Statistical Analysis Plan

Protocol A8241022

AN OPEN LABEL EXTENSION STUDY TO INVESTIGATE THE LONG TERM SAFETY, TOLERABILITY AND EFFICACY OF PF-02545920 IN SUBJECTS WITH HUNTINGTON'S DISEASE WHO PREVIOUSLY COMPLETED STUDY A8241021

Statistical Analysis Plan
(SAP)

Version: 4.0

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APPENDICES

1. AMENDMENTS FROM PREVIOUS VERSION(S)

Version 3 is amended from version 2 to include the following:

Change	Date	Section(s) Affected	Statistician
Updated the FAS definition	Feb. 15, 2017	Section 5.1	PPD
Added the improvement directions for efficacy endpoints	Feb. 15, 2017	Section 6.8	PPD
CCI [redacted]	Feb. 15, 2017	Section 6.8.2	PPD
CCI [redacted]	Feb. 15, 2017	Section 6.8.3	PPD
CCI [redacted]	Feb. 15, 2017	Section 6.8.7	PPD
CCI [redacted]	Feb. 15, 2017	Section 6.12	PPD
Update Statistical Method	Feb. 15, 2017	Section 8.1	PPD
Update Statistical Analyses	Feb. 15, 2017	Section 8.2	PPD
Update Summary of Efficacy Analyses	Feb. 15, 2017	Section 8.5	PPD

Version 4 is amended from version 3 to include following:

Change	Date	Section(s) Affected	Statistician
Modified Statistical Method to exclude the ET data due to unexpected study termination.	Mar. 29, 2017	Section 8.1	PPD

2. INTRODUCTION

HD is an autosomal dominant neurodegenerative disease that targets the corticostriatal system and results in (1) progressive movement disorder, generally presenting as chorea in the early stages of the disease; (2) progressive cognitive disturbance culminating in dementia; and (3) various behavioral disturbances that may precede the emergence of diagnostic motor signs and can vary, depending on the disease state. The mean age of onset is 35-44 years and the median survival time is 15-18 years after onset.

HD is caused by an expansion of a CAG trinucleotide in the first exon of the IT15 gene on the short arm of chromosome 4, which codes for the huntingtin (Htt) protein. The CAG repeats are translated into polyglutamine repeats (polyQ) that confer toxic activity to huntingtin and lead to widespread corticostriatal pathology and ultimately to neuronal death most prominent in the striatum. Htt gene alleles containing ≥36 CAG repeats are disease causing.

The diagnosis of HD relies on characteristic clinical findings and the detection of an expansion of 36 or more CAG repeats in the Htt gene, often associated with a positive family history.

The neuropathological hallmark of HD is the accumulation of aggregates of mutated Htt in neurons and the progressive loss of medium spiny neurons (MSNs), beginning in the tail of the caudate nucleus with subsequent progression to the ventromedial striatum[2] with significant, albeit less pronounced, neuronal loss in other subcortical and cortical structures.

Depending on the species, MSNs account for approximately 74% (humans) to more than 90% (rodents) of the striatal neuronal population. MSNs are the output system of the striatum, and they receive glutamate input from cortical pyramidal cells, which also undergo substantial degeneration and loss in HD. Although damage occurs in other brain regions, corticostriatal circuitry pathology and dysfunction appear to be the primary substrate of the cognitive, behavioral and motor abnormalities that characterize HD. Impairment in the corticostriatal circuitry is also present in transgenic mice and rats expressing mutant Htt as demonstrated by electrophysiological studies in corticostriatal brain slices from these animals and by in vivo recordings from basal ganglia structures. Aberrant frontostriatal connectivity in response to cognitive tasks is present in pre-symptomatic HD subjects and worsens as the disease progresses. There also appears to be an association between connectivity strength of frontostriatal circuits and several clinical measures and genetic markers, including Unified Huntington's Disease Rating Scale motor score, predicted years to manifest symptom onset, as well as CAG repeat length.

Phosphodiesterase 10A (PDE10A) is an enzyme that has an important role in the regulation of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) levels and is highly enriched in the medium-sized spiny neurons of the striatum. Reduced PDE10A mRNA and protein levels have been found in homogenates from the striatum of HD patients. Results from a recent pilot PET imaging study with the PDE10A ligand [F] MNI-659, showed decreased PDE10A binding sites in HD stage I/II patients, as expected considering the degeneration of MSNs in HD. A cross-sectional study on quantification of PDE10A levels in pre-manifest, early and mid-stage disease HD subjects and healthy

volunteers is currently ongoing at the Karolinska Institute. Preliminary results from this study confirmed previous reports suggesting that PDE10A enzyme expression in the brains of HD subjects is compatible with further clinical development of PF-02545920 for the symptomatic treatment of HD. Preclinical HD models have demonstrated that PDE10A enzyme levels ≥20% of normal can elicit robust biochemical signatures by increasing cyclic nucleotide signaling in response to PDE10A inhibition.

PF-02545920 is a potent and highly selective inhibitor of PDE10A in in vitro systems being developed for symptomatic treatment of both HD and schizophrenia (Note as of Jan 2015: the development of this compound for schizophrenia has been terminated based on lack of efficiacy for study A8241019). In vivo PF-02545920 administration resulted in increased striatal levels of cGMP and cAMP and in the putative activation of a number of downstream signaling molecules regulated by cyclic nucleotide cascades in MSNs, leading to overall increased striatal activation and decreased locomotor hyperactivity. The presence of mutated huntingtin has been found to impair cAMP signaling and cAMP responsive-element binding protein (CREB) mediated transcription of genes responsible for neurotransmitter synthesis, release and signaling pathway as well as the production of brain derived neurotrophic factor (BDNF). Inhibition of PDE10A has been found to modulate striatal signaling towards neuroprotective pathways, to decrease neurodegenerative changes in the striatum of animal models of HD and to restore cAMP dependent CREB signaling. The accumulated data strongly support targeting of the deficient cAMP and cGMP signaling as a therapeutic strategy to correct cortico-striatal-thalamic-cortical circuitry dysfunction and relieve both motor and cognitive symptoms of HD.

Preclinical studies conducted in collaboration with the CHDI Foundation, Inc. demonstrated that PDE10A inhibition is effective in reversing multiple parameters of aberrant excitability of MSNs, and in improving elements of corticostriatal connectivity in brain slices derived from symptomatic R6/2 and Q175 knock-in mice. Chronic (4 months) dosing of Q175 HD transgenic mice with PF-02545920 significantly improved dysfunction of the corticostriatal circuits, which develops with disease progression.

Moreover, recent studies in two additional transgenic models of HD, BACHD mice and BACHD rats showed that both acute and chronic (2 weeks) administration of PF-02545920 results in functional improvement of indirect pathway activity. Most importantly, in vivo functional improvement measured as a reversal of the impaired subthalamic nucleus firing rate, was demonstrated in the full length mHtt transgenic BACHD rat, following acute treatment with PF-02545920.

In summary, these preclinical observations suggest that treatment with PF-02545920 preferentially activates the function of the indirect pathway of the basal ganglia which is primarily impaired in the earlier stages of HD and thus may lead to functional normalization of affected corticostriatal brain circuitry. For this reason, the PDE10A inhibitor, PF-02545920, may offer HD patients amelioration of motor and cognitive symptoms, and potentially slow disease progression.

2.1. Study Design

This study is a 12 month open label extension study of PF-02545920 20 mg dosed BID following study A8241021.

The study includes a Screening visit (V1) to assess eligibility followed by a Baseline visit (V2) and visits after 2 weeks, 4 weeks, 3 months, 6 months, 9 months, and 12 months of treatment. The final scheduled visit is a Follow-up visit 7-14 days after the last dose. Screening visit (V1) and Baseline visit (V2) will coincide with Week 19 and Week 26 Visits from study A8241021, respectively. For the Screening visit (V1) and Baseline visit (V2) procedures and assessments, the investigator will use data collected during Week 19 and Week 26 visits for study A8241021, respectively. Subjects, who meet study entry criteria, will be assigned to the 20 mg BID dose. During the 12-month treatment phase, subjects will return for study assessments at Week 2 (V3), Week 4 (V4), Month 3 (V5), Month 6 (V6), Month 9 (V7), Month 12 (V8), and for a Follow-up visit (V9).

Subjects, who were assigned to the 20 mg PF-02545920 dose group in the preceding A8241021 study, will continue to receive 20 mg PF-02545920 in this study without any titration. All other subjects will be titrated to the 20 mg BID dose as follows: 5 mg BID for 7 days, 10 mg BID for 7 days, 15 mg BID for 7 days, then 20 mg BID for the remainder of the treatment phase. Titration is in place to reduce incidence of AEs, frequent monitoring is in place for neutropenia, and an option for de-escalation by 5 mg decrements (temporary or permanent) will be available should the investigator consider the AE intolerable.

Subjects who are discontinued (Early Termination) at or after Day 14 should complete as many of the Month 12 (V8) assessments as possible. Subjects should return to complete the Follow-up visit whenever possible.

Based on the total number of 260 subjects expected to be randomized in study A8241021, up to 260 subjects may take part in this open label extension. CCI [redacted] CCI [redacted] CCI [redacted] (CCI) CCI [redacted] CCI .

2.2. Study Objectives

Primary Objective:

- *To assess long-term safety and tolerability of 20 mg BID of PF-02545920 in subjects with HD.*

Secondary Objectives:

- *To assess motor function after 6 and 12 month oral dosing with 20 mg BID of PF-02545920 in subjects with HD.*
- *To assess the efficacy of 6 and 12 month oral dosing with 20 mg BID of PF-02545920 on chorea severity in subjects with HD.*

- *To assess whether 6 and 12 month oral dosing with 20 mg BID of PF-02545920 can improve overall clinical impression in subjects with HD.*

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3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No interim analysis will be performed in the study.

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4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

The primary trial variables examine long-term safety and tolerability of therapy with 20 mg BID of PF-02545920. The primary analysis of long-term safety will be focused on Adverse events, weight, vital signs (pulse, blood pressure and body temperature), electrocardiogram (ECG), clinical laboratory findings (hematology, biochemistry and urinalysis), suicidal ideation and behavior (SIB) assessments *and* white blood count (WBC) and absolute neutrophil count (ANC). No formal statistical hypothesis will be conducted for the primary trail variables.

The secondary efficacy variables are:

- *Change from baseline in the Total Motor Score (TMS) assessment of the Unified Huntington Disease Rating Scale (UHDRS) after 6 and 12 months of treatment.*
- *Change from baseline in the Total Maximum Chorea (TMC) score of the UHDRS after 6 and 12 months of treatment.*
- *Clinical Global Impression-Improvement score after 6 and 12 months of treatment.*

Change from baseline in change in TMS and TMC will be calculated, decreases indicate improvement. The null hypothesis is that the change from baseline to a certain time-point is greater or equal to 0. The corresponding alternative hypothesis is that change from baseline to a certain time-point is less than 0. If the true mean change from baseline is denoted by μ then the hypothesis tested will be:

H_0: $\mu \geq 0$
H_a: $\mu < 0$

For *Clinical Global Impression-Improvement* (CGI-I) score a lower score indicates improvement. The null hypothesis is that the CGI-I value at a certain time-point is greater or equal to 4 (no change to very much worse). The corresponding alternative hypothesis is that the CGI-I value to a certain time-point is less than 4 (very much improved to minimally improved). If the true mean change from baseline is denoted by μ then the hypothesis tested will be:

H_0: $\mu \geq 4$
H_a: $\mu_{PF} < 4$

Both the change from baseline for all subjects (pooled) and by three cohorts (defined by dose level in A8241021 study: PF-20mg, PF-5mg, or Placebo) will be analyzed.

Statistical hypotheses for exploratory endpoints will be specified in a similar fashion as above.

4.2. Statistical Decision Rules

All one-sided tests for secondary and exploratory endpoints are described as to be performed using the nominal alpha-level of 0.025, this corresponds to a two-sided test with alpha-level of 0.05. In addition to the p-values, two-sided 95% confidence intervals will be provided.

5. ANALYSIS SETS

5.1. Full Analysis Set

All efficacy endpoints will be evaluated over the Full Analysis Set (FAS), which is the set of subjects who have an open label extension study baseline efficacy evaluation and have completed at least the Week 2 visit with a valid UHDRS TMS score*, and took ≥1 dose of open-label study medication. Subjects without post-dose measurements will not contribute to the analysis, except in the description of the baseline values.*

5.2. 'Per Protocol' Analysis Set

No Per Protocol analysis will be conducted.

5.3. Safety Analysis Set

All subjects who entered the extension study with at least one dose of study medication will be included in the safety analyses.

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5.5. Treatment Misallocations

Subjects who are undergoing the titration phase and do not titrate in the intended order will reported under the dose level they actually received.

5.6. Protocol Deviations

The criteria and determination of protocol violation/deviations will be determined by Pfizer prior to database release.

6. ENDPOINTS AND COVARIATES

6.1. Safety Endpoint(s)

Primary Endpoints: In this section, the safety endpoints that will be measured during the study are detailed. Where applicable, details of the endpoints to be derived and definition of baseline are also provided.

The following data are considered in standard safety summaries (see protocol for collection days and list of parameters):

- The number and proportion of subjects with adverse events.
- Assessment of clinical laboratory parameters.

- Assessment of vital signs.
- Assessment of ECG parameters.
- White blood count (WBC) and absolute neutrophil count (ANC) at each visit.
- Abnormal laboratory findings from baseline.
- Frequency and severity of adverse events related to extrapyramidal symptoms (EPS) including dystonia and akathisia, as assessed by the investigator.
- C-SSRS (suicide severity assessment).
- Adverse events, weight, vital signs (pulse, blood pressure and body temperature), physical examination, neurological examination, electrocardiogram (ECG) and clinical laboratory findings (hematology, biochemistry and urinalysis). The endpoints are:
    - The number and proportion of subjects with adverse events.
    - Assessment of clinical laboratory parameters.
    - Assessment of vital signs.
    - Assessment of ECG parameters.
    - White blood count (WBC) and absolute neutrophil count (ANC) at each visit.
    - Abnormal laboratory findings from baseline.
    - Frequency and severity of adverse events related to extrapyramidal symptoms (EPS) including dystonia and akathisia, as assessed by the investigator.
    - C-SSRS (suicide severity assessment).

6.2. Adverse Events

All AEs occurring during the course of the study will be coded using the most current MedDRA coding dictionary.

All AEs (serious and non-serious) reported from the first day of study treatment through and including 28 calendar days after the last administration of the study drug will be considered treatment emergent AEs (TEAEs).

6.3. Laboratory Safety Tests

Safety laboratory tests will be performed as described in the protocol.

To determine if there are any clinically significant laboratory abnormalities, the haematological, clinical chemistry (serum) and urinalysis safety tests will be assessed against the criteria specified in the sponsor reporting standards. The assessment will take into account whether each subject's test result is within or outside the laboratory reference range for the particular laboratory parameter.

Assessment results collected at Week 26 for Study A8241021 will be used for Baseline Day 1.

6.3.1. WBC and Neutrophil Monitoring

WBC counts with differential will be recorded or performed at each study visit starting with Baseline Day 1 (V2). The results of these assessments will be reviewed by the investigator as soon as possible once they are available, but no later than 2 business days after receipt of the lab results. After reviewing the results, the investigator must confirm and document that the WBC and/or ANC do not meet stopping criteria (See Protocol Section 3.1) *for the subject to continue in the study.*

6.3.2. Neutropenia Assessment

Subjects who meet any of the "subject stopping criteria" or the study stopping criteria for WBC or ANC should receive a hematology consultation and assessment for all potential etiologies of the WBC and ANC findings. This assessment should adhere to clinical standard of care for evaluation of neutropenia, but at a minimum include the following assessments: clinical assessment for infections and physical examination; review of relevant past medical history, prior concomitant medications, and prior WBC and ANC counts when available; repeated complete blood count with WBC, ANC, and a peripheral blood smear; bone marrow sampling for subjects who have an ANC <500 unless medically contraindicated or otherwise unobtainable. Additional assessments indicated by the standard of care for evaluation of neutropenia should be pursued in accordance with the investigator's and consultant's judgment.

6.4. Vital Signs

Vital signs will include blood pressure, pulse, and oral or tympanic body temperature. For orthostatic vitals, blood pressure and pulse should be collected or recorded while the subject is in the supine and standing position at the following visits: Baseline Day 1 (V2), Month 6 (V6), Month 12 (V8) or early termination visit. Blood pressure and pulse should be collected while the subject is sitting at all other visits.

The following vital signs endpoints will be determined:

- The maximum decrease and increase from baseline over all measurements taken postdose for supine and standing systolic and diastolic blood pressures;
- Postural differences (supine – standing) for systolic and diastolic blood pressures and for pulse rate.

The maximum increase from baseline will be calculated by first subtracting the baseline value from each post dose measurement to give the change from baseline. The maximum of these values over the respective period will then be selected, except in the case where a subject does not show an increase. In such an instance, the minimum decrease should be taken.

Similarly, the maximum decrease from baseline will be determined by selecting the minimum value of the changes from baseline. In cases where a subject does not show a decrease, the minimum increase should be taken.

6.5. Electrocardiogram (ECG)

Single 12 lead ECGs will be recorded at Baseline Day 1 (V2), and collected at Month 3 (V5), Month 6 (V6), Month 9 (V7) and Month 12 (V8), or at early termination, and may be performed at Unscheduled Visit(s).

Subjects must rest in the supine position for at least 10 minutes before the ECG recording is started. The ECG should be recorded during the period of rest required before blood collection and the measurements of orthostatic blood pressure and pulse. A qualified physician will review the ECGs and any clinically important finding will be recorded on the appropriate CRF. The investigator is responsible for providing interpretation of all ECGs. The results will include heart rate (RR), PR interval, QRS interval, QT interval, and correct QT (QTc) interval, and assessment of rhythm and morphology. If necessary (eg, suspected QTc prolongation), a manual reading of the ECG data will be performed.

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

QTcF = QT / (RR)**1/3 where RR = 60/HR (if not provided).

6.6. Suicidal Ideation and Behavior (SIB) Assessments During the Clinical Trial

The Columbia Suicide Severity Rating Scale (C-SSRS) is an interview-based rating scale to systematically assess suicidal ideation and suicidal behavior[33]. The scale should be administered to the subject by an individual with appropriate training, who has also taken the specific rater training for the scale, which will be provided by an agent of the sponsor prior to the study start. This scale will be recorded or administered ("since Last Visit") at each study visit from Baseline Day 1 (V2) to Follow-up visit (V9), including early termination.

C-SSRS responses will be mapped to the Columbia Classification Algorithm of Suicide Assessment (C-CASA). (See Appendix 2).

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. 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.

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6.8. Efficacy Endpoint(s)

Secondary Endpoints:

- *Change from baseline in the Total Motor Score (TMS) assessment of the Unified Huntington Disease Rating Scale (UHDRS) after 6 and 12 months of treatment.* The score decreases indicate improvement.
- *Change from baseline in the Total Maximum Chorea (TMC) score of the UHDRS after 6 and 12 months of treatment.* The score decreases indicate improvement.
- *Clinical Global Impression-Improvement score after 6 and 12 months of treatment.* The score decreases indicate improvement.

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- CCI [redacted].

6.8.1. Unified Huntington's Disease Assessment Scale (UHDRS)

In this study four subscales of the UHDRS will be administered to the subject by a trained certified rater of the site investigational staff (clinician): the Total Motor Score (TMS), CCI [redacted] (CCI, CCI [redacted] CCI.

The UHDRS is a clinical rating scale which has been developed by the Huntington Disease Study Group (HSG) to provide a uniform assessment of the clinical features and course of HD. The UHDRS scale has undergone reliability and validity testing and has been used as a major outcome measure in controlled clinical trials and observational studies. CCI [redacted] CCI.

The total motor score (TMS) will be recorded from study A8241021 at Baseline Day 1 (V2) visit, and will be administered at each study visit from Week 2 (V3) to Month 12 (V8) and in case of early termination.

The TMS assesses motor features of HD with standardized ratings of oculomotor function, dysarthria, chorea, dystonia, gait, and postural stability. Some items (such as chorea and dystonia) require grading each extremity (face, bucco-oral-lingual, and trunk) separately. Eye movements require both horizontal and vertical grades. The total motor impairment scores is the sum of all the individual motor ratings, with higher scores indicating more severe motor impairment than lower scores.

The Total Maximum Chorea (TMC) is a subset of the TMS assessment. It is composed of the scoring of 7 chorea assessments (face, orobuccolingual, trunk, right and left upper extremities, right and left lower extremities). Each assessment is rated from 0 to 4 (absent to prolonged). The TMC score can be derived from the TMS score at visits at which the TMS is collected.

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CCI [redacted]

Administration and scoring guidelines will be provided to the investigator site during rater training sessions prior to initiation of the study.

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6.8.3. CCI

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6.8.4. CCI

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CCI [redacted]

- CCI [redacted]

6.8.5. Clinical Global Impression of Severity/Improvement (CGI-S/CGI-I)

The CGI-S/CGI-I is a global measure of severity of illness (CGI-S) and improvement or change (CGI-I) based on the clinician's assessment of all available clinical data obtained from interviewing the subject.

The CGI-S consists of a single 7-point rating score of illness severity that is based on how ill the subject is relative to other subjects he/she has had experience with. Raters select one response based on the following question, "Considering your total clinical experience with this particular population, how ill is your subject at this time?" Scores are: 1, Normal, not ill at all; 2, Borderline ill; 3, Mildly ill; 4, Moderately ill; 5, Markedly ill; 6, Severely ill; or 7, Among the most severely ill subjects.

The CGI-I consists of a single 7-point rating of total improvement or change from baseline CGI-S, regardless of whether or not the change is due entirely to drug treatment. Raters select one response based on the following question, "Compared to your subject's condition at the beginning of treatment, how much has your subject changed?" Scores are: 1, Very much improved; 2, Much improved; 3, Minimally improved; 4, No change; 5, Minimally worse; 6, Much worse; or 7, Very much worse.

The CGI-S/CGI-I rater can have access to all clinical information related to subject severity and change, and does not need to be independent of other assessments. However, the rater who assesses the initial CGI-S should be the clinician who rates overall change via the CGI-I during the study.

The CGI-S will be performed at Baseline Day 1 (V2). The CGI-I will be administered at Month 6 (V6), Month 12 (V8), and in case of early termination. This assessment will be administered by a trained rater from the site investigational team (eg, clinician).

6.8.6. CCI

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6.9. CCI [redacted]

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6.11. PD Endpoints

None.

6.12. CCI [redacted]

CCI [redacted]

7. HANDLING OF MISSING VALUES

For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied.

For scales used in this study (eg, UHDRS), no missing response will be allowed in the study. A query will be sent to the site if there is missing response.

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.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

The Safety population will be used in the analyses of the safety data. The FAS analysis set will be utilized for efficacy endpoints.

All efficacy endpoints will be summarized descriptively at each visit for all subjects as well as separated by three groups (ie, from PF 20mg, from PF 5mg, and from Placebo). 90%CI will be provided for the mean. Plots with the mean over time with 90%CI will be generated for all subjects as well as by three different groups.

Baseline and change from baseline for each efficacy endpoints will also be summarized descriptively at each visit for all subjects as well as separated by three groups. Plots with mean change from baseline over time with 90%CI will be generated for all subjects as well as by three different groups.

Due to the unexpected termination of the study, any early termination visits (ET), which occurred on and after Dec. 16th, 2016, will not be included in the summary tables and plots. These data will be listed only.

8.2. Statistical Analyses

8.2.1. Analysis of Secondary Endpoints

The efficacy variables are:

- Change from baseline in the Total Motor Score (TMS) assessment of the Unified Huntington Disease Rating Scale (UHDRS) after 6 and 12 months of treatment.

- Change from baseline in the Total Maximum Chorea (TMC) score of the UHDRS after 6 and 12 months of treatment.

- Clinical Global Impression-Improvement score after 6 and 12 months of treatment.

Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) and 90% confidence interval will be provided to summarize results for each visit. The baseline and change from baseline values will be summarized as well by visit. A two-sided, paired *t*-tests at the 10% level of significance will also be used to summarize results. The paired *t*-tests will be done on all subjects and on three different groups. Baseline is defined as the final visit (Week 26) in the preceding double-blind study A8241021.

Clinical Global Impression-Improvement score after 6 and 12 months of treatment will be evaluated with descriptive statistics that includes n, mean, standard deviation (SD), median, minimum, and maximum. A two-sided, one-sample *t*-tests at the 5% level of significance will be applied to evaluate results.

Plots will be generated for mean change from baseline as well as mean over time as described in Section 8.1.

8.2.2. CCI

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8.3. Analysis of Safety Data

8.3.1. Safety Analysis

A set of summary tables will be produced to evaluate any potential risk associated with the safety and toleration of administering PF-02545920.

The safety and other endpoints detailed here will be listed and summarized in accordance with sponsor reporting standards, where the resulting data presentations will consist of subjects from the safety analysis set. All safety endpoints will be summarized for all subjects as well as separated by three groups (ie, from PF 20mg, from PF 5mg, and from Placebo).

8.3.2. Treatment and Disposition of Subjects

Subject evaluation groups will show end of study subject disposition and will show which subjects were analyzed for FAS, safety (adverse events and laboratory data), and pharmacokinetics. Frequency counts will be supplied for subject discontinuation(s).

Data will be reported in accordance with the sponsor reporting standards.

8.3.3. Demographic Data and Clinical Examination Data

A breakdown of demographic data will be provided for age, race, weight, body mass index and height. Each will be summarized by sex at birth and 'All Subjects' in accordance with the sponsor reporting standards.

Medical history will be summarized and listed.

8.3.4. Discontinuation(s)

Subject discontinuations, temporary discontinuations or dose reductions due to adverse events will be detailed and summarized.

Data will be reported in accordance with the sponsor reporting standards.

8.3.5. Adverse Events

Adverse events will be reported in accordance with the sponsor reporting standards.

8.3.6. Suicidal Ideation and Behavior

A frequency distribution of C-CASA scores (predose/post dose) will be reported. No hypotheses associated with the C-SSRS or C-CASA scales will be tested.

The denominator used in the percentages will be the number of subjects assessed for suicidal ideation and behavior (SIB). For 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 baseline, and at any time post-baseline without regard to baseline will be reported.

8.3.7. Laboratory Data

Laboratory data will be listed and summarized by treatment in accordance with the sponsor reporting standards. Baseline is as defined in Section 6.3.

A listing of subjects who meet any of the study stopping criteria for WBC or ANC counts will be presented.

8.3.8. Physical Exam/Weight

Physical examination data will be presented in a data listing and summary table using counts and percentages. Summary of new/intensified physical examination findings from Baseline to Month 12/ET will be presented.

Body weight absolute values and change from baseline will be summarized using descriptive statistics.

8.3.9. Vital Signs

Absolute values and changes from baseline in standing, supine and postural changes for systolic and diastolic blood pressure and pulse rate will be summarized, time postdose and day, according to sponsor reporting standards. Tables will be paged by parameter.

Baseline will be defined as the predose recordings on Day 1(V2).

Maximum absolute values and changes from baseline for vital signs (for supine and standing) will also be summarized descriptively by using categories as defined in Appendix 1. Numbers and percentages of subjects meeting the categorical criteria will be provided. All planned and unplanned postdose timepoints will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

Standing vital signs will be listed only.

8.3.10. ECG

Absolute values and changes from baseline in PR, QT, QRS, heart rate (RR) and QTcF will be summarized, time postdose and day using sponsor reporting standards. Tables will be paged by parameter.

ECG endpoints and changes from baseline (QTcF, PR, QRS) will also be summarized descriptively by using categories as defined in Appendix 1 (for QTc these correspond to ICH E14[1]). Numbers and percentages of subjects meeting the categorical criteria will be provided. All planned and unplanned postdose timepoints will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

Listings of subjects with any single postdose value ≥500 msec will also be produced for QTcF.

8.3.11. Prior and Concomitant Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be provided in the listings.

Frequency and type of medication will be summarized categorically.

8.3.12. Screening and Other Special Purpose Data

Serum FSH concentrations and urine drug screen will be obtained at screening (for drug screen, and at any time at the discretion of the investigator).

8.4. CCI

8.4.1. CCI

CCI

8.5. Summary of Efficacy Analyses

Endpoint	Analysis Set	Statistical Method	Model/ Covariates/ Strata	Missing Data	Interpretation
Δ from Baseline UHDRS Total Motor Score	FAS	Paired *t*-test	NA	Excluded	Secondary Analysis
Δ from Baseline UHDRS Total Maximum Chorea Score	FAS	Paired *t*-test	NA	Excluded	Secondary Analysis
CGI-I	FAS	One-Sample *t*-test	NA	Excluded	Secondary Analysis

CCI

[redacted]

Endpoint	Analysis Set	Statistical Method	Model/ Covariates/ Strata	Missing Data	Interpretation
CCI					

9. REFERENCES

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

Appendix 1. Categorical Classes for ECG and Vital Signs

Categories for QTcF

QTcF (ms)	450≤ max. <480	480≤ max.<500	max. ≥500
QTcF (ms) increase from baseline	30≤ max. <60	max. ≥60	

Categories for PR and QRS

PR (ms)	max. ≥300	
PR (ms) increase from baseline	Baseline >200 and max. ≥25% increase	Baseline ≤200 and max. ≥50% increase
QRS (ms)	max. ≥140	
QRS (ms) increase from baseline	≥50% increase	

Categories for Vital Signs

Systolic BP (mm Hg)	min. <90	
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mm Hg)	min. <50	
Diastolic BP (mm Hg) change from baseline	max. decrease ≥20	max. increase ≥20
Supine pulse rate (bpm)	min. <40	max. >120
Standing pulse rate (bpm)	min. <40	max. >140

Appendix 2. C-SSRS Mapped to C-CASA

Table 1. C-CASA Suicidality Events and Codes

Event Code	Event
1	Completed suicide
2	Suicide attempt
3	Preparatory acts towards imminent suicidal behavior
4	Suicidal ideation
5	Self-injurious behavior, intent unknown
6	Not enough information, fatal
7	Self-injurious behavior, no suicidal intent
8	Other, accident, psychiatric; mental
9	Not enough information, non fatal

* Note: Event Codes 5, 6, 8 and 9 are not applicable to prospectively collected data

Table 2. 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: • "Aborted attempt", or • "Interrupted attempt", or • "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?"

Appendix 3. Definition and Use of Visit Windows in Reporting

Statistical analyses for full analysis set will be based on time intervals that are constructed according to the duration of treatment. The planned time interval definitions are summarized below.

Scheduled Visit number	Time interval (label)	Time interval (days)	Target time point (day)
1	Screening[1]	[-52,-46]	-49
2	Baseline[2]	[-7,0]	0
3	Week 2	[11, 17]	14
4	Week 4	[25, 31]	28
5	Month 3	[84, 98]	91
6	Month 6	[168, 196]	182
7	Month 9	[266, 280]	273
8	Month 12	[351, 379]	365
9	Follow-up	[373, 385]	379

1. Screening visit will take place during the Week 19 Visit for study A8241021.

2. Assessment results collected at Week 26 for Study A8241021 will be used for Baseline Day 1 (V2).

If data obtained from the multiple visits are included in the same interval, the one closest to the target date in that time interval will be used for analysis. If two visits are equally distant from the target date, then the later one will be used.

The study day associated with a given date will be calculated as: (date of interest) – (first dosing date) + 1. Consequently, Day 0 indicates the day before Day 1, the first dosing date in the study.

The baseline reference period for assessing treatment emergent adverse events (TEAEs) will be the period prior to Day 1.

The frequency distribution of study days for each visit will be reviewed by clinician to expand visit windows for the analyses, if necessary, before locking and unblinding the database.