Protocol B7601017

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

Statistical Analysis Plan
(SAP)

Version: 1

Date: 28 July 2017

[redacted]

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APPENDICES

1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study B7601017 is based on Final Protocol Amendment 1, 31 March 2017.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Initial version.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study B7601017. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

Text taken directly from the protocol is *italicized.*

PF-06649751 is a highly selective dopamine D1/D5 receptor partial agonist being evaluated for the symptomatic treatment of PD (Parkinson's disease)*. In PD, motor function can be pharmacologically rescued with activation of either or both D1R-containing direct and D2R-containing indirect striatal output pathways. 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.*

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 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 SAP Section 2.2.2 *Table 2* and Section 2.2.2 *Table 3. 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.

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.

This study is designed to evaluate the safety and tolerability of PF-06649751 in subjects with PD.

2.1. Study Objectives

2.1.1. Primary Objective

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

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- CCI [redacted]

2.2. Study Design

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 Wk15 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 (See Section 2.2.1.1).

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 2.2.1.2.

Carefully review the conditions for the "Exceptional Circumstance" Exception in Section 2.2.1.

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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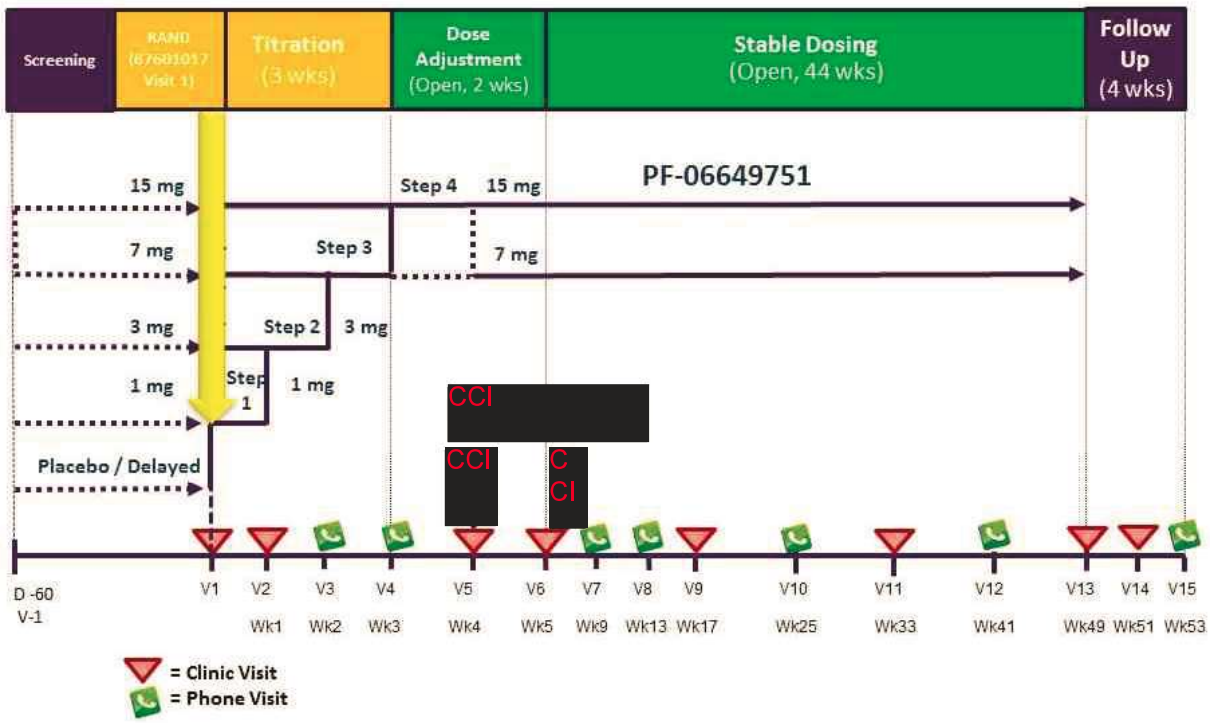
The study design is illustrated in the figure below. For details on the dosing during the titration phase, see Section 2.2.2.

Figure 1. B7601017 Study Schematic



2.2.1. *Screening/Randomization*

Subjects who are eligible may fall into one of two groups: Direct Rollover Subjects and Delayed Rollover Subjects, as defined in 2.2.1.1 and 2.2.1.2, 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.

2.2.1.1. *Direct Rollover Subject*

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 2).

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 2.

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 2. 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*

2.2.1.2. *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 2.2.1).

Subjects who were down-titrated to 7 mg QD during study B7601003 will follow the treatment protocol (see Table 3).

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 3). Delayed Rollover Subjects will enter a 3-week titration of PF-06649751 starting from 1 mg QD (Table 3). 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 3. Subjects who cannot tolerate 7 mg QD will be discontinued.

Table 3. 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*

2.2.2. *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).

2.2.3. *Open Label Period*

2.2.3.1. *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.

2.2.3.2. *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 Protocol *Section 5.8, Concomitant Treatment(s) and Protocol Appendix 3 and* Protocol *Appendix 4.*

2.2.3.3. *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 Protocol Section *Subject Withdrawal*.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

Adverse events, ECGs, Vital Signs, C-SSRS, PWC-20, physical and neurological exam data, and safety laboratory data are the primary endpoints for this safety and tolerability study.

3.1.1. Adverse Events

An adverse event is considered treatment emergent relative to a given treatment if:

- the event occurs for the first time during the effective duration of treatment and was not seen prior to the start of treatment (for example, during the baseline or run-in period), or
- the event was seen prior to the start of treatment but increased in severity during treatment.

The effective duration of treatment is determined by the lag time. Any event occurring within the lag time, whether this occurs during a break in treatment or at the end of treatment, is attributed to the corresponding treatment period. An infinite lag will be used for the study.

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers (See Section 6.1.1).

Tier-1 events: These are pre-specified events of clinical importance and are maintained in a list in the product's Safety Review Plan (no Target Medical Events {TMEs} have been defined at this point in time)

Tier-2 events: These are events that are not tier-1 but are "common". A MedDRA PT is defined as a Tier-2 event if there is at least a frequency ≥1% in any treatment group.

Tier-3 events: These are events that are neither Tier-1 nor Tier-2 events. Pfizer standard safety output where all AEs will be included (ie, no new outputs).

3.1.2. Laboratory Data

Safety laboratory tests will be performed at times defined in the Study Procedures section of this protocol. CCI [redacted]. The Data Blinding Plan will provide details.

Refer to Section 3.4 for the baseline definition.

Determine if there are any laboratory data abnormalities of potential clinical concern as defined in Pfizer Data Standards.

3.1.3. Vital Signs (Blood Pressure, Pulse Rate and Temperature)

Blood pressure and pulse rate will be measured at times specified in the STUDY PROCEDURES section of this protocol. Subject temperature must also be assessed at all in-clinic visits, except at Randomization for Direct Rollover Subjects. 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.

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.

Refer to Section 3.4 for the baseline definition.

Determine if there is any blood pressure or pulse rate data abnormalities of potential clinical concern as defined in Pfizer Data Standards.

3.1.4. Electrocardiogram (ECG)

Electrocardiograms (ECGs) are collected at times specified in the STUDY PROCEDURES section of this protocol.

The average of the triplicate readings collected at each assessment time will be calculated prior to analyzing each ECG parameter. If more than three readings are collected at one triplicate ECG assessment time, average across all readings will be calculated. If any of the three individual ECG tracings has a QTc value ≥500 msec, but the mean of the triplicates is not ≥500 msec, the data from the subject's individual tracing will be described in a safety section of the study report in order to place the ≥500 msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are ≥500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also ≥500 msec. The mean measurement is reported.

Refer to Section 3.4 for the baseline definition. Baseline will be the average of the triplicate ECG measurements. Change and percent change from baseline will be calculated at each time point for each ECG parameter.

If not supplied, QTcF will be derived using Fridericia's heart rate correction formula:

$$QTcF = QT / (RR)^{1/3} \qquad \text{where RR = 60 bpm/HR (if not provided)}$$

If QTcB is collected, then it should be listed only.

Determine if there are any ECG data abnormalities of potential clinical concern as defined in Pfizer Data Standards.

3.1.5. Physical Examination

Physical Examination will be measured at times specified in the STUDY PROCEDURES section of the protocol.

3.1.6. Neurological Examination

Neurological Examination will be measured at times specified in the STUDY PROCEDURES section of the protocol.

3.1.7. 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. 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.

C-SSRS responses will be mapped to the Columbia Classification Algorithm of Suicide Assessment (C-CASA).

Table 4. C-SSRS Mapped to C-CASA - Suicidality Events and Codes

C-CASA Event Code	C-CASA Event	C-SSRS Response
1	Completed suicide	As captured in the safety database
2	Suicide attempt	"Yes" on "Actual Attempt"
3	Preparatory acts towards imminent suicidal behavior	"Yes" on any of the following: 1. "Aborted attempt", or 2. "Interrupted attempt", or 3. "Preparatory Acts or Behavior"
4	Suicidal ideation	"Yes" on any of the following: ➢ "Wish to be dead", or ➢ "Non-Specific Active Suicidal Thoughts", or ➢ "Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act", or ➢ "Active Suicidal Ideation with Some Intent to Act, without Specific Plan", or ➢ "Active Suicidal Ideation with Specific Plan and Intent"
7	Self-injurious behavior, no suicidal intent	"Yes" on "Has subject engaged in Non-suicidal Self-Injurious Behavior?"

The following 3 endpoints are key endpoints for suicidality data analysis and evaluation:

- Suicidal Behavior;
- Suicidal Ideation;
- Suicidal Behavior or Ideation.

Suicidal behavior: A subject is said to have suicidal behavior if the subject has experienced any of the following events (C-CASA event codes 1-3):

- Completed suicide;
- Suicide attempt; or
- Preparatory acts toward imminent suicidal behavior.

Suicidal ideation: Any observed suicidal ideation maps to a single C-CASA category. Depending on the scale used, more granularity of observed ideation (sub-categories of C-CASA category 4) may be displayed. The C-SSRS, for example, includes five ideation questions (that map to C-CASA category 4) with increasing severity.

Subjects with new onset suicidality: A subject will be considered to have a new onset of suicidality if the subject reported no ideation and no behavior at the baseline assessment (note that self-injurious behavior, no suicidal intent [C-CASA code 7] is not considered to be suicidal ideation or behavior) and reported any behavior or ideation post-baseline. Data observed at screening is not considered in the definition of new onset.

Subjects with worsening suicidality relative to baseline: A subject will be considered to have a worsening of suicidality if the subject moved to a lower numbered C-CASA category (observed in categories 1-4) than was reported at baseline. Movement within C-CASA categories 5-9 would not be considered worsening. In addition, worsening will be considered within the suicide ideation C-CASA category 4 if there is an increase in severity identified in the C-SSRS which captures additional granularity on suicide ideation. A subject who reports only ideation at baseline and who reports any behavior post-baseline is considered to have worsened. Data observed at screening is not considered in the definition of worsening.

Table 5. shows examples of new onset suicidality and worsening suicidality for C-SSRS after mapping to C-CASA.

Table 5. C-SSRS Mapped to C-CASA – Examples of Worsening/New Onset

New Onset		Worsening	
Baseline	**Any post-baseline (or by visit)**	**Baseline**	**Any post-baseline (or by visit)**
No ideation and no behavior	C-CASA code=4 (any ideation) or C-CASA code=1, 2, or 3 (any behavior)	Only C-CASA code=4 (Ideation only)	C-CASA code=3, 2, or 1 (any behavior)
		Lowest C-CASA code=4	C-CASA code=3, 2, or 1 (any behavior)
		Lowest C-CASA code=3	C-CASA code=2, or 1
		Lowest C-CASA code=2	C-CASA code=1

With the C-SSRS, worsening may also be observed within suicidal ideation. In this case, the order of suicidal ideations with increasing worsening is as follows: wish to be dead, non-specific active suicidal thoughts, active suicidal ideation with any methods (not plan) without intent to act, active suicidal ideation with some intent to act, without specific plan, and active suicidal ideation with specific plan and intent. All of these values will be considered worsening for reporting.

3.1.8. 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. The PWC-20 is collected after the completion of study treatment and also at the first visit of follow-up.

Determine the number of subjects with each symptom present (eg, mild or higher severity) and categorize each subject by severity (eg, mild, moderate, and severe). Only non-missing items are considered in summary presentations, and will establish the denominator.

The total PWC-20 score is the sum of 20 item-scores and ranges between 0 and 60. The higher score indicates more frequent/severe symptoms. If more than 5 of the 20 individual items are missing then the total PWC-20 score will be set to missing, otherwise, the total PWC-20 score will be imputed as follows: sum of the non-missing item scores X (total number of items)/ (number of items non-missing).

3.2. Secondary Endpoint(s)

Not applicable.

3.3. Other Endpoints

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CCI

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CCI

[redacted]

CCI

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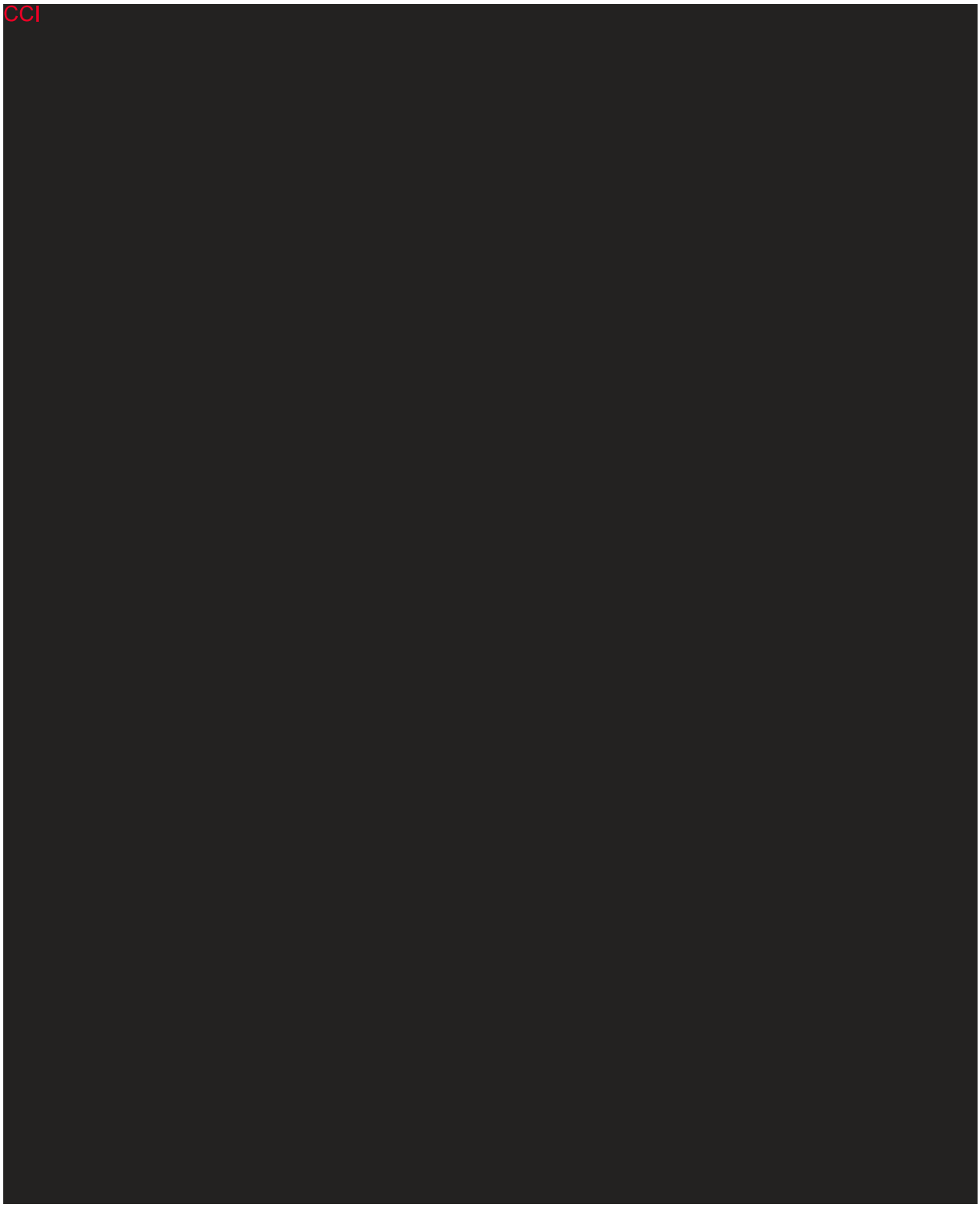
CCI

CCI



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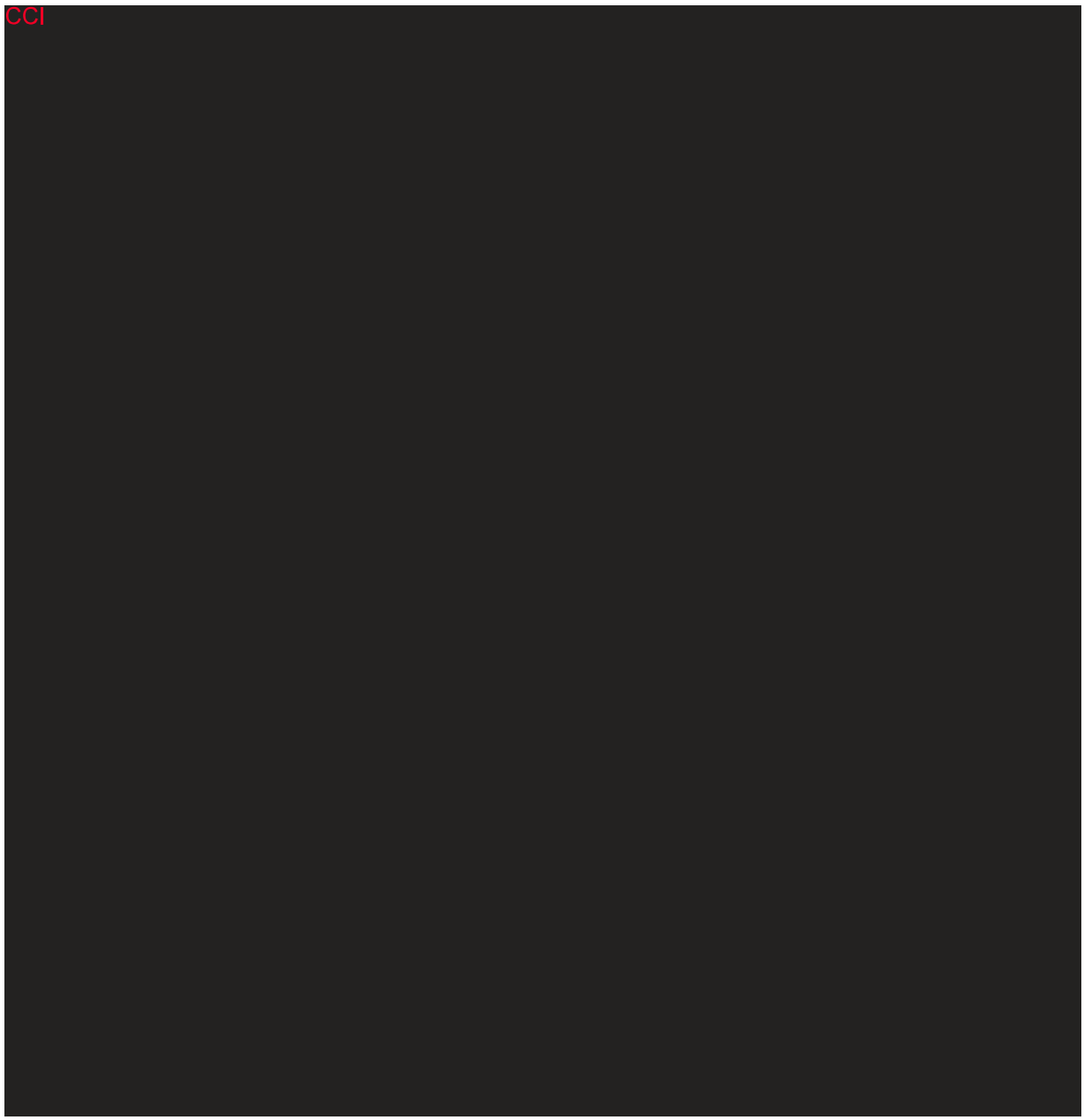

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3.4. Baseline Variables

Baseline for the primary and exploratory endpoints will be defined in two ways. Given the delayed rollover subjects are essentially starting over, it was deemed important to also look at the B7601017 baseline along with the baseline from the efficacy study (B7601003).

1. B7601017 Randomization/Day -1: For delayed rollover subjects this is data captured at this visit in this study B7601017, and for the direct rollover subjects this is data captured at B7601003 Week 15.

2. B7601003 Randomization/Day 0: All rollover subjects came from the B7601003 parent study.

If a subject is missing Baseline, the last prior measurement will be used.

Baseline variables include

- Demographics, medical history, prior medication, MMSE Total Score, Hoehn & Yahr Stage while the subject is ON (if applicable), Primary diagnosis and duration, Prescribed L-Dopa dose and Background concomitant Parkinson's Disease medications (ATC level classification and a combination of the different classifications)

    - Data for delayed rollover subjects will be attained from B7601017 screening period and data for the direct rollover subjects from B7601003 screening period.

- CCI [redacted]

[redacted]

- Defined in points 1 and 2 above.

These data will be summarized as part of the baseline characteristics.

The sponsor or designee may verify critical elements of the screening and enrollment process and, in cases where verification is required, will provide written authorization (eg, e-mail) concurring with the investigator assessment that the subject is eligible to return for Day -1 assessments. Eligibility may also be documented via telephone authorization followed by written confirmation. The key elements to be reviewed by the sponsor may include Parkinson's disease diagnosis, MDS-UPDRS scores, medical history, concomitant medications, and select screening safety assessments including labs, ECGs, and vital signs.

Concomitant and prior medications will be coded using the WHO-drug coding dictionary. In addition, concomitant and prior non-drug treatments/procedures will also be coded using the MedDRA coding dictionary.

3.5. Safety Endpoints

All safety endpoints have been described as Primary Endpoints (See Section 3.1).

4. ANALYSIS SETS

Data for all subjects will be assessed to determine if subjects meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

4.1. Full Analysis Set

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). The safety analysis set is the primary population for the study, treatment administration/compliance and safety.

All subjects who receive at least one dose of study medication will be classified according to the actual study treatment received. A randomized but not treated subject will be excluded from the safety analyses. A treated but not randomized subject or a randomized but took incorrect treatment subject will be reported under the treatment actually received.

4.2. Per Protocol Analysis Set

Not applicable

4.3. Safety Analysis Set

The safety analysis set is described under the FAS (See Section 4.1).

4.4. Other Analysis Sets

4.4.1. PK Concentration Analysis Set

The PF-06649751 PK concentration analysis set is defined as all subjects treated who have at least 1 concentration of interest.

A treated but not randomized subject or a randomized but took incorrect treatment subject will be reported under the treatment actually received.

4.4.2. Intent-to-Treat (ITT) Analysis Set

The dataset used in the efficacy analyses will be the Intent-to-Treat (ITT) population, consisting of all subjects randomized who receive at least 1 post-dose efficacy measurement. The ITT analysis set is the population for efficacy.

All subjects who receive at least 1 post-dose efficacy measurement will be classified according to their randomized treatment assignment. Randomized but took incorrect treatment subjects and randomized but not treated subjects will be reported under their randomized treatment group for all efficacy analyses. Treated but not randomized subjects will be excluded from the efficacy analyses since randomized treatment is missing.

5. GENERAL METHODOLOGY AND CONVENTIONS

The blind for the study will be broken and the final analysis of the study data will be conducted once the last remaining subject has completed the study or is withdrawn from the study prior to completion, all data have been entered into the database, all data issues resolved, the per protocol population has been determined, and the database has been locked.

5.1. Hypotheses and Decision Rules

There are no formal statistical hypotheses in this study.

5.2. General Methods

Descriptive summaries for the safety, exploratory, baseline, and other endpoints will be displayed as follows.

<u>B7601017 Baseline (according to B7601003 randomized group or dose at the end of B7601003 study):</u>

<u>Safety</u>

- Placebo (direct randomized group + all delayed rollover);
- PF-06649751 1 mg (direct randomized group);
- PF-06649751 3 mg (direct randomized group);
- PF-06649751 7 mg (direct randomized group);
- PF-06649751 15 mg (direct randomized group);
- PF-06649751 15-15 mg (direct randomized group + B7601003 final dose).
- PF-06649751 15-7 mg (direct randomized group + B7601003 final dose).

Efficacy

- Placebo (direct randomized group + all delayed rollover);
- PF-06649751 1 mg (direct randomized group);
- PF-06649751 3 mg (direct randomized group);
- PF-06649751 7 mg (direct randomized group);
- PF-06649751 15 mg (direct randomized group);

B7601003 Baseline (according to B7601003 randomized group or dose at the end of B7601003 study):

- Same as the B7601017 Baseline above.

5.2.1. Analyses for Binary Data

Analyses for any binary data output will show the number and percentage of subjects in each response category, and the response rate and its 90% confidence interval (CI) will be calculated. The confidence interval of the response rate will be calculated based on a normal approximation method.

5.2.2. Analyses for Continuous Data

Descriptive statistics n, mean, median, standard deviation, minimum, and maximum and 90% CI be used to summarize the endpoints.

5.2.3. Analyses for Categorical Data

Categorical data CCI [redacted] will show the number and percentage of subjects for each category and include mean/median descriptive statistics similar to the continuous data (See Section 5.2.2).

5.3. Methods to Manage Missing Data

For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied (eg, partial dates for AEs and concomitant medications will be imputed according to CCI [redacted]

CCI [redacted]

For scales used in this study, scores will be imputed according to the imputation rules and algorithms for missing component scores that are provided in the data standard documents, or scale documentation. Details are included for each endpoint in Section 3.

Efficacy endpoint analyses in this study will be primarily based on observed cases (OC) and missing data will not be imputed, except for L-Dopa reduction binary and ordinal categorical analyses, in which case last observation carried forward (LOCF) will be utilized.

Efficacy and safety analyses will be based on nominal visits as recorded on the CRFs. The only exception will be the early termination (ET) visit if a subject terminates before completion of Week 49. If the subject terminates before Week 49, the data collected at the early termination visit will be assigned to the closest planned office visit (target day) for that efficacy or safety assessment. If the early termination visit is equidistant to 2 visits, it will be assigned to the later visit. If the early termination visit is associated with a visit that already exists, the non ET visit will be the representative visit. However, for purposes of LOCF, if more than one value is in a visit window the latter value will be used to carry forward. For all safety categorical determinations, early termination visits are considered even if they are not assigned to a visit.

Concentrations below the limit of quantification

In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. (In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification).

Deviations, missing concentrations and anomalous values

In summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

1. A concentration has been collected as ND (ie, not done) or NS (ie, no sample);
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

6. ANALYSES AND SUMMARIES

The primary analysis of long-term safety will be focused on the safety endpoints.

6.1. Primary Endpoint(s)

6.1.1. Adverse Events

Adverse events will be listed and summarized in accordance with the Pfizer Data Standards.

The details of Tier-1, Tier-2 and Tier-3 AEs are described in Section 3.1.1.

The Tier-1, Tier-2 and Tier-3 adverse events will be described as part of the standard overall AE summary.

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an adverse event or a group of adverse events. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is generally considered as an exploratory analysis and its purpose is to generate hypotheses for further investigation. The 3-tier approach facilitates this exploratory analysis.

6.1.2. Laboratory Data

Laboratory data will be listed and summarized in accordance with the Pfizer Data Standards.

Incidence of laboratory test abnormalities will be summarized.

6.1.3. Vital Signs (Blood Pressure, Pulse Rate and Temperature)

For each planned time point, baseline values and change from baseline values will be summarized with descriptive statistics (using Pfizer Data Standards).

Maximum decrease and increase values and changes from baseline for vital signs (for supine and standing) will also be summarized descriptively using categories as defined in the Pfizer Data Standards. Numbers and percentages of subjects meeting the categorical criteria will be provided. All planned and unplanned post-dose time points will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

Vital signs collected at additional positions will be listed only.

The following non-standard safety tables will be included:

- A summary of postural change from supine to standing systolic and diastolic blood pressures
- Incidence of subjects with orthostatic hypotension (defined in Section 3.1.3 above), for each visit, last visit and any post-baseline incidence or orthostatic hypotension or minimum absolute change in postural blood pressure.

6.1.4. Electrocardiogram

For each planned time point, baseline values, absolute values and change from baseline values will be summarized with descriptive statistics for each ECG parameter (using Pfizer Data Standards).

A plot of QTcF versus plasma concentration will be generated at nominal time points. Maximum decrease and increase values and changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, PR interval and QRS interval will be summarized by time post dose using Pfizer Data Standards.

The number (%) of subjects with maximum post dose QTc values and maximum increases from baseline in the following categories will be tabulated:

Table 6. Safety QTcF[1]

	Borderline (msec)	Prolonged (msec)
Absolute Value	≥450 - <480	≥480
Absolute Change	30-<60	≥60

In addition, the number of subjects with corrected and uncorrected QT values ≥500 msec will be summarized.

ECG endpoints and changes from baseline (QTcF, PR, QRS) will also be summarized descriptively using categories as defined in Pfizer Data Standards (for QTc, these correspond to ICH E14). Numbers and percentages of subjects meeting the categorical criteria will be provided. All planned and unplanned post dose time points will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

6.1.5. Physical Examination

Physical examination data will be presented in accordance with the Pfizer Data Standards.

6.1.6. Neurological Examination

Neurological examination data will be presented in accordance with the Pfizer Data Standards.

6.1.7. Columbia Suicide Severity Rating Scale (C-SSRS)

In general, the denominator used in the percentages will be the number of subjects assessed for suicidality or worsening, the denominator would include the subset of subjects who had any level of suicidality reported at baseline. For new onset, the denominator would include the subset of subjects with no suicidality reported at baseline.

A subject listing of C-CASA categories as well as the underlying C-SSRS scale data will be presented.

In addition, a summary table with the number and percent of subjects within each C-CASA category at screening, baseline, and at any time post-baseline without regard to baseline will be reported.

6.1.8. Physician Withdrawal Checklist (PWC-20)

Summaries of the count and percentage of patients experiencing each symptom and severity listed in the PWC-20 will be provided. Follow the PDS used for reporting incidence and severity of Adverse Events.
The Total PWC-20 score will be presented using continuous summary statistics for the raw data.

6.2. Other Endpoint(s)

CCI [redacted]

CCI [redacted]

CCI [redacted]

- CCI
-
-

CCI

CCI

Figures

- None

CCI

CCI

Figures

None

CCI

Figures

None

CCI

CCI

[redacted]

Figures

None

CCI

[redacted]

6.3. Baseline and Other Summaries and Analyses

6.3.1. Study Conduct and Subject Disposition

Data will be reported in accordance with Pfizer Data Standards.

The number of subjects by region and country will be displayed.

6.3.2. Baseline Summaries

A breakdown of demographic data will be provided for age, race, weight, body mass index, height, and temperature. Each parameter will be summarized with tables and listings presented in accordance with the Pfizer Data Standards. Use geriatric age categories for the demographic summaries (<65, 65-74, 75-84, and ≥85). Physical Measurements at Baseline will include weight, height, BMI, and temperature.

Also, medical history and primary diagnosis will be tabulated and listed in in accordance with the Pfizer Data Standards.

Females of childbearing potential are excluded from the study. Information will be captured in the listings only.

The following baseline characteristics will be summarized:

- CCI [redacted]
- CCI [redacted]
- ESS Total Score
- MMSE Total Score (continuous data)
- Hoehn & Yahr Stage while the subject is ON (categorical data)
- CCI [redacted] at Baseline (continuous data)
- Prescribed CCI [redacted] (continuous data)
- Number of Background concomitant Parkinson's Disease medications @ Randomization (categorical)

6.3.3. Study Treatment Exposure

Duration of exposure will be presented in tables and listings in accordance with the Pfizer Data Standards. Exposure will consider information in only B7601017 and combined B7601003/B7601017.

Compliance for the blister packs through Day 35 will be calculated and summarized across the whole titration/dose adjustment periods, and by visit. Compliance will be based on the blister pack dosing record, and calculated as:

%Compliance = 100 x (Actual # of Capsules Taken) / (Total # Capsules Prescribed)

Compliance for the Stable Dosing Period will be calculated and summarized across the whole period, and by visit. Compliance will be based on the oral dosing log record, and calculated as:

%Compliance = 100 x (Actual # of Dosing Days) / (Planned # of Dosing Days)

6.3.4. Concomitant Medications and Non-Drug Treatments

All prior and concomitant medication(s) as well as non-drug treatment(s) will be provided in tables and listings in accordance with the Pfizer Data Standards. Concomitant Parkinson 's disease medication(s) use will also be summarized.

Frequency and type of medication will be summarized categorically and descriptive statistics of doses of background antipsychotic medication will also be summarized.

The number and percentage of subjects with a change in their background PD medications will be summarized as categorical data.

6.4. Safety Summaries and Analyses

The safety summaries and analyses are described under the Primary Endpoints (See Section 6.1).

7. INTERIM ANALYSES

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 for the purpose of safety assessment, facilitating pharmacokinetic (PK)/pharmacodynamic (PD) modeling, and/or to support clinical development.

8. REFERENCES

1. ICH E14 - The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. CHMP/ICH/2/04.

2. Goetz, et al. Handling Missing Values in the MDS-UPDRS. Movement Disorders (2015).

9. APPENDICES

Appendix 1. DATA SET DESCRIPTIONS

The [redacted] calculations will need to utilize the Index value Calculator ([redacted] Crosswalk_Index_Value_Calculator and table lookup.xls) and the respective user guide ([redacted]_UserGuide_2015.pdf).

CCI

[redacted]