A PHASE 2, OPEN LABEL EXTENSION STUDY TO INVESTIGATE THE LONG TERM SAFETY AND TOLERABILITY OF PF-06649751 IN SUBJECTS WITH MOTOR FLUCTUATIONS DUE TO PARKINSON'S DISEASE

Investigational Product Number:	PF-06649751
Investigational Product Name:	Not Applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	118647
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Protocol Number:	B7601017
Phase:	2a

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Document History

Document	Version Date	Summary of Changes
Amendment 1	31 March 2017	1. Protocol Summary and throughout the protocol: Removed 'Minor' and 'Major' Delayed Rollover categories. "Direct Rollover Subjects" are now defined as able to dose within 48 hrs of their last IP dose in Study B7601003. Subjects with an IP dosing gap of more than 48 hrs and up to 60 days between the studies are now defined as 'Delayed Rollover Subjects'. Subjects with an IP dosing gap of more than 60 days since their last dose of IP in study B7601003 are no longer eligible for study B7601017 due to the inability to control for activities between studies and limited validity of the of the open label data when comparing with B7601003 data. 2. Protocol Summary and throughout: In order to maintain the blind for study B7601003 in conjunction with the clinical decision to not re-challenge subjects down-titrated in B7601003, eligible subjects who were blindly down-titrated (real or dummy down-titration) during study B7601003 will not dose higher than 7 mg QD in study B7601017. 3. CCI [redacted] 4. CCI [redacted] 5. Background & Rationale, Section 3.1, Section 3.1.1.1, Section 3.1.1.2 and Section 3.1.3.2: Changed language to allow de-escalation to 7 mg QD for intolerable AEs *at any time* in the study. 6. Schedule of Activities: Screening window for Delayed Rollover Subjects extended to 60 days.

		7. Schedule of Activities: Added a Randomization Procedure *"Document rollover status (Direct/Delayed) & IP reduction in prior study (Y/N)"*. 8. Schedule of Activities and Section 6: For Direct Rollover Subjects, the following procedures have been changed, removed, or added at the Screening and Randomization visits: SAE monitoring, Demography, Concomitant Medications, Medical History, Contraception Check, Weight and BMI, Temperature, Urinalysis, Vasculitis Panel, Urine Drug Screen, CCI [redacted] 9. Schedule of Activities and Section 6: For Delayed Rollover Subjects, the following procedures have been changed, removed, or added at the Screening and Randomization visits: Medical History, Contraception Check, Full physical and neurological exam, Brief physical and neurological exam, Weight and BMI, ECG, Temperature, Safety laboratory, Urinalysis, CCI [redacted], Banked Biospecimens, Vasculitis Panel, FSH test, Serological testing, Urine Drug Screen, CCI [redacted]. 10. Schedule of Activities and Section 6: Delayed Rollover Subjects Screening will use available data from study B7601003 Week 15. An additional short "In Clinic" Screening visit will occur for the collection of procedures unique to the B7601017 study and is now indicated in the Schedule of Activities. 11. Schedule of Activities and Section 6: Urinalysis removed from Visit 2 and Visit 14. 12. Schedule of Activities and Section 6: Temperature measurement added at all clinic visits (except Direct Rollover Subject Randomization). 13. Schedule of Activities and Section 6: C-SSRS

		was added to Visit 5, 6 and 11. 14. Schedule of Activities and Section 6: Hoehn and Yahr removed from SOA and Section 7. 15. Schedule of Activities and Section 6: Phone Visits 10, 12, 14, and 16 were removed. 16. Schedule of Activities: Symbol '(O)' added to denote data from procedures conducted as part of study B7601003 that are not repeated for study B7601017. 17. Schedule of Activities: Footnotes no longer applicable were removed. 18. Schedule of Activities, Footnote #2: Process of handling ongoing AEs/SAEs clarified. 19. Schedule of Activities, Footnote #6: Single vitals measurement for all subjects, with triplicate only required as necessary per Section 7.2.5. 20. Schedule of Activities, Footnote #8: During subject eligibility review, the sponsor may request repeat of abnormal laboratory results. 21. Schedule of Activities and Section 6: Contraception Check added for all subjects at Randomization (Day -1), V5, V6, V9, V11 and V15. 22. Schedule of Activities, Section 1.4.5, Section 2, Section 6, and Section 7.5: Banked DNA Biospecimens collection was removed (already collected in B7601003). 23. Schedule of Activities, Section 6, and Section 7.2.1: FSH and Serological Testing removed. 24. Schedule of Activities: 'Request Eligibility Review from Sponsor' added line item. 25. Section 1.5.2: The original section described Dosing Schedule rather than dosing Rationale and was a repeat of other section. It was removed and

		an adequate Dosing Rationale Section was added. 26. Section 2: Objectives and Endpoints Table updated to reflect motor first and removal of Biospecimen-related endpoints. 27. Section 3 Figure 1: Study Schematic updated to reflect changes to visit schedule and to provide additional clarification during titration and dose adjustment period. 28. Section 3.1, Summary Background and Rationale, Study Design, EC #8: added Definition and Reference to Section 3.1.1 for Details on "Exceptional Circumstance" Exception. 29. Section 3.1: added clarification about Rescreening. 30. Table 3 was updated to reflect changes to 2 groups of subjects only and handling of subjects with de-escalated IP in study B7601003. 31. IC #7: age range corrected to account for subject being older than in Study B7601003. 32. IC #6 added: Subjects successfully completed study B7601003 through Wk 15, with an IP dosing gap of no more than 60 days between the 2 studies (carefully review the conditions for the "Exceptional Circumstance" Exception in Section 3.1.1). 33. EC #5: added definition for Herbals. 34. Use of the name IMPALA as the centralized randomization system and removed other names (IWT, IRT). 35. Section 4.2, Exclusion Criteria #20: Updated exclusion window from 30 days to 60 days. 36. Section 5.1: Updated text with description of CRF capturing added documentation of Rollover Status (Direct or Delayed) and information on any IP dose reduction during prior study

		B7601003 (Yes/No). 37. Section 5.3: added a Medication Compliance Formula. 38. Updated Section 5.5, Administration. 39. Section 5.8.2, Prohibited Medications (dopamine receptor agonists, istradefylline, zonisamide and inhaled L-Dopa) for Parkinson's disease: Clarified that Direct Rollover Subjects must continue to refrain from taking these medications, while the exclusion window for Delayed Rollover Subjects taking these medications was updated from 28 days to 60 days. 40. Section 5.8.3, Prohibited Other Concomitant Medications: Clarified that Direct Rollover Subjects must continue to refrain from taking these medications, while the exclusion window for Delayed Rollover Subjects taking these medications was updated from 28 days to 60 days. 41. Section 6: Dose accountability procedure added at all required visits with a reference to Section 7.1.5 instead of repeated text. CCI [redacted] Procedures were reordered and updated to match SOA. 42. Section 7.1.1: Added Assessment description for added SOA Procedure: "Document rollover status (Direct/Delayed) & IP reduction in prior study (Y/N)". 43. Section 7.1.4: Clarification was provided for the Sponsor Eligibility Verification Process. 44. Section 7.1.3, Medical History/Prior Medications Procedures: Guidance on handling resolved and ongoing AEs from B7601003 now included. 45. Section 7.1.5, Drug Accountability Verification: Section added to clarify process of IP compliance and accountability during phone and clinic visits.

		46. Section 7.2: tests list corrected in table. 47. Section 7.2.4, Neurological Examinations: The full neurological examination is required at times specified in the Schedule of Activities and Section 6. The exam(s) must include assessment of the visual fields and of the right and left optic fundus; cranial nerves; mental state; muscle strength and tone, abnormal movements; deep tendon reflexes; sensory exam, coordination, gait and station. 48. Section 7.2.5: clarification added on timing of temperature collection. 49. Section 7.4.1, Blood Volume table was removed since maximum volumes are in the text. Volumes updated to reflect removal of FSH, Serological testing, and banked biospecimens. 50. Section 7.5.1: Corrected to reflect that C-SSRS will only use the "Since Last Visit" version. Clarification about criteria for Suicidality Risk Assessment. 51. Section 7.5.2: Updated for PHQ-8. CCI [redacted] CCI [redacted] 54. Section 9.4: Clarification added that the DMC will be a program-level DMC. 55. Section 13: Definition of End of Trial: definition of end of trial updated to 60 days post LSLV for B7601003. 56. Reference Section 16: References not cited in the text were removed. 57. Appendix 3, Criteria for Safety Values of

		Potential Clinical Concern removed and replaced with Permitted/Prohibited Concomitant medications. 58. New Appendix 4 (Prohibited Moderate or Strong CYP3A Inhibitors and Inducers) has been added. 59. Removed references to a Prohibited Medications and CYP3A Guide and added references to new Appendices 3 and 4. CCI [redacted] 61. Editorial changes throughout for consistency and clarity.
Original protocol	22 December 2016	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 (PD), 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.[1] Efforts to develop selective D1R agonists have been ongoing for decades. Unlike D2/D3R agonists (such as pramipexole, ropinorole and rotigotine), 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 PD who are experiencing motor complications associated with L-Dopa use.

PF-06649751 is a highly selective dopamine D1/D5 receptor partial agonist being evaluated for the symptomatic treatment of PD. 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 PD 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.

A total of 104 healthy subjects (88 received PF-06649751) and 63 PD subjects (63 received PF-06649751) have participated in Phase 1 trials. PF-06649751 has been evaluated in 63 PD subjects in one completed open-label ascending dose trial (B7601005 n=45, 45 subjects received PF-06649751), and one completed double-blind, placebo-controlled, single ascending dose trial (B7601009 n=18, 18 subjects received PF-06649751). To date, PF-06649751 has been shown to be safe and well tolerated, for further details, please refer to the Investigator Brochure or Section 1.4.3 Safety.

The results of Phase 1/1b studies in healthy subjects and PD subjects, and the possible risks associated with the administration of PF-06649751 are summarized in the Investigator's Brochure (IB).

Two additional Phase 2 studies in PD subjects are ongoing: study B7601003 in PD subjects with motor fluctuations (198 subjects planned) and study B7601011 in PD subjects at early stage of the disease (88 subjects planned). The current study is an open label extension of the double-blind B7601003 study.

B7601003 is an ongoing randomized, double-blind, placebo-controlled parallel group, dose-ranging study in PD subjects with motor fluctuations. Approximately 198 subjects from approximately 60 centers in approximately 6 countries will be randomized to 5 treatment groups (15 mg quaque die (QD, once daily), 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).

All subjects who successfully completed Week (Wk) 15 Visit in study B7601003 and who can be randomized in order to receive their first dose of investigational product (IP) in Study B7601017 within 60 days (inclusive) of their last dose of IP in study B7601003 will have the opportunity to screen for this open label extension study (B7601017). The only exception to the 60 day gap will be for subjects who completed study B7601003 before the open label is approved at their site (See details in Section 3.1.1). Up to 198 subjects may be randomized. Depending on the actual treatment the subject received in B7601003, subjects will be randomized to one of 4 treatment groups (15 mg QD, 7 mg QD, 3 mg QD, or 1 mg QD group) and titrated up to 15 mg QD over a 3 week period, as appropriate. All subjects who were blindly down-titrated during the B7601003 study will remain at/or be titrated to 7 mg QD only and remain at that dose for the rest of the B7601017 study in order to protect the blind for the prior study. Subjects who successfully titrate to 15 mg QD will enter the Adjustment Period at that dose. Subjects who cannot tolerate 15 mg QD at any time during the study will be allowed to down-titrate to 7 mg QD (but not lower) and will stay at that dose for the rest of the study. Subjects who cannot remain at a stable dose (7 mg or 15 mg QD) will be discontinued.

Study Objectives

Primary Objective

- To evaluate the long-term safety and tolerability of PF-06649751 administered QD in subjects with PD.

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Endpoints

Primary Endpoints

- Adverse events.
- Physical and neurological examination findings.
- Clinical laboratory parameters.
- Vital signs.
- Electrocardiogram (ECG) parameters.
- Columbia Suicidality Severity Rating Scale (C-SSRS).
- Physician Withdrawal Checklist (PWC-20).

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Study Design

This study begins with a 3-week blinded titration phase, followed by an open label design for the remainder of the study (12 months) and is only available for PD subjects who successfully completed study B7601003 up to Wk 15. All subjects (and investigators) will remain blinded to the B7601003 study treatment group. Delayed Rollover Subjects, defined as having a gap in dosing of >48 hr and up to 60 days after their last IP dose in study B7601003, will undergo a *de novo* 3-week titration and will not be blinded to their treatment during B7601017. All subjects who completed study B7601003 and who wish to enter the open label extension study B7601017 (up to 198 subjects) will be reviewed for eligibility and, if approved, will be randomized and receive active PF-06649751 treatment using a central randomization system (IMPALA).

Subjects who successfully completed study B7601003 up to the Wk 15 visit will be handled as follows (see Table 1):

- Direct Rollover Subjects, defined as having an IP dosing gap of no more than 48 hours from their last IP administration in B7601003.
- Delayed Rollover Subjects defined as having an IP dosing gap between >48 hours and no more than 60 days from their last IP administration in B7601003.

Subjects with a gap of more than 60 days since their last dose of IP in B7601003 will not be permitted to randomize in B7601017 due to the inability to control for their activities between studies and the limited validity of the open label data when comparing them with the B7601003 data (carefully review the conditions for the "Exceptional Circumstance" Exception in Section 3.1.1).

Table 1. Screening and Baseline Data Collection for Rollover Subjects

B7601017	Direct Rollover Subjects (≤48 Hours gap in dosing)	Delayed Rollover Subjects (>48 Hours and ≤60 Days gap in dosing)
SCREENING	Use data from B7601003 Wk 10	Use data from B7601003 Wk 15 and SHORT SCREENING VISIT For additional Screening procedures
BASELINE	Use data from B7601003 Wk 15	NEW BASELINE VISIT

Each subject will participate in the study for approximately 53 weeks, including, 3 weeks of up titration, 2 weeks of open label dose adjustment, and 44 weeks stable, open label dosing (49 weeks total treatment duration), and an approximately 4 week Follow-up period.

Statistical Methods

The primary analysis will examine the long-term safety and tolerability of PF-06649751 administered QD in subjects with PD. The details of the statistical 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 table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Visit Identifier	**DIRECT Rollover Subjects** (up to 48 hr between IP dosing)		**DELAYED Rollover Subjects** (>48 hr and up to 60 days between IP dosing)		**Titration Period** (blinded for Direct rollover subjects)			**Dose Adjustment Period** (Open Label)		**Stable Dosing Period** (Open Label)							**Follow Up Period**	
					V2	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13/ Early Term**	**V14**	**V15**
Protocol Activity	**Screening (Wk 10 of B7601003)**	**V1 RAND (Week 15 of B7601003) (D -1)**	**Screening (Wk 15 of B7601003+ In Clinic Visit)**	**V1 RAND (D -1)**	**D 7 +3**	**D 14 +3**	**D 21 +3**	**D 28 ±3**	**D 35 ±3**	**D 63 ±5**	**D 91 ±5**	**D 119 ±5**	**D 175 ±5**	**D 231 ±5**	**D 287 ±5**	**D 343 ±5**	**D 357 ±5**	**D 371 ±5**
Weeks					**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 9**	**Wk 13**	**Wk 17**	**Wk 25**	**Wk 33**	**Wk 41**	**Wk 49**	**Wk 51**	**Wk 53**
Informed consent[1]	X		X															
Document rollover status *(Direct/Delayed)* & IP reduction in prior study *(Y/N)*		X		X														
Inclusion/ Exclusion Criteria Verification	X	X	X	X														
Serious and non-serious AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Visit Identifier	**DIRECT Rollover Subjects** (up to 48 hr between IP dosing)		**DELAYED Rollover Subjects** (>48 hr and up to 60 days between IP dosing)		**Titration Period** (blinded for Direct rollover subjects)			**Dose Adjustment Period** (Open Label)		**Stable Dosing Period** (Open Label)							**Follow Up Period**	
	V2					**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13/ Early Term**	**V14**	**V15**
Protocol Activity	**Screening (Wk 10 of B7601003)**	**V1 RAND (Week 15 of B7601003) (D -1)**	**Screening (Wk 15 of B7601003+ In Clinic Visit)**	**V1 RAND (D -1)**	**D 7 +3**	**D 14 +3**	**D 21 +3**	**D 28 ±3**	**D 35 ±3**	**D 63 ±5**	**D 91 ±5**	**D 119 ±5**	**D 175 ±5**	**D 231 ±5**	**D 287 ±5**	**D 343 ±5**	**D 357 ±5**	**D 371 ±5**
Weeks					**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 9**	**Wk 13**	**Wk 17**	**Wk 25**	**Wk 33**	**Wk 41**	**Wk 49**	**Wk 51**	**Wk 53**
Prior/ Concomitant medications assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Demography	X		X															
Review/Update Medical History[2]	X	X	X	X														
Contraception Check		X		X				X	X			X		X				X
Full physical and neurological examination	(O)	(O)	(O)	X												X		
Brief physical and neurological examination[3]									X			X		X			X	
Weight and BMI[4]		X	X	X								X				X		
ECG[5]	(O)	(O)	(O)	X	X			X	X			X		X		X	X	
Supine and standing BP and HR (singles)[6]	(O)	(O)	X	X	X			X	X			X		X		X	X	
Temperature	X		X	X	X			X	X			X		X		X	X	
Columbia Suicidality Severity Rating Scale (C-SSRS)[7]	(O)	(O)	X	X	X			X	X			X		X		X	X	

Visit Identifier	DIRECT Rollover Subjects (up to 48 hr between IP dosing)		DELAYED Rollover Subjects (>48 hr and up to 60 days between IP dosing)		Titration Period (blinded for Direct rollover subjects)			Dose Adjustment Period (Open Label)		Stable Dosing Period (Open Label)							Follow Up Period	
					V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13/ Early Term	V14	V15
Protocol Activity	Screening (Wk 10 of B7601003)	V1 RAND (Week 15 of B7601003) (D -1)	Screening (Wk 15 of B7601003+ In Clinic Visit)	V1 RAND (D -1)	D 7 +3	D 14 +3	D 21 +3	D 28 ±3	D 35 ±3	D 63 ±5	D 91 ±5	D 119 ±5	D 175 ±5	D 231 ±5	D 287 ±5	D 343 ±5	D 357 ±5	D 371 ±5
Weeks					Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 9	Wk 13	Wk 17	Wk 25	Wk 33	Wk 41	Wk 49	Wk 51	Wk 53
Safety laboratory (Hematology, Blood Chemistry)	(O)	(O)	(O)[8]	X	X				X			X		X		X	X[8]	
Urinalysis	(O)	(O)	(O)[8]	X					X			X		X		X		
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]					[redacted]			[redacted]		[redacted]		[redacted]		
Blood sample/ PF-06649751 concentration[9]	(O)	(O)							X			X		X		X		
Vasculitis Panel	X		X[10]													X		
Urine Drug Screen[11]	X		X															
CCI [redacted]								[redacted]	[redacted]									
Investigational product accountability	(O)	(O)	(O)		X			X	X			X		X		X		
Dosing compliance verification via phone[13]						X	X			X	X		X		X			
Physician Withdrawal Checklist (PWC-20)																X	X	

[redacted]

Visit Identifier	DIRECT Rollover Subjects (up to 48 hr between IP dosing)		DELAYED Rollover Subjects (>48 hr and up to 60 days between IP dosing)		Titration Period (blinded for Direct rollover subjects)			Dose Adjustment Period (Open Label)		Stable Dosing Period (Open Label)							Follow Up Period	
					V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13/ Early Term	V14	V15
Protocol Activity	Screening (Wk 10 of B7601003)	V1 RAND (Week 15 of B7601003) (D -1)	Screening (Wk 15 of B7601003+ In Clinic Visit)	V1 RAND (D -1)	D 7 +3	D 14 +3	D 21 +3	D 28 ±3	D 35 ±3	D 63 ±5	D 91 ±5	D 119 ±5	D 175 ±5	D 231 ±5	D 287 ±5	D 343 ±5	D 357 ±5	D 371 ±5
Weeks					Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 9	Wk 13	Wk 17	Wk 25	Wk 33	Wk 41	Wk 49	Wk 51	Wk 53
CCI	■		■		■			■	■			■		■				
On-site Dispensing of Investigational product	(O)	X		X	X			X	X			X		X				
CCI		■		■				■	■			■		■		■		
CCI	■	■	■	■	■				■			■		■		■		
	■	■	■	■					■			■		■		■		
	■	■	■	■					■			■		■		■		
Patient Health Questionnaire (PHQ-8)			X															
Register Subject in Central Randomization System (IMPALA)	X		X															
Request Eligibility Review from Sponsor	X		X															
Randomization		X		X														
Administration of IP[15]					IP dosing starting on Day 1 and through V13/Early termination													

Abbreviations: AE = adverse event; BMI = body mass index; BP = blood pressure; ECG = electrocardiogram; C-SSRS = Columbia Suicidality Severity Rating Scale; CCI [redacted]; HR = heart rate; IP = investigational product; CCI [redacted]; PHQ-8 = Patient Health Questionnaire; CCI [redacted];

PWC-20 = physician withdrawal checklist; rBA= relative bioavailability; V = Visit; Wk = Week = Phone Visit

Footnotes:

(O) = Procedure conducted as part of the B7601003 study for which data will be used for the B7601017 study.

X = Procedure conducted as part of the B7601017 study.

1. Informed Consent must be obtained prior to any Screening procedure. For Delayed Rollover Subjects additional Screening procedures must take place before Randomization (D-1).
2. Assess resolved and ongoing AEs/SAEs for potential entry into subject medical history. For Delayed Rollover Subjects Medical History will be assessed during a short "In clinic" Screening visit to confirm no change in history post completion of B7601003.
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.
4. Height collected during B7601003 study will be used to calculate subjects BMI in B7601017 study.
5. Triplicate ECG at all visits.
6. Vitals should be collected first while the subject is in the supine position and then in the standing position (Section 7.2.5).
7. Columbia Suicidality Severity Rating Scale (C-SSRS) "Since Last Visit" at all timepoints.
8. Laboratory results may be repeated at the sponsor's request, to confirm subject eligibility for Delayed Rollover Subjects prior to Randomization (Day -1). Refer to Section 7.2.1 for additional safety laboratory tests (blood and urine) to be completed at Screening and Wk 51 Follow-up visits, and/or, as deemed necessary throughout the study after consultation with the Medical Monitor/Sponsor per Section 7.2.8.
9. CCI [redacted]
10. Complete the Vasculitis Panel IF the Delayed rollover subject did not have this sample collected at Wk 17 in study B7601003 (see Section 7.2.1 for details).
11. Urine test for drugs of abuse (including THC).
12. CCI [redacted]
13. During Phone visits, in addition to compliance verification done by asking the subject to describe blister cards during titration, subjects will be reminded which blister card to use for the following week. During stable dosing, compliance will be assessed by asking the subject about missed doses and reasons.

CCI [redacted]

15. First dose will be administered the morning of Day 1 which will be the morning after all procedures for Randomization (Day -1) have been completed.

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 PD.

1.2. Purpose of Study

This study will evaluate the long-term safety and tolerability of PF-06649751 in subjects with PD who have completed the B7601003 study.

1.3. Background and Rationale

1.3.1. Parkinson's Disease

PD 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 PD is approximately 1%, increasing to 3% for individuals in their 80s. The lifetime risk for developing PD may be as high as 1 in 40.[2] PD 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 PD include dopaminergic neuronal loss and regional intracellular aggregation of the protein alpha-synuclein.[3] 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 PD.[4]

Currently available pharmacological treatment strategies for PD 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.[5] 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.[6] The initial consistent relief of symptoms resulting from dopamine replacement is ultimately replaced by a relentlessly narrowing therapeutic window.

In PD, 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 PD,[5] the maximal efficacy observed is considered inferior to L-Dopa.

Unlike D2/D3R agonists, (such as pramipexole, ropinorole and rotigotine) 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 PD subjects, the selective full D1/D5R agonists dihydrexidine,[6] ABT-431,[7,8] and CY 208 243[9] 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 PD (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.[10]

1.3.2. 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 PD. 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 (inhibition constant (Ki) = 7 nM). In vitro binding studies demonstrated that PF-06649751 (molecular weight (MW) = 391.35 g/mol) displayed moderate binding affinity for recombinant hD1 (Ki = 9 nM) and hD5 (Ki = 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 cyclical adenosine monophosphate (cAMP) formation with EC50 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 PD, 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_{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 PD.

In an evaluation of secondary (off target) pharmacology in vitro, PF-06649751 at 10 μM 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 non-adverse 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 non-pigmented animals and, because of the protection afforded by uveal pigment in the eye of non-albino animals, not expected to be an adverse finding relevant to humans administered PF-06649751 in clinical trials.

Central Nervous System

Adverse central nervous system (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_{max} (19.8 ng/mL) at a dose of 15 mg. Non-adverse 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 (≥0.15 mg/kg/day), cage biting, excessive scratching, jerky movements (≥0.75 mg/kg/day), head pressing, decreased activity, skin picking (≥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 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.[11] 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.[12] 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 trials following oral administration.[13] 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 no observed adverse event level (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 ≥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 non-degenerative 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 with 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 (≤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 (HR), QTc interval, and cardiac contractility. Results of an in vitro human ether-a-go-go-related gene (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 μM, 25400 ng/mL) is ≥940x 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 μM (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 ≥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 (≥1 mg/kg/day), therefore the NOAEL in female rats was undetermined. However, this eye finding was considered an adverse effect relevant only to non-pigmented 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 trials 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 (SRSD), which for this study is the Investigator Brochure.

1.4. Human Clinical Experience

1.4.1. Completed Clinical Studies

PF-06649751 has been evaluated in 3 completed clinical studies in 104 healthy subjects (88 receiving PF-06649751) which are described in the Investigator's Brochure:

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

- Protocol B7601002 (n=77) was a Phase 1, placebo controlled, randomized, multiple ascending dose trial to evaluate the safety and tolerability of PF-06649751 following multiple oral doses (with and without titration) with QD 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 QD 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 trimethobenzaminde (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 PD subjects which are described in the Investigator's Brochure:

- Protocol B7601005 (n=45, 45 subjects received PF-06649751) was a Phase 1b, 2 period, open label, multicenter, dose escalation study of PF-06649751 in subjects with PD experiencing motor fluctuations and, in Cohort 5, in subjects with PD 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 PD subjects 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 PD, with no new safety findings.

- Protocol B7601009 (n=18, 18 subjects received PF-06649751) 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 PD 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. Ongoing Clinical Studies

PF-06649751 is currently being evaluated in 2 clinical studies in PD subjects which are described in the Investigator's Brochure:

Protocol B7601003 is an ongoing (198 subjects planned) 15-week, Phase 2, double-blind, randomized, placebo-controlled, parallel group dose ranging study to investigate the efficacy, safety and tolerability of PF-06649751 in subjects with motor fluctuations due to PD. The primary objectives of the study are to evaluate the effect on motor symptoms of PF-06649751 administered QD as adjunctive treatment with stable doses of L-Dopa in PD, and to determine the therapeutic window for motor symptom improvement of PF-06649751 administered QD, ie, determining a dose, or a range of doses, for adequate control of motor symptoms. The current B7601017 study is an open label extension study of the double-blind B7601003 study.

Protocol B7601011 is an ongoing (88 subjects planned) 15-week, Phase 2, double-blind, randomized, placebo-controlled flexible dose study to investigate the efficacy, safety and tolerability of PF-06649751 in subjects with early stage PD. Subjects with PD to be enrolled will be dopaminergic treatment naïve or not have been treated with dopaminergic treatment for more than 28 days.

1.4.3. Safety

B7601001

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

B7601002

One multiple ascending dose study in healthy subjects 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 this 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

This was a Phase 1b, 2-period, open label, multi-center, PF-06649751 dose escalation study in PD subjects experiencing motor fluctuations with one cohort including PD subjects 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 PD, 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 [redacted].

B7601009

This 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 PD subjects(n=18). 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 PD. 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 corrected QT (Fredericia correction) (QTcF) values in the higher dose groups (PF-06649751 6 mg and PF-066449751 9 mg) between 2 and 8 hours post dose, but no subject had a QTcF ≥500 msec or an increase of QTcF ≥60 msec.

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

1.4.4. Pharmacokinetics

PF-06649751 has exhibited generally consistent pharmacokinetic characteristics across a wide range of doses. Pharmacokinetics of PF-06649751 following oral administration as immediate release formulations are characterized by rapid absorption and an average terminal elimination half-life of about 24 hrs. Approximately dose proportional increase in PF-06649751 exposures was observed after single doses in both healthy subjects and PD subjects. Increase in exposures at steady state was found to be slightly less than dose proportional in healthy subjects and between 15 mg and 25 mg in PD subjects. Japanese subjects in B7601002 (at 1.5 mg PF-06649751) had PF-06649751 exposures similar to Western subjects. Exposures in PD subjects at 5 mg QD (B7601005) dosing were slightly greater (approximately 1.5 fold) than those observed in healthy subjects (B7601002). Food had minimal impact on PF-06649751 C_{max} and AUC_{inf} at 0.75 mg dose in healthy subjects, Urinary recovery of PF-06649751 was low, with approximately 0.2% or less of the dose recovered unchanged in urine. Steady state PF-06649751 exposures in PD subjects at different doses from B7601005 are presented in Table 2.

Table 2. Steady State Exposures of PF-06649751 after Multiple Dosing in PD subjects with Motor Fluctuations

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

1.4.5. Additional Information

Additional information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the latest version of the Investigator's Brochure of PF-06649751.

1.5. Rationale

1.5.1. Study Rationale

This study will evaluate the long-term safety and tolerability of PF-06649751 as a potential novel therapeutic agent in subjects with PD. CCI [redacted]

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 PD who are experiencing significant OFF time despite their current dopaminergic therapy. Following an initial double-blind titration phase, which is intended to mitigate potential dopaminergic adverse events such as nausea and vomiting and maintain the B7601003 study blind, subjects will self-administer oral doses of PF-06649751 daily as adjunctive treatment with L-Dopa.

After Wk 5, if the investigator is willing to attempt reducing the subject's L-Dopa dose to evaluate the extent to which PF-06649751 may replace L-Dopa, the investigator will be required to contact the sponsor clinical team and present the proposed dosing plan and careful monitoring for potential resulting AEs.

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 (≤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.

The study population will include male subjects as well as female subjects of non-childbearing potential diagnosed with PD who experience motor fluctuations who have successfully completed through Wk 15 of the B7601003 study.

1.5.2. Dose Rationale

PF-06649751 doses for this study were 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_{eff} was established at 27.6 ng/mL. Based on the human Phase 1 pharmacokinetic data, a dose of 3 mg QD or above 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. The selection of a 15 mg QD dose was chosen to establish safety and efficacy at a dose that is at the top part of the dose-response curve. The alternate 7 mg QD optional de-escalation dose will provide safety, tolerability and efficacy data at a dose lower than 15 mg QD to establish adequate safety in case of safety/tolerability issues at 15 mg QD PF-06649751 dose group.

1.5.3. Summary of Benefit-Risk Assessment

The study is designed to evaluate the safety and tolerability of PF-06649751 in subjects with PD. Based on the clinical safety data available to-date, PF-06649751 doses in this study are not anticipated to pose any specific significant risk to study participants. The up-titration to reach 15 mg QD was designed to mitigate AEs of nausea, emesis and abdominal discomfort that have been seen in prior studies in healthy subjects and subjects with PD. Any potential risks will be further minimized by close safety monitoring during the study and follow up for the subjects' well-being.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective:	Primary Endpoints:
• To evaluate the long-term safety and tolerability of PF-06649751 administered once daily in subjects with PD	• Adverse events • Physical and neurological exam findings • Clinical laboratory parameters • Vital signs • Electrocardiogram (ECG) parameters • Columbia Suicidality Severity Rating Scale (C-SSRS). • Physician Withdrawal Checklist (PWC-20).
CCI [redacted]	

3. STUDY DESIGN

3.1. Study Overview

This study begins with a 3-week titration period (double-blinded for Direct Rollover Subjects, single-blinded for Delayed Rollover Subjects), followed by an open label treatment dose adjustment period and a stable dosing period in PD subjects who successfully completed Wk 15 in study B7601003. Up to 198 PD subjects will have the opportunity to be randomized in this study and receive 15 mg QD of PF-06649751, using a central randomization system. All eligible subjects must at least attempt to be titrated to 15 mg QD during the titration period, except for subjects who were de-escalated from 15 mg QD to 7 mg QD in study B7601003 and who will rollover at 7 mg QD. If a subject is not able to tolerate 15 mg QD they will be allowed to adjust to the lower 7 mg QD dose in an open label fashion.

Most subjects will be expected to rollover directly (with no more than 48 hrs between IP doses) into the Open Label Extension study after successful completion of Wk 15 in study B7601003. These subjects will be called "Direct Rollover Subjects" and their data will be handled as described in Direct Rollover Subjects.

A minority of subjects may experience a delay in entering the Open Label Extension study due to changing their mind. For data integrity purposes, and to insure subject stability, only up to 60 days of IP dosing gap will be allowed between the 2 studies. These subjects will be called "Delayed Rollover Subjects" and their data will be handled as described in Section 3.1.1.2.

Carefully review the conditions for the "Exceptional Circumstance" Exception in Section 3.1.1.

Subjects will be in the study for ~54 weeks as follows: they will receive treatment for approximately 49 weeks (3 weeks of blinded up-titration (open label for Delayed Rollover subjects), 2 weeks of open label dose adjustment, 44 weeks of stable open label dosing), followed by a Follow-up period of up to 4 weeks.

Subjects who are unable to complete the titration period up to 7 mg QD of PF-06649751 (or remain at 7 mg QD for subjects de-escalated during study B7601003) due to tolerability issues will not be allowed to continue in the study and will be discontinued.

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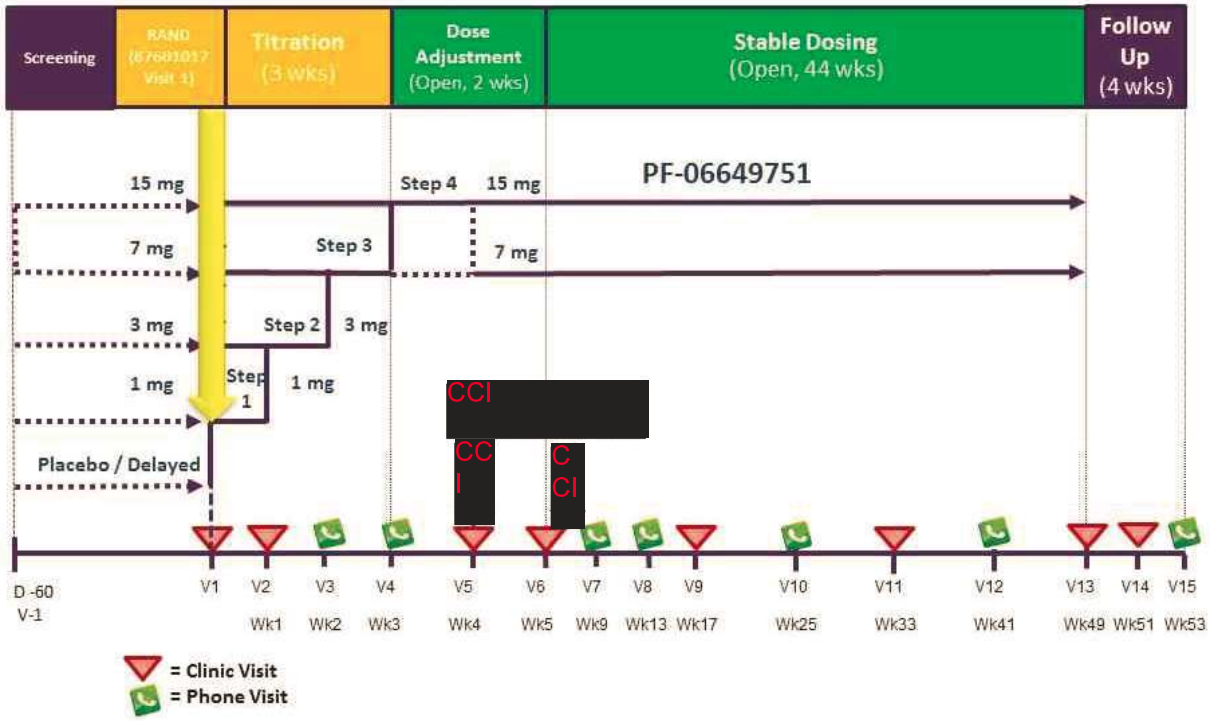
The study design is illustrated in the figure below. For details on the dosing during the titration phase, see Section 3.1.2.

Figure 1. B7601017 Study Schematic



3.1.1. Screening/Randomization

Subjects who are eligible may fall into one of two groups: Direct Rollover Subjects and Delayed Rollover Subjects, as defined in Direct Rollover Subjects and 3.1.1.2, respectively.

Subjects who fail to successfully complete the Wk 15 Visit in study B7601003 will not be eligible to screen for this extension study. Subjects who cannot perform their Randomization Visit in order to dose within 60 days of their last IP dose in study B7601003 will not be eligible to screen for this extension study. Please carefully review the conditions for the "**Exceptional Circumstance**" Exception below:

Only one exception will be permitted to the 60-day IP dosing gap rule, specifically for subjects who successfully complete study B7601003 through Wk 17 before the site receives official approval to enroll subjects in the open label extension. In this specific case, the PI will be required to initiate a discussion with the Sponsor before the subject reached Wk 17 to propose a plan to maintain the subject eligibility for the open label study and avoid for the subject to enter another investigational trial. If the plan is adequate the Sponsor will provide approval for the subject to wait until the open label study B7601017 is available at their site and permit them to screen. These subjects will still be required to meet all other eligibility criteria in order to be randomized. **These subjects would be handled exactly like "Delayed Rollover Subjects".** This exception will become obsolete as soon as the site is approved to enroll for the open label study.

For re-screening, decisions will be made on a case-by-case basis by the Sponsor. If a subject fails to meet criteria for CSSRS, PHQ-8 or ECGs, re-screening will not be permitted.

3.1.1.1. Direct Rollover Subjects

Direct Rollover Subjects are subjects with up to 48 hrs between last dose of IP in study B7601003 and first dose of IP in study B7601017.

For Direct Rollover Subjects, the Screening Visit will correspond to the Wk 10 visit in study B7601003 and the Randomization Visit will correspond to the Wk 15 visit in study B7601003. For these subjects, the Wk 10 data collected during study B7601003 will be used as the Screening data for the open label extension study B7601017, and the Wk 15 data collected during study B7601003 will be used as their Randomization visit (Visit 1) data for the extension study.

Direct Rollover Subjects will then enter a 3-week double-blind titration of PF-06649751 based on the dose they received in study B7601003 and on de-escalation they may have undergone during that study (Table 3).

In order to maintain the blind for study B7601003 in conjunction with the clinical decision to not re-challenge subjects down-titrated in B7601003, eligible subjects who were blindly down-titrated (real or dummy down-titration) during study B7601003 will not dose higher than 7 mg QD in study B7601017 and will be dosed according to the schedule shown in Table 3.

In the case of unacceptable dopaminergic AEs at 15 mg QD, subjects will be permitted a dose reduction to 7 mg QD. Subjects who cannot tolerate 7 mg QD will be discontinued.

Table 3. Dosing Schedule for Direct Rollover Subjects Transitioning into B7601017

	Treatment Received in B7601003	Screening, (Wk 10 of B7601003 Study)	Visit 1 (Wk 15 of B7601003 Study)	Visit 2 (Wk 1)	Visit 3 (Wk 2)	Phone Visit 4 (Wk 3)	Clinic Visit 5 (Wk 4)	Clinic Visit 6 (Wk 5)
A	15 mg	15 mg →	15 mg	15 mg	15 mg	15 mg	15 mg/7 mg[1]	15 mg/7 mg[1]
	De-escalated 15 mg down to 7 mg	7 mg →	7 mg	7 mg	7 mg	7 mg	7 mg	7 mg
B	7 mg	7 mg →	7 mg	7 mg	7 mg	15 mg	15 mg/7 mg[1]	15 mg/7 mg[1]
	Dummy De-escalated 7 mg to 7 mg	7 mg →	7 mg	7 mg	7 mg	7 mg	7 mg	7 mg
C	3 mg	3 mg →	3 mg	3 mg	7 mg	15 mg	15 mg/7 mg[1]	15 mg/7 mg[1]
	Dummy De-escalated 3 mg to 3 mg	3 mg →	3 mg	3 mg	7 mg	7 mg	7 mg	7 mg
D	1 mg	1 mg →	1 mg	3 mg	7 mg	15 mg	15 mg/7 mg[1]	15 mg/7 mg[1]
	Dummy De-escalated 1 mg to 1 mg	1 mg →	1 mg	3 mg	7 mg	7 mg	7 mg	7 mg
E	Placebo	Placebo →	1 mg	3 mg	7 mg	15 mg	15 mg/7 mg[1]	15 mg/7 mg[1]
	Dummy De-escalated Placebo to Placebo	Placebo →	1 mg	3 mg	7 mg	7 mg	7 mg	7 mg
			Titration Period				**Dose Adjustment**	

1. In the case of unacceptable dopaminergic AEs at 15 mg QD, subjects will be permitted a dose reduction to 7 mg QD

3.1.1.2. Delayed Rollover Subjects

Delayed Rollover Subjects are subjects who completed the B7601003 study through Wk 15, but will have a PF-06649751 dosing gap of more than 48 hrs and up to 60 days between the two studies (review the conditions for the "Exceptional Circumstance" Exception in Section 3.1.1).

Subjects who were down-titrated to 7 mg QD during study B7601003 will follow the treatment protocol (see Table 4).

Delayed Rollover Subjects will be allowed to screen for the extension study by using their Wk 15 data from study B7601003 and also completing a Short 'In Clinic" Screening visit within 60 days of their Randomization visit (See Table 4). Delayed Rollover Subjects will enter a 3-week titration of PF-06649751 starting from 1 mg QD (Table 4). Subjects who were not de-escalated during study B7601003 will undergo a full titration up to 15 mg QD.

As already described above, in order to maintain the blind for study B7601003 in conjunction with the clinical decision to not re-challenge subjects down-titrated in B7601003, eligible subjects who were blindly down-titrated (real or dummy down-titration) during study B7601003 will not dose higher than 7 mg QD in study B7601017 and will be dosed according to the schedule shown in Table 4.

Subjects who cannot tolerate 7 mg QD will be discontinued.

Table 4. Dosing Schedule for Delayed[3] Rollover Subjects transitioning into B7601017

Screening (up to 60 days)	**Visit 1** (Day -1)	**Visit 2** (W 1)	**Visit 3** (Wk 2)	**Phone Visit 4**[1] (Wk 3)	**Clinic Visit 5**[1] (Wk 4)	**Clinic Visit 6**[1] (Wk 5)
N/A	1 mg	3 mg	7 mg	15 mg	15 mg/7 mg	15 mg/7 mg
De-escalated[2] in B7601003	1 mg	3 mg	7 mg	7 mg	7 mg	7 mg
	Titration period				**Dose adjustment**	

1. In the case of unacceptable dopaminergic AEs, subjects are permitted one dose reduction.
2. Subjects who have completed a dose reduction to 7 mg QD in Study B7601003 will continue on the lower dose for the remainder of the study.
3. Defined as subjects who have successfully completed Wk 15 of B7601003 and have an IP dosing gap of more than 48 hours and up to 60 days between studies

3.1.2. Blind Titration Period

All eligible Rollover Subjects will enter a 3 week blinded titration phase of PF-06649751 administered QD (double blind for Direct Rollover and single blind for Delayed Rollover Subjects). They will remain blinded to their previous B7601003 treatment group.

Subjects who were blindly de-escalated during study B7601003 (real or dummy de-escalation) will remain/only be titrated up to 7 mg QD (as explained above).

3.1.3. Open Label Period

3.1.3.1. Dose Adjustment

For subjects titrating up to 15 mg QD, after completing the Titration Period and reaching the 15 mg QD target dose at Visit 4, there will be a 2-week Dose Adjustment Period during which it will be possible for the PI to mitigate tolerability issues by lowering the subject's dose from 15 mg QD to 7 mg QD of PF-06649751 (see Figure 1). If subjects continue to experience tolerability issues related to PF-06649751 at the 7 mg QD dose, they will not be allowed to reduce their dose further and must be discontinued from the study and undergo an Early Termination Visit.

Subjects who were de-escalated in study B7601003 will remain at 7 mg QD during the dose adjustment period.

3.1.3.2. Stable Dosing Period

The stable dosing period is a forty-four (44) weeks of open label stable dosing of PF-06649751 15 mg or 7 mg administered QD.

Subjects will return to the clinic at the end of Weeks 17, 33 and 49. Phone visits will take place at regular intervals between clinic visits. For guidance on concomitant medications for PD and other disorders during that time, refer to Section 5.8, Concomitant Treatment(s) and Appendix 3 and Appendix 4.

3.1.3.3. Follow-up Period

For subjects who completed study B7601017, a Follow-up clinic visit will take place about two weeks after last dose of PF-06649751 (Wk 51) to evaluate subject safety and a phone Follow-up visit will occur approximately 28 days after last dose of PF-06649751 at Wk 53 for subject safety assessment. Early termination follow-up requirements are addressed in Subject Withdrawal.

4. SUBJECT ELIGIBILITY CRITERIA

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.

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before Eligibility Approval is requested from the Study Sponsor and before subjects are included in the study.

4.1. Inclusion Criteria

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

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 at Screening.

2. Subjects must have successfully completed the B7601003 study through Wk 15, continue to meet all safety criteria at Screening and through Randomization visit, and must be considered compliant in the opinion of the investigator and the Sponsor.

3. No change since B7601003 study in any significant medical, rheumatologic, oncologic, neurologic, psychiatric or surgical conditions that are deemed to increase risk for participation in the extension study.

4. Willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures[redacted].

5. Subjects are willing and able to continue to refrain from any medication not permitted by the protocol throughout participation in the study (Appendix 3 and Appendix 4).

6. Subjects successfully completed study B7601003 through Wk 15, with an IP dosing gap of no more than 60 days between the 2 studies (carefully review the conditions for the "Exceptional Circumstance" Exception in Section 3.1.1).

7. Females of non-childbearing potential and/or male subjects between the ages of 40 and 87 years, inclusive. Male subjects able to father children must agree to use 1 highly effective method of contraception throughout the study and for at least 28 days after the last dose of assigned treatment.

Female subjects of non-childbearing potential must 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.

8. Subjects must still be able to recognize their "wearing off" symptoms and confirm that they usually improve after their next dose of PD medication.

4.2. Exclusion Criteria

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

Concomitant Medications:

1. Currently receiving an antipsychotic, metoclopramide, reserpine, or amphetamine.
2. Currently receiving moderate or strong CYP3A4 inducers or CYP3A4 inhibitors (except for topical administration) (Appendix 4).
3. Previous implantation of apomorphine pump, or surgery for intraduodenal use of Duodopa®.
4. Dopamine receptor agonist medications including pramipexole, ropinirole, rotigotine and apomorphine taken within 60 days prior to Day -1.
5. Herbal supplements taken within 28 days prior to Day -1 (Herbal supplements defined as concentrated/manufactured capsules or tablets).
6. Prohibited concomitant medications as outlined in Section 5.8, Concomitant Treatment(s) and in the Prohibited Concomitant Medication List (Appendix 3).

Screening Assessments:

7. 12-lead ECG (average of triplicate measures) demonstrating QTcF >450 msec (>470 msec for females) or a QRS interval >120 msec at Screening.

General and Administrative:

8. Subjects who would have a gap of more than 60 days between their last IP dose in Study B7601003 and their first dose in Study B7601017 (carefully review the conditions for the "Exceptional Circumstance" Exception in Section 3.1.1).

9. Investigator 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, including their family members, directly involved in the conduct of the study.

10. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 56 days prior to Day -1.

11. Unwilling or unable to comply with the lifestyle requirements described in Section 4.4 of this protocol.

Medical History:

12. Emergence of severe acute or chronic medical condition, or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior, 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.

Screening Assessments:

13. Females of childbearing potential assessed at Screening; Pregnant female subjects; breastfeeding female subjects; male subjects with partners currently pregnant; fertile male subjects who are unwilling or unable to use 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.

14. Finding of 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") not cleared by a mental health professional evaluation.

15. Screening supine blood pressure ≥160 mm Hg (systolic) or ≥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.

16. 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).

17. A positive urine drug screen for drugs of abuse unless explained by a medically indicated medication.

18. 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 transminase (SGOT) **or** alanine aminotransferase (ALT)/serum glutamic pyruvic transminase (SGPT) ≥2x upper limit of normal (ULN);

    - Total bilirubin ≥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 ≤ ULN.

19. Subjects with clinically significant depression: Patient Health Questionnaire-8 (PHQ-8) total score ≥15 [for Delayed Rollover Subjects ONLY].

General and Administrative:

20. Participation in other studies involving investigational drug(s), or treatment with any investigational drug within 60 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study medication (whichever is longer) other than the B7601003 parent study.

4.3. Randomization Criteria

Subjects will be randomized into the study provided they have satisfied all subject selection criteria. Using a central randomization system (IMPALA), subjects from the B7601003 study will be randomized to PF-06649751 using the same randomization number used in study B7601003.

4.4. Lifestyle Requirements

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 and star fruit) from 7 days prior to the first dose of Investigational Product until the end of the study.

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 blood 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 and 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 fertile male subjects who are of childbearing potential who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject [and his or her partner(s)] from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or 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:

- Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the subject or male subject's female partner 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.
- Correctly placed copper-containing intrauterine device (IUD).

- Male condom or female condom used WITH a separate spermicide product (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.

- Male sterilization with absence of sperm in the postvasectomy ejaculate.

- Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

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

4.5. Sponsor's Qualified Medical Personnel

The contact information for the Sponsor's appropriately qualified medical personnel for the study is documented in the study 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 product identifiers, subject study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator 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 investigator 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 investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator 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 investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator 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).

For this study, the investigational product(s) are PF-06649751 1 mg, 5 mg, 15 mg and a placebo to match the 1 mg and 5 mg tablets. Subjects will receive oral QD doses of either, 1 mg, 3 mg, 7 mg or 15 mg using 1 mg, 5 mg or matching placebo or 15 mg tablets. Subjects will be dosed QD for the duration of the study.

5.1. Allocation to Treatment

Allocation of subjects to treatment groups will be done through the use of an interactive central randomization system (IMPALA). 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, Rollover Status (Direct or Delayed) and information on any IP dose reduction during prior study B7601003 (Yes/No). This information will also be captured in a case report form (CRF). Rollover status and IP reduction information are critical criteria in assigning the adequate IP titration and dose for the open label study in IMPALA, to insure subject safety as well as protect the blind for prior study B7601003.

The site personnel will then be provided with a treatment assignment, randomization number, and dispensable unit (DU) or container number when investigational product is being supplied via IMPALA. This randomization number will be identical to the randomization number allocated in the preceding double-blind study B7601003.

The IMPALA system will provide a confirmation report containing the subject number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

The study-specific IMPALA reference manual will provide the contact information and further details on the use of this system.

5.2. Breaking the Blind *(During Titration Period, if applicable)*

The study will be subject and investigator blinded during the titration period, up to Visit 4.

At the initiation of the study, the investigator site will be instructed on the method for breaking the blind. The method will be an electronic process. Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the subject. Investigators are encouraged to discuss with a member of the study team if they believe that unblinding is necessary. When the blinding code is broken, the reason must be fully documented and entered on the case report form (CRF).

5.3. Subject Compliance

PF-06649751 will be administered by the subject or caregiver in the outpatient setting (each morning, daily for the duration of the treatment period). Site staff will verbally assess compliance with the subject during phone visits. During Phone visits, in addition to compliance verification done by asking the subject to describe blister cards during titration, subjects will be reminded which blister card to use for the following week. During stable dosing, compliance will be assessed by asking the subject about missed doses and reasons. Compliance will be confirmed by the site on clinic visits by pill count. A subject will be considered compliant with the protocol at a study treatment compliance range of 80%-120%.

Medication Compliance Formula:

$$\%\text{Compliance} = \frac{\text{Actual \# of Capsules Taken}}{\text{Total \# of Capsules Prescribed}} \times 100$$

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.

In addition to compliance verification during titration, subjects will be reminded on which blister card to use for the following week at each phone visit. The verification of blister card may be performed the day following the phone visits during titration. During stable dosing, compliance will be assessed using bottle pill count.

5.4. Investigational Product Supplies

5.4.1. Dosage Form(s) and Packaging

The following PF-06649751 and its matched placebo will be provided as tablets for oral administration:

Period	Dosage Form
Blinded Titration Period	PF-06649751 (1 mg tablet)
	PF-06649751 (5 mg tablet)
	Placebo to match (1 mg and 5 mg tablets)
Dose Adjustment	PF-06649751 (1 mg tablet)
	PF-06649751 (5 mg tablet)
Stable Dosing (Open Label Period)	PF-06649751 (1 mg tablet)
	PF-06649751 (5 mg tablet)
	PF-06649751 (15 mg tablet)

PF-06649751 1 mg, 5 mg and its matching placebo tablets will be provided as tablets in blinded blister cards for oral administration during the titration. PF-06649751 1 mg and 5 mg tablets will be provided in open label blister cards for oral dosing during the dose adjustment phase. The stable dosing period will utilize 1 mg 5 mg or 15 mg tablets in High Density Polyethylene (HDPE) bottles. All products will be supplied in appropriate bottles and blister cards and labeled according to local regulatory requirements.

5.4.2. Preparation and Dispensing

PF-06649751 will be dispensed using the IMPALA drug management system at clinic visits as noted in the schedule of activities (SOA). A qualified staff member will dispense the investigational product via unique container numbers in the blister cards and bottles provided, in quantities appropriate for the study visit schedule. The subject/caregiver should be instructed to maintain the product in the bottle (or blister cards, as appropriate) provided throughout the course of dosing and return the bottle (or blister cards, as appropriate) to the site at the next study visit.

IP should be provided as outlined in the Investigational Product Manual.

5.5. Administration

Subjects may take a different number of tablets during the up-titration phase than in the open label maintenance phase. During the titration phase subjects will take 3 tablets at each administration. Starting at Visit 6, subjects who are at 15 mg QD will take a single 15 mg tablet during the open label maintenance phase. During that same phase Subjects that are at 7 mg QD will take three tablets: one 5 mg and two 1 mg tablets

Regardless of the phase or quantity of tablet, for PF-06649751, subjects (and caregivers, as applicable) should be instructed as follows:

- Take tablet(s) at approximately the same time each morning.
- Subjects will swallow the investigational product whole, and will not manipulate or chew the investigational product prior to swallowing.
- If dosing with multiple tablets, all tablet(s) should be swallowed within approximately a 5 minute timeframe.
- The tablet(s) may be taken with or without food.
- If L-Dopa is taken in the morning, the PF-06649751 may be taken before or after the morning dose of L-Dopa.

CCI [redacted]

5.5.1. Titration of PF-06649751

In order to maintain the blind for the still ongoing prior study B7601003, subjects will be titrated in a blind fashion (double-blinded for Direct Rollover Subjects, single-blinded for Delayed Rollover Subjects) up to the 15 mg QD target dose level of PF-06649751, according to the titration scheme detailed in Section 3.1.1.1 Table 3 and Section 3.1.1.2 Table 4. All subjects de-escalated during study B7601003 will only be titrated up to 7 mg QD in order to maintain the blind for study B7601003. All other subjects will be required to attempt dosing at 15 mg QD for at least one dose. Subjects who experience intolerable adverse events at 15 mg QD will be allowed to down titrate to 7 mg QD. Subjects experiencing intolerable AEs at 7 mg QD or lower will need to be discontinued.

5.5.2. Dose Adjustment Period of PF-06649751

Starting at Visit 4 (Day 21, Wk 3), subjects will continue to receive the 15 mg QD or 7 mg QD of PF-06649751 for the remainder of the study in an open label fashion. Subjects who experience unacceptable adverse events related to the dose increase after having achieved the target dose of 15 mg QD will be allowed to reduce the dose to 7 mg QD. No adjustment will be made for the subjects already on 7 mg QD. If subjects continue to experience tolerability issues related to PF-06649751 at the 7 mg QD dose, they will not be allowed to reduce their dose further and must be discontinued from the study an Early Termination Visit will be conducted.

5.5.3. Stable Dosing of PF-06649751

From Visit 6/Wk 5 subjects will continue receiving the same QD dose (7 mg or 15 mg) of PF-06649751 until the end of the study in an open label fashion. In case of intolerable AEs subjects will be allowed one de-escalation to 7 mg QD and stay in the study.

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.

Investigational products should be stored in their original containers and in accordance with the labels.

See the single reference safety document (SRSD), for this study, the Investigator's Brochure for PF-06649751 for storage conditions of the product.

Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

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 evaluation for

excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

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

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

5.7. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record. All unused tablets must be returned to the investigator by the subject for dosing compliance verification at clinic visits. All bottles or blister cards of investigational product must be returned to the investigator by the subject at each clinic visit and at the end of the trial.

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 investigator 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 (Allowed and Prohibited Medications) and in Appendix 4 (Prohibited Moderate or Strong CYP3A Inhibitors and Inducers) for:

- The treatment of adverse events.

- 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.

Any medications taken between last dose of IP in study B7601003 and before the first dose of study drug in study B7601017 must be documented as a prior medication. Medications taken after the first dose (Day 1) of IP in B7601017 will be documented as concomitant medications.

5.8.1. Permitted Medications for Parkinson's disease:

- Monoamine Oxidase-B (MAO-B) inhibitors or COMT inhibitors, amantadine, and anticholinergics are permitted but should remain at stable dose from 28 days prior to Day -1 (Randomization) through the end of the treatment period.

5.8.2. Prohibited Medications for Parkinson's disease:

- Direct Rollover subjects must continue to refrain from taking dopamine receptor agonist medications including pramipexole, ropinirole, rotigotine and apomorphine which were prohibited in study B7601003. Delayed Rollover Subjects must abstain from these medications for at least 60 days prior to Randomization and through the end of the treatment period.

- Direct Rollover Subjects must continue to refrain from taking istradefylline and zonisamide which are prohibited in study B7601003. Delayed Rollover Subjects must abstain from these medications for 60 days prior to Randomization and through the end of the treatment period.

- Direct Rollover Subjects must continue to refrain from the use of inhaled L-Dopa which is prohibited in study B7601003. Delayed Rollover Subjects must abstain from using inhaled L-Dopa for at least 60 days prior to Randomization and through the end of the treatment period.

- Subjects with prior implantation of apomorphine pump, or surgery for intraduodenal use of Duodopa® are not eligible.

5.8.3. Prohibited Other Concomitant Medications

The following medications continue to be prohibited for Direct Rollover Subjects and are prohibited for Delayed Rollover Subjects for at least 60 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 the Prohibited Concomitant Medication document reference tool provided as a separate document from the protocol.

- CYP3A4 inhibitors: the use of moderate or strong inhibitors of CYP3A4 is not permitted throughout the study since these may lead to increased levels of PF-06649751 with concomitant use. A list of potential CYP3A4 inhibitors is provided in Prohibited Concomitant Medication document reference tool provided as a separate document from the protocol.

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

The following medications continue to be prohibited for Direct Rollover Subjects and are prohibited for Delayed Rollover Subjects for at least 60 days prior to Randomization.

- The use of amphetamines, methylphenidate and other stimulants.

- Antipsychotics (except stable low dose quetiapine), metoclopramide, or reserpine are not permitted.

- Lithium, MAO-A/B inhibitor antidepressants (including moclobemide, tranylcypromine, 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).

5.8.4. Permitted Concomitant Medications

Subjects may use background L-Dopa (for example, Sinemet, Menesit, Madopar, Prolopa, or EC-Doparl). Subjects should remain on the same formulation(s) of L-Dopa from Screening through the duration of the study.

During the titration and Adjustment Periods (Wks 1 – 5), reduction of L-Dopa may occur at the decision of the investigator, consistent with best medical practice and only in case of intolerable dopaminergic AEs.

- For example, subjects taking L-Dopa alone or with other dopaminergic medications have reported AEs such as dyskinesia, hallucinations/psychotic-like behavior, impulse control/compulsive behaviors, and orthostatic hypotension with or without symptoms such as dizziness, nausea, syncope and sweating which may be responsive to dose reduction in L-Dopa.

After Wk 5 only, if the investigator is willing to attempt reducing the subject's L-Dopa dose to evaluate the extent to which PF-06649751 may replace L-Dopa, the investigator will be required to contact the sponsor clinical team and present the proposed dosing plan and careful monitoring for potential resulting AEs.

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 (DDI) with PF-06649751 and primary substrates of CYP3A4 (especially those with a narrow therapeutic index; eg, vinca alkaloids), and breast cancer resistant proteins (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 CYP3A4 substrates (eg, alfentanil, ergotamine, irinotecan, ticagrelor, simvastatin, etc.). Further information on potential DDI's and data available to date can be found in Section 5.2.7 Pharmacokinetic-Drug Interactions of the latest version of the Investigator'sBrochure for PF-06649751.

Allowed and Prohibited Medications are listed in Appendix 3 and Appendix 4.

6. STUDY PROCEDURES

6.1. Screening

Screening procedures will differ for Direct Rollover Subjects and Delayed Rollover Subjects, and are described below:

Screening for Direct Rollover Subjects (Wk 10 of B7601003, Day -35):

Procedures conducted during the Week 10 Visit for study B7601003 will be used as data for the Screening visit of B7601017 for Direct Rollover Subjects. Only the following additional procedures will be required for Direct Rollover Subjects at Screening:

- Obtain written Informed Consent. Consent should be collected on or before the Screening Visit.
- Review Inclusion and Exclusion criteria.
- Review and assess any ongoing and resolved non-serious and serious adverse events (AEs).
- Assess prior/concomitant medications.
- Collect Demographic information.
- Collect Medical History. *Assess resolved and ongoing AEs/SAEs for potential entry into subject medical history. Ongoing AEs will be entered in Medical History as "Ongoing condition".*
- Measure subject's temperature.

- Collect blood for the Vasculitis Laboratory Panel.
- Collect urine for a Urine Drug Screen (UDS) which tests for drugs of abuse (including tetrahydrocannabinol (THC) performed at the central lab).
- Register subject in the central randomization system (IMPALA). Subjects will be assigned unique, 8-digit number, which will be retained throughout the study.
- Request eligibility review from Sponsor.

Screening for Delayed Rollover Subjects (window Day -60 to Day -1):

Procedures conducted during the Week 15 visit for Study B7601003 will be used as data for the Screening visit of B7601017 for Delayed Rollover Subjects. Only the following additional procedures will be required for Delayed Rollover Subjects at Screening:

- Obtain written Informed Consent. Informed Consent may be obtained up to 60 days prior to Day -1 (Randomization). All Screening procedures should take place during this period (D -60 to D -1).
- Review Inclusion and Exclusion criteria.
- Review and assess any ongoing and resolved non-serious and serious adverse events (AEs).
- Assess prior/concomitant medications.
- Collect Demographic information.
- Collect Medical History. *Assess resolved and ongoing AEs/SAEs for potential entry into subject medical history. Ongoing AEs will be entered in Medical History as "Ongoing condition". For Delayed Rollover Subjects Medical History will be assessed during a short "In clinic" Screening visit to confirm no change in history post completion of B7601003.*
- Measure Weight and calculate body mass index (BMI). Height collected during the B7601003 study will be used to calculate subject's BMI in B7601017 Study.
- Perform standard supine and standing vitals heart rate (HR) and blood pressure (BP).
- Measure subject's temperature.
- Collect any additional safety laboratory samples that may be requested by Sponsor to confirm eligibility.
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS), Since Last Visit" Assessment.

- Collect blood for Vasculitis Laboratory Panel (if not intending to collect this sample at Wk 17 in Study B7601003).
- Collect urine for the Urine drug Screen (UDS) which tests drugs of abuse (including tetrahydrocannabinol (THC) performed at the central lab).
- CCI [redacted]
- Perform the Patient Health Questionnaire-8 (PHQ-8).
- Register subject in the central randomization system (IMPALA). Subjects will be assigned unique, 8-digit number, which will be retained throughout the study.
- Request eligibility review from Sponsor.

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 Wks 4 and 5, the visit window for scheduling visits will be ±3 days.
- For Wks 9-53, the visit window for scheduling visits will be ±5 days.

6.3. Randomization: Visit 1 (Day -1)

Randomization procedures will differ for Direct Rollover Subjects and Delayed Rollover Subjects, and are described below:

Randomization for Direct Rollover Subjects (Wk 15 of B7601003):

Procedures conducted during the Wk 15 visit in study B7601003 will be used as data for the Randomization visit of B7601017 for Direct Rollover Subjects. Only the following additional procedures will be required for Direct Rollover Subjects at Randomization:

- Document rollover status (Direct/Delayed) & IP reduction in prior study (Y/N).
- Review Inclusion and Exclusion criteria.
- Review and assess any ongoing and resolved adverse events (AEs).
- Assess prior/concomitant medications.
- Review/Update Medical History.
- Perform Contraception Check.

- Collect Weight and calculate body mass index (BMI). Height collected during B7601003 study will be used to calculate subjects BMI in B7601017 Study.
- Register subject as Randomized in the central randomization system (IMPALA).
- Dispense blinded IP. Subjects will begin PF-06649751 dosing the following morning (Day 1).

Randomization for Delayed Rollover Subjects:

Delayed Rollover Subjects will complete all the following procedures during Randomization:

- Document rollover status (Direct/Delayed) & IP reduction in prior study (Y/N).
- Review Inclusion and Exclusion criteria.
- Review and assess any ongoing and resolved adverse events (AEs).
- Assess prior/concomitant medications.
- Review/Update Medical History.
- Perform Contraception Check.
- Collect Weight and calculate body mass index (BMI). Height collected during B7601003 study will be used to calculate subjects BMI in B7601017 Study.
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard supine and standing vitals (HR and BP).
- Measure subject's temperature.
- Conduct full physical and neurological examination.
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS) "Since Last Visit" assessment.
- Collect blood samples for Hematology, Blood Chemistry [redacted].
- Collect Urine for Urinalysis.
- [redacted]

[redacted]

[redacted]

CCI [redacted]

- Register subject as Randomized in the central randomization system (IMPALA).
- Dispense blinded IP. Subjects will begin PF-06649751 dosing the following morning (Day 1).

6.4. Titration Period

6.4.1. Visit 2 (Day 7, Wk 1)

- Review and assess adverse events (AEs).
- Assess prior/concomitant medications.
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Measure subject's temperature.
- Perform standard supine and standing vitals (HR and BP).
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS) "Since Last Visit" assessment.
- Collect blood samples for Hematology and Blood Chemistry
- Dosing accountability verification (as described in Section 7.1.5).
- CCI [redacted]

CCI [redacted]

- Dispense IP (3 blister cards).

6.4.2. Visit 3 (Day 14, Wk 2): Telephone Visit

- Review and assess adverse events (AEs).
- Assess prior/concomitant medications.
- Dosing compliance verification via phone (as described in Section 7.1.5).
- CCI [redacted]

6.4.3. Visit 4 (Day 21, Wk 3): Telephone Visit

- Review and assess adverse events (AEs).
- Assess prior/concomitant medications.
- Dosing compliance verification via phone (as described in Section 7.1.5).
- CCI [redacted]

6.5. Dose Adjustment Period (Open Label)

6.5.1. Visit 5 (Day 28, Wk 4)

- Review and assess adverse events (AEs).
- Assess prior/concomitant medications.
- Perform Contraception Check.
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard supine and standing vitals (HR and BP).
- Measure subject's temperature.
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS), 'Since Last Visit" Assessment.
- Dosing accountability verification (as described in Section 7.1.5).
- CCI [redacted]
- CCI [redacted]
- Dispense Investigational Product.
- CCI [redacted]

6.5.2. Visit 6 (Day 35, Wk 5)

- Review and assess adverse events (AEs).
- Assess prior/concomitant medications.
- Perform Contraception Check.

- Conduct brief physical and neurological examination.
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard supine and standing vitals (HR and BP).
- Measure subject's temperature.
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS), 'Since Last Visit" Assessment.
- Collect blood samples for:
  - Hematology and Blood Chemistry (safety lab tests);
  - CCI [redacted]
  - CCI [redacted]
- CCI [redacted]
- Collect urine for Urinalysis (safety lab test).
- Dosing accountability verification (as described in Section 7.1.5).
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted].
- Dispense investigational product.

6.6. Stable Dosing Period (Open Label)

6.6.1. Visit 7 (Day 63, Wk 9): Telephone Visit

- Review and assess adverse events (AEs).

- Assess prior/concomitant medications.
- Dosing compliance verification via phone (as described in Section 7.1.5).

6.6.2. Visit 8 (Day 91, Wk 13): Telephone Visit

- Review and assess adverse events (AEs).
- Assess prior/concomitant medications.
- Dosing compliance verification via phone (as described in Section 7.1.5).
- CCI [redacted]

6.6.3. Visit 9 (Day 119, Wk 17)

- Review and assess adverse events (AEs).
- Assess prior/concomitant medications.
- Perform Contraception Check.
- Conduct brief physical and neurological examination.
- Measure Weight and calculate BMI.
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard supine and standing vitals (HR and BP).
- Measure subject's temperature.
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS) "Since Last Visit" assessment.
- Collect blood samples for:
  - Hematology and Blood Chemistry (safety laboratory tests);
  - CCI [redacted]
  - CCI [redacted]
- Collect urine for Urinalysis (safety lab test).
- Dosing accountability verification (as described in Section 7.1.5).

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Dispense Investigational Product.

6.6.4. Visit 10 (Day 175, Wk 25): Telephone Visit

- Review and assess adverse events (AEs).
- Assess prior/concomitant medications.
- Dosing compliance verification via phone (as described in Section 7.1.5).

6.6.5. Visit 11 (Day 231, Wk 33)

- Review and assess adverse events (AEs).
- Assess prior/concomitant medications.
- Perform Contraception Check.
- Conduct brief physical and neurological examination.
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard supine and standing vitals (HR and BP).
- Measure subject's temperature.
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS), 'Since Last Visit" Assessment.
- Collect blood samples for the following:
  - Hematology and Blood Chemistry (safety laboratory tests);
  - CCI [redacted]
  - CCI [redacted]

[redacted]

- Collect urine for Urinalysis (safety lab test).
- Dosing accountability verification (as described in Section 7.1.5).
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Dispense Investigational Product.

6.6.6. Visit 12 (Day 287, Wk 41): Telephone Visit

- Review and assess adverse events (AEs).
- Assess prior/concomitant medications.
- Dosing compliance verification via phone (as described in Section 7.1.5).
- CCI [redacted]

6.6.7. Visit 13 (Day 343, Wk 49/Early Termination)

- Review and assess adverse events (AEs).
- Assess prior/concomitant medications.
- Conduct full physical and neurological examination.
- Measure Weight and calculate BMI.
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard supine and standing vitals (HR and BP).
- Measure subject's temperature.
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS) "Since Last Visit" assessment.
- Collect blood samples for:
  - Hematology and Blood Chemistry (safety laboratory tests);

- CCI [redacted]
- CCI [redacted]
- Vasculitis Laboratory Panel.

- Collect urine for Urinalysis (safety lab test).
- Dosing accountability verification (as described in Section 7.1.5).
- Perform Physician Withdrawal Checklist (PWC-20).
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

6.7. Follow-Up Period

6.7.1. Visit 14 (Day 357/Wk 51)

- Review and assess adverse events (AEs).
- Assess prior/concomitant medications.
- Conduct brief physical and neurological examination.
- Perform standard supine triplicate 12-lead electrocardiogram (ECG).
- Perform standard supine and standing vitals (HR and BP).
- Measure subject's temperature.
- Perform the Columbia Suicidality Severity Rating Scale (C-SSRS) "Since Last Visit" assessment.
- Collect blood samples for Hematology and Blood Chemistry (safety laboratory tests).
- Perform Physician Withdrawal Checklist (PWC-20).

6.7.2. Visit 15 (Day 371/Wk 53): Telephone Visit

- Review and assess adverse events (AEs).
- Contraception Check.

6.8. 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.

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;
- Temperature;
- Standard supine triplicate 12-lead electrocardiogram (ECG);
- Columbia Suicidality Severity Rating Scale (C-SSRS) "Since Last Visit";
- Weight/BMI;
- Blood and/or urine specimens for safety laboratory tests;
- Vasculitis Panel;
- Blood sample for pharmacokinetic analysis;
- CCI [redacted]
- CCI [redacted];
- CCI [redacted];
- CCI [redacted];
- Physician Withdrawal Checklist (PWC-20).

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 IP 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.

Lost to follow-up:

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).

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 locally permissible 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.

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 manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

7.1. Eligibility

7.1.1. Document Rollover Status (Direct/Delayed) & IP Reduction in Prior Study (Y/N)

At randomization, the site will document the subject Rollover status, as Direct or Delayed rollover, and also document if the subject had an IP dose reduction during prior study B7601003 (Yes/No). These two criteria are critical in assigning the adequate IP titration and dose for the open label study in IMPALA, to insure subject safety as well as protect the blind for prior study B7601003.

7.1.2. Review of Inclusion/Exclusion Criteria

All inclusion and exclusion criteria must be carefully reviewed and compared against the screening and randomization data for the subject. Protocol deviations related to subject eligibility are of particular concern and may be specifically monitored by the sponsor via a Sponsor Eligibility Verification Process (Section 7.1.4).

7.1.3. 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 abuse will need to 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 Clinician(s).

Guidance on handling resolved and ongoing AEs: All resolved AEs/SAEs will be reviewed for potential entry into medical history. Ongoing AEs will be entered in Medical History as "Ongoing condition".

Medical History must be assessed at Screening for Delayed Rollover Subjects to confirm no change in history post completion of B7601003. Ongoing AEs/SAEs must be entered as Medical History.

7.1.4. Sponsor Eligibility Verification Process

Prior to randomization the sponsor (medical monitor and clinicians) will verify all critical inclusion and exclusion criteria based on screening data, request clarifications if needed and provide written authorization (eg, e-mail) to the site within 5 business days, confirming that the subject is eligible to return for Day -1 (Randomization). Full instructions on the Sponsor Eligibility Verification process will be provided as part of training. It is critical that the

sponsor be provided with all requested data in a timely fashion in advance of the planned Day -1 visit.

7.1.5. Drug Accountability Verification

Dosing accountability verification (IP accountability and documentation) will be performed while subject is present at the site or over the phone to confirm reasons for missed/additional doses. During site 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.

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 (STUDY PROCEDURES). Day -1 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.

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count (w/differential) Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN/urea and Creatinine Glucose Calcium Sodium Potassium Chloride Total CO_2 (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[a] Specific gravity Urine creatinine	Urine Drug Screen[b] <u>Vasculatis Panel:</u> Anti-neutrophil cytoplasmic antibody panel (C-ANCA and P-ANCA)[c,d] Qualitative Antinuclear antibody (ANA) [c,d] Fibrinogen [c,d] C-Reactive Protein (CRP) [c,d] Erythrocyte Sedimentation Rate (ESR) [c,d] Complement (C3, C4, and CH50/CH100) [c,d] Rheumatoid Factor [c,d] Immunoglobulin panel (IgG, IgA, and IgE) [c,d] If ANCA positive: Proteinase-3 Ab and Myeloperoxidase Ab tests
	Additional Tests (Needed if Hy's law tests are triggered)		
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT PT/INR Total bile acids Acetaminophen drug and/or protein adduct levels		

a. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.

b. UDS for drug of abuse (including THC) Must be collected at Screening for all subjects.

c. At Screening and V13 (Wk 49) or Early Termination, for all subjects.

d. The Vasculitis Panel will be performed at Screening, at V13 (Wk 49) or Early Termination, and at the discretion of the investigator for all subjects as per Section 7.2.8. If ANCA is positive or questionable, then quantitative Proteinase-3 Ab and Myeloperoxidase Ab tests will be performed by the central lab using existing specimen. Will always be completed at Early Termination visit.

- Minimum requirement for UDS includes: cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines and amphetamines.

- Subjects may undergo random UDS at the discretion of the investigator. UDS conducted prior to dosing must be negative for subjects to receive IP.

7.2.2. Pregnancy Testing

Females of childbearing potential are excluded from the study.

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 and musculoskeletal 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.

All items of the Neurological Examinations must be performed as listed in the case report form. Specifically, the full neurological examination must include assessment of the visual fields and of the right and left optic fundus; cranial nerves; mental state; muscle strength and 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 performed and recorded on the source documents, which will be monitored at the clinical study site. Abnormal neurological examination results deemed to be clinically significant and occurring after Day -1 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. Vitals should be collected first while the subject is in the supine position and then in the standing position. 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 BP measurements.

Subject temperature must also be assessed at all in-clinic visits, except at Randomization for Direct Rollover Subjects.

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.

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 ≥20 mmHg for systolic blood pressure or ≥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 (≥30 beats per minute (BPM).

7.2.6. Electrocardiogram

Electrocardiograms (ECGs) are 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 at Randomization (Wk 15 in the B7601003 study) 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 (≥45 msec from the baseline; or is ≥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 (≥45 msec from the baseline; or is ≥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 ≥500 msec (or ≥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. Physician Withdrawal Checklist (PWC-20)

The PWC-20 is collected at times specified in the STUDY PROCEDURES section of this protocol. 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 subjects 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.[14]

7.2.8. Vasculitis Panel

The Vasculitis Panel is collected at times specified in the STUDY PROCEDURES section of this protocol. 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).

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7.5. Assessment of Suicidal Ideation and Behavior

7.5.1. 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.[18] The "Since last visit" version will be used for all time points for all Subjects.

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 may be administered at any time in the study at the discretion of the investigator based on reasonable concern.

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

randomization 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.

Subjects who respond "YES" to items 4, 5 of the C-SSRS at any time after the randomization visit will undergo a Suicidality Risk Assessment by clinician/MHP to determine whether it is safe for the subject to continue in the trial. Depending on the specifics (ie more than one such occurrence, social situation) of the subject as assessed by the investigator and/or clinician/MHP, the subject may be discontinued from the trial.

7.5.2. 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 for Delayed Rollover Subjects. The following criterion will lead to exclusion of the subject:

- PHQ-8 total score ≥15.

7.5.3. Other Procedures

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[redacted]

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[redacted]

CCI [redacted]

7.6. Rater Qualifications

Qualified individuals who have been previously certified and/or trained through the Pfizer rater qualification program in the B7601003 study will complete refresher training prior to conducting any relevant assessments in the B7601017 trial. For all new raters, please see below for further details:

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 additional 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. 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. Recertification may be required at periodic intervals during 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.

Although not required, every effort should be made to have the same certified rater perform the ratings for an individual subject throughout the course of the study. CCI [redacted]

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

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

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and 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 Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious 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.

8.1.1. Additional Details On Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Subject Withdrawal section)

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

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product.

For subjects who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety 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 must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

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.

8.1.5. 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 on the CRF, 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. 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, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. 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.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study 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 signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;

- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- 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 any protocol-specified 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 recording as an AE.

8.2.3. 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.

Or that is considered to be:

- An important medical event.

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.

8.2.4. 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 is 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 a 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 randomization 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 SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

If required on the AE page of the CRF, 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.

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.4.2. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject’s individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For subjects with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

- Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN or if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The subject should return to the investigator 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 and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a co-formulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (LFT) abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.3.1. Exposure During Pregnancy

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

- 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).
- 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 subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT 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) to Pfizer Safety 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 Safety 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 pre-procedure 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 to Pfizer Safety 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 sponsor. 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 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.

8.4.3.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.3.3. 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 Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.4.4. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

8.4.4.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- 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.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

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

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

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9.2. Endpoint Analysis

9.2.1. Analysis of the Primary Endpoint (Safety and Tolerability)

The primary study objective is to examine the long-term safety and tolerability of PF-06649751 administered once daily in subjects with PD. The primary analysis of long-term safety will be focused on the following endpoints:

- Adverse events.

- Physical and neurological exam findings.
- Clinical laboratory parameters.
- Vital signs.
- Electrocardiogram (ECG) parameters.
- Columbia Suicidality Severity Rating Scale (C-SSRS).
- Physician Withdrawal Checklist (PWC-20).

Adverse events will be coded for analysis with the medical dictionary for regulatory affairs (MedDRA®), and the number and percent of subjects reporting each event will be summarized. Descriptive statistics will be displayed to provide an overview of the safety results. For categorical parameters, these consist of the number and percent of subjects in each category. The denominator for percentages will be based on the number of subjects appropriate for the purpose of analysis. For continuous parameters, descriptive statistics includes n, mean, standard deviation (SD), median, minimum, and maximum. Subjects who prematurely discontinued the trial will be evaluated on the basis of data collected at each visit attended.

Further information about the safety analysis can be found in Section 9.3.

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9.3. Safety Analysis

The safety analysis set will include all subjects who received at least 1 dose of study medication during the study period (titration, dosing adjustment or stable dosing periods).

Adverse events, ECGs, blood pressure, pulse rate, C-SSRS, 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, 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.

9.4. Interim Analysis

No formal interim analysis will be conducted for this study. However, as this is an open label extension study, the sponsor may conduct blinded and/or unblinded reviews of the data during the open label course of the study (including the rBA sub-study) for the purpose of safety assessment, facilitating pharmacokinetic (PK)/pharmacodynamic (PD) modeling, and/or to support clinical development.

9.5. Data Monitoring Committee

This study will use a program-level external data monitoring committee (E-DMC).

The E-DMC will be responsible for ongoing monitoring of the safety and/or efficacy of subjects in the study according to the charter. The recommendations made by the E-DMC 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 investigator site may be subject to review by the IRB/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 investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator 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 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 or the physician subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/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 (EC)

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 the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

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 numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. The investigator 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 and any subject recruitment materials 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 and any subject recruitment materials must be reviewed and approved by Pfizer, 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. 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 regulatory 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

Randomization for B7601017 will stop 60 days after the last subject last visit (LSLV) for B7601003 has occurred.

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. 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.

For this study, the End of trial in European Union (EU) Member States is defined as Last Subject Last Visit (LSLV) based on the total of randomized subjects in accordance with the protocol.

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, 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 (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or 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

Pfizer posts clinical trial US Basic Results on 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 (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD 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 pre-specified 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 PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

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 for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, 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 it is 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 investigator sites, and that any subsequent publications by the PI 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.

16. REFERENCES

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Appendix 1. Abbreviations

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

Abbreviation	Term
ADR	Adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{0-12}	area under the concentration-time curve from time 0 to 12 hours
BCRP	Breast cancer resistant protein
BMI	Body mass index
BP	Blood pressure
BPM	Beats per minute
cAMP	cyclical adenosine monophosphate
C_{eff}	efficacious concentration
CK	creatine kinase
C_{max}	Steady state maximum plasma concentration
CNS	central nervous system
COMT	Catechol-O methyltransferase
CRF	case report form
CSA	clinical study agreement
CSF	cerebrospinal fluid
CSSR-S	Columbia Suicidality Severity Rating Scale
CSR	clinical study report
CT	Clinical trial
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Pre-dose plasma PF-06649751 concentrations
DDI	Drug-drug interaction
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dispensable unit
EBR	Eye blink rate
EC	ethics committee
ECG	electrocardiogram
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EEG	electroencephalography
CCI [redacted]	[redacted]
EU	European Union
EudraCT	European Clinical Trials Database
FIH	First in human

Abbreviation	Term
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HAM-A	Hamilton Anxiety Rating Scale
HDPE	High Density Polyethylene
hERG	Human ether-a-go-go-related gene
HIV	human immunodeficiency virus
HPD	hours post dose
hr	hour
HR	Heart rate
HRQL	health-related quality of life
HY	Hoehn & Yahr
IB	Investigator Brochure
ICH	International Conference on Harmonisation
ID	identification
IMPALA	centralized randomization system
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IR	Immediate release
IRB	institutional review board
IRC	internal review committee
IUD	intrauterine device
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
Ki	inhibition constant
L-Dopa	Levodopa
LFT	liver function test
LID	Levodopa induced dyskinesia
LMA	Locomotor activity
LSLV	last subject last visit
MAO-B	Monoamine Oxidase – B
CCI [redacted]	[redacted]
MedDRA	Medical dictionary for regulatory affairs
MHP	Mental health professional
MnB	meningitidis serogroup B
MPTP	1-methyl-4-phenyl-1 2, 3, 6-tetrahydropyridine
MW	molecular weight
N/A	not applicable
NDA	new drug application
NOAEL	No observed adverse event limit
PCD	primary completion date
PD	Pharmacodynamics(s)

Abbreviation	Term
PET	Positron emission tomography
PFS	prefilled syringe
CCI	[redacted]
PGx	Pharmacogenomics(s)
PHQ-8	Patient Health Questionnaire-8
PI	principal investigator
PK	pharmacokinetic
PT	prothrombin time
PWC-20	Physician Withdrawal Checklist – 20
QD	"quaque die", once per day
qEEG	Quantitative electroencephelography
QTcF	corrected QT (Fridericia correction)
rBA	Relative bioavailability
REM	Rapid eye movement
RNA	ribonucleic acid
RO	Receptor occupancy
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SGOT	serum glutamic oxaloacetic transminase
SGPT	serum glutamic pyruvic transminase
SOA	Schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
SWS	Slow wave sleep
TBili	total bilirubin
TG	Therapeutic group
THC	Tetrahydrocannabinol
T_{max}	Time for C_{max}
TMB	trimethobenzamide
UDS	urine drug screen
ULN	upper limit of normal
US	United States
Wk	Week

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Appendix 3. Permitted/Prohibited Concomitant Medications

Use Category	Type of Medication	Guidance
Permitted	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[1]
	Hypnotics, sedatives, anxiolytics	Stable low doses of benzodiazepines are permitted. Planned prescription of benzodiazepines "prn" use throughout the study should be discussed with the medical monitor/Pfizer Clinician. For insomnia, non-benzodiazepine hypnotics are permitted.
	Monoaminooxidase B (MAO-B) inhibitors	Permitted if at a stable dose for at least 60 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 60 days prior to Randomization.
	Antidepressants except MAO-A/B inhibitor antidepressants	Permitted if subject is taking a stable dose at least 60 days prior to Randomization.
	Anticholinergics	Permitted if at a stable dose for at least 60 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 60 days prior to Randomization. No dose changes should be anticipated for the duration of the study.
Prohibited	Dopamine receptor agonist medications including pramipexole, ropinirole, rotigotine and apomorphine	Prohibited for at least 60 days prior to Randomization and through the study.
	Istradefylline and zonisamide	Prohibited for at least 60 days prior to Randomization and through the study.
	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 (i.e.gabapentin or pregabalin).
	Lithium, MAO-A/B inhibitor antidepressants (including moclobemide, tranylcypromine, and phenelzine)	Prohibited for at least 60 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/clinician.
	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 60 days prior to Randomization
	Marijuana	Prohibited from Screening through the end of the study.

1. Investigator to discuss with sponsor as needed.

Appendix 4. Prohibited Moderate or Strong CYP3A Inhibitors and Inducers

(non-exhaustive list)

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

[1] Not a marketed drug.

Appendix 5. Country-Specific Appendix – (Text Required for France)

The following supplementary text should be read in conjunction with the B7601017 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.