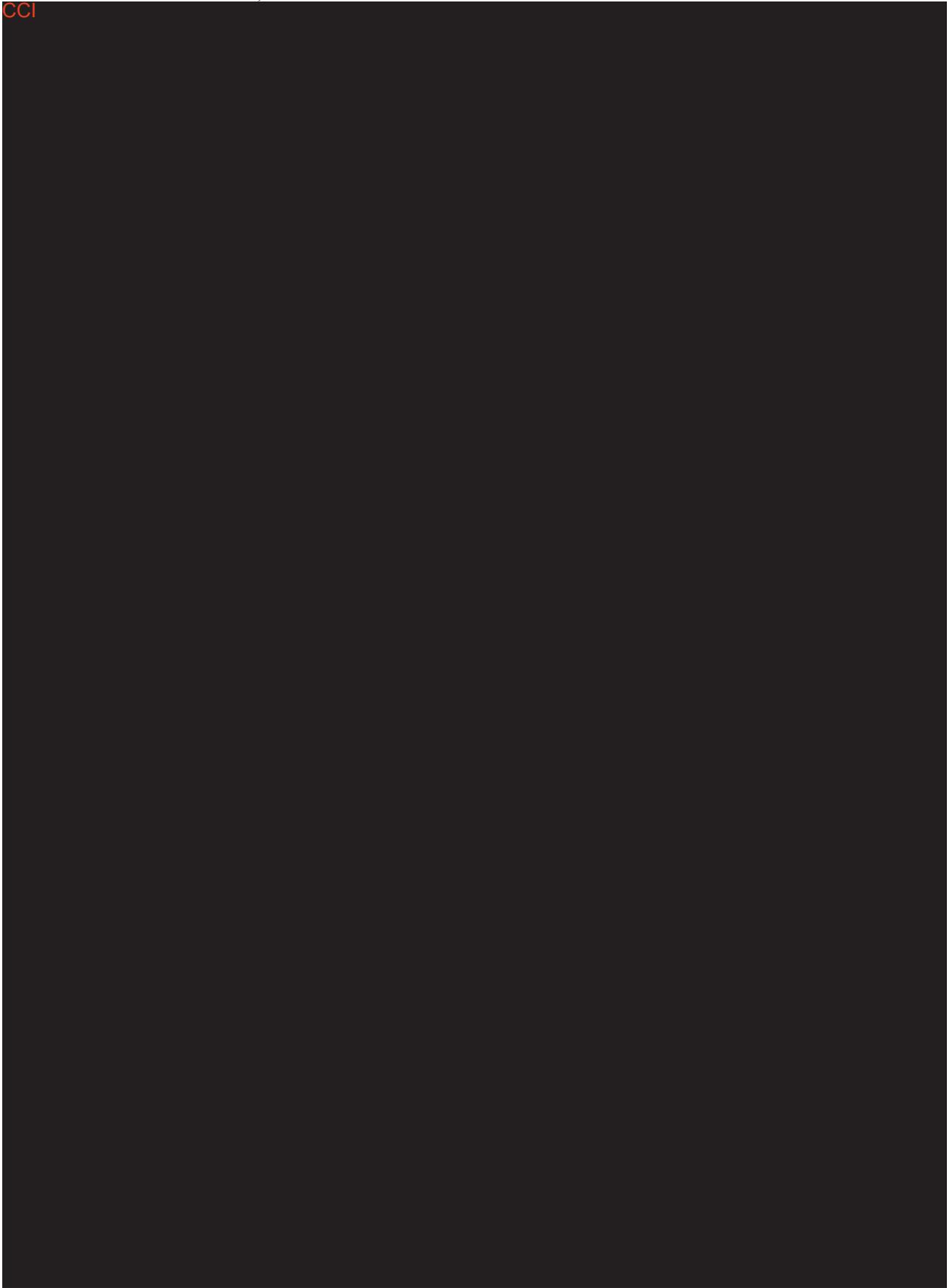
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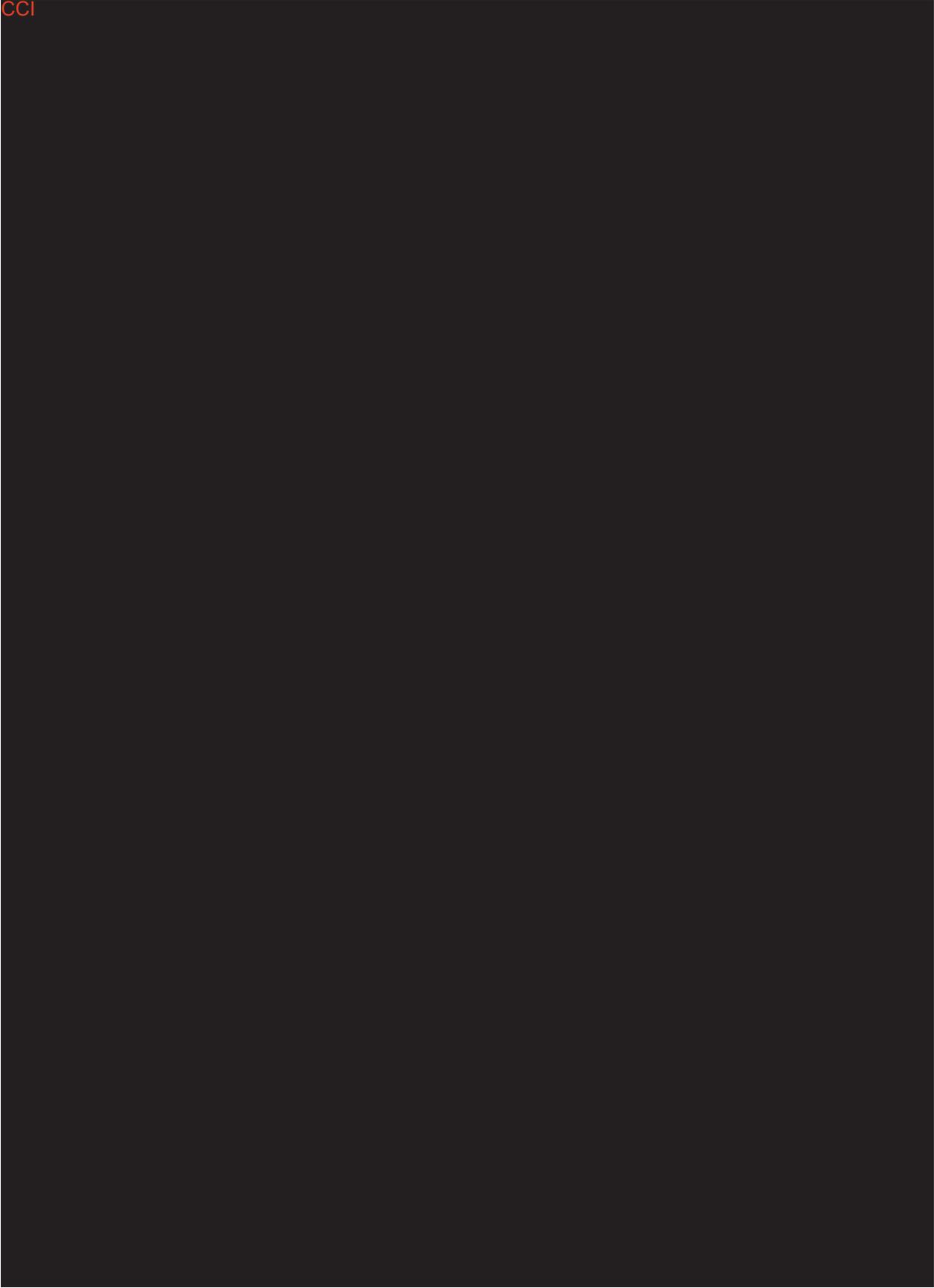
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