CLINICAL PROTOCOL

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

Compound:	PF-02545920
Compound Name:	N/A
United States (US) Investigational New Drug (IND) Number:	118,646
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Universal Trial Number:	U1111-1162-4293
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Phase:	Phase 2a

Document History

Document	Version Date	Summary of Changes
Original protocol	23 October 2014	Not Applicable

Table 1. Abbreviations

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

Abbreviation	Term
ACE	angiotensin converting enzyme
AE	adverse event
ALT	alanine transaminase
ANC	absolute neutrophil count
AST	aspartate transaminase
BACHD	transgenic mouse and rat model of Huntington's disease using a bacterial artificial chromosome
BID	twice a day (bis in die)
BP	blood pressure
BPM	beats per minute
CAG	cytosine adenine guanine codon for glutamine
CCI	CCI
CGI	clinical global impression
CHDI	Cure Huntington's Disease Initiative
CNS	central nervous system
CRF	case report form
CSA	clinical study agreement
CSF	cerebrospinal fluid
CSSRS	Columbia suicide severity rating scale
CTA	clinical trial application
DAI	dosage and administration instructions
DBS	Deep brain stimulation
DMC	data monitoring committee
DNA	deoxyribonucleic acid
CCI	CCI
EC	ethics committee
ECG	Electrocardiogram
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EDTA	edetic acid (ethylenediaminetetraacetic acid)
EHDN	European Huntington's Disease Network
ET	early termination
EudraCT	European Clinical Trials Database
FAS	full analysis set
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FSH	follicle-stimulating hormone
FU	follow-up
GCP	good clinical practice
HD	Huntington's disease

CCI	CCI
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HR	hour
CCI	CCI
IB	investigator's brochure
ICH	International Conference on Harmonisation
ICD	informed consent form
ID	Identification
IND	investigational new drug application
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
LFT	liver function test
LSLV	last subject last visit
MAOI	monoamino oxydase inhibitor
MDMA	methylenedioxy methylamphetamine (ecstasy)
MHP	medical health practitioner
CCI	
N/A	not applicable
NSAID	nonsteroidal anti-inflammatory drug
CCI	
PANSS	positive and negative syndrome scale
CCI	CCI
PCD	primary completion date
PDE10A	phosphodiesterase 10A
PET	positron emission tomography
PI	principle investigator
CCI	
POC	proof of concept
CCI	CCI
PT	prothrombin time
CCI	CCI
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
CCI	CCI
SIB	suicidal ideation and behavior
SRSD	single reference safety document
TCA	tricyclic antidepressants
CCI	CCI
TMS	total motor score

UHDRS	unified Huntington's disease rating scale
ULN	upper limit of normal
US	United States
UTN	Universal Trial Number
WBC	white blood cell

PROTOCOL SUMMARY

INDICATION

PF-02545920 is a highly selective phosphodiesterase 10A (PDE10A) inhibitor that is being developed for the symptomatic treatment of Huntington's disease (HD).

BACKGROUND AND RATIONALE

The Disease:

HD is an autosomal dominant neurodegenerative disease that targets the corticostriatal system and results in (1) progressive movement disorder, initially manifesting as chorea; (2) progressive cognitive disturbance culminating in dementia; and (3) various behavioral disturbances that often precede diagnosis and can vary depending on the state of disease. 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 translated trinucleotide cytosine adenine guanine codon or CAG, coding for a glutamine repeat in the 5′- region of the *Htt* gene on the short arm of chromosome 4, resulting in widespread corticostriatal pathology.

The diagnosis of HD relies on characteristic clinical findings and the detection of an expansion of CAG equal to or greater than 36 repeats in the *Htt* gene, which is often associated with a positive family history.

The neuropathological hallmark of HD is the accumulation of aggregates of mutated huntingtin protein and progressive loss of medium spiny neurons (MSNs), beginning in the dorsal medial head of the caudate with subsequent progression to the ventrolateral striatum with significant, if less pronounced, neuronal loss in other subcortical and cortical structures.

The Compound:

PF-02545920 is a highly selective PDE10A inhibitor. PDE10A is an enzyme which is highly enriched in the MSNs of the striatum and has an important role in the regulation of cAMP and cGMP levels. PF-02545920 is a selective inhibitor of PDE10A in *in vitro* systems. Reduced PDE10A mRNA and protein levels have been found in homogenates from the striatum of HD subjects. Results from a recent pilot positron emission tomography (PET) imaging study with the PDE10A ligand [^{18}F]MNI-659 showed decreased PDE10A binding sites in HD stage I/II patients as expected, consistent with 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 HD brain 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.

In vivo PF-02545920 administration results 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 Mechanism:

Preclinical studies conducted in collaboration with the Cure Huntington's Disease Initiative (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 improves dysfunction of the corticostriatal circuits, which develops with disease progression.

Moreover, recent studies in two additional transgenic models of HD using a bacterial artificial chromosome, 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 improves activity of the indirect pathway of the basal ganglia, which is primarily impaired in the earlier stages of HD, and thus it may lead to functional normalization of affected corticostriatal brain circuitry and alleviate motor symptoms, and potentially behavioral and cognitive symptoms in individuals with HD.

Complete information for this compound may be found in the single reference safety document (SRSD), which for this study is the Investigator Brochure.

Safety:

To date, evaluation of PF-02545920 has been completed in 7 clinical studies included in the 2014 Investigator Brochure.

Interpretation of the study results and the possible risks associated with the administration of PF-02545920 are summarized in Section 7 of the Investigator's Brochure (IB 2014 version).

Dose Rationale:

Based on the previous pre-clinical efficacy data and clinical safety data, a dose of 20 mg is estimated to produce the most robust PDE10A inhibition while still being well tolerated. Therefore, the present study with 20 mg BID PF-02545920 will continue to evaluate safety and tolerability in subjects with HD. A double blind titration scheme will be used to mitigate the potential risk of dystonia for subjects who did not receive 20 mg in the preceding study (A8241021). The incidence rate of dystonia for the titrated 15 mg BID dose group in study A8241012 was substantially lower than the rate observed in a similar study (A8241006) population with a non-titrated 15 mg BID dosing regimen.

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 the overall clinical impression in subjects with HD.

CCI [redacted]:

- CCI [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

STUDY ENDPOINTS

Primary Endpoint:

- 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).

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.
- 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.

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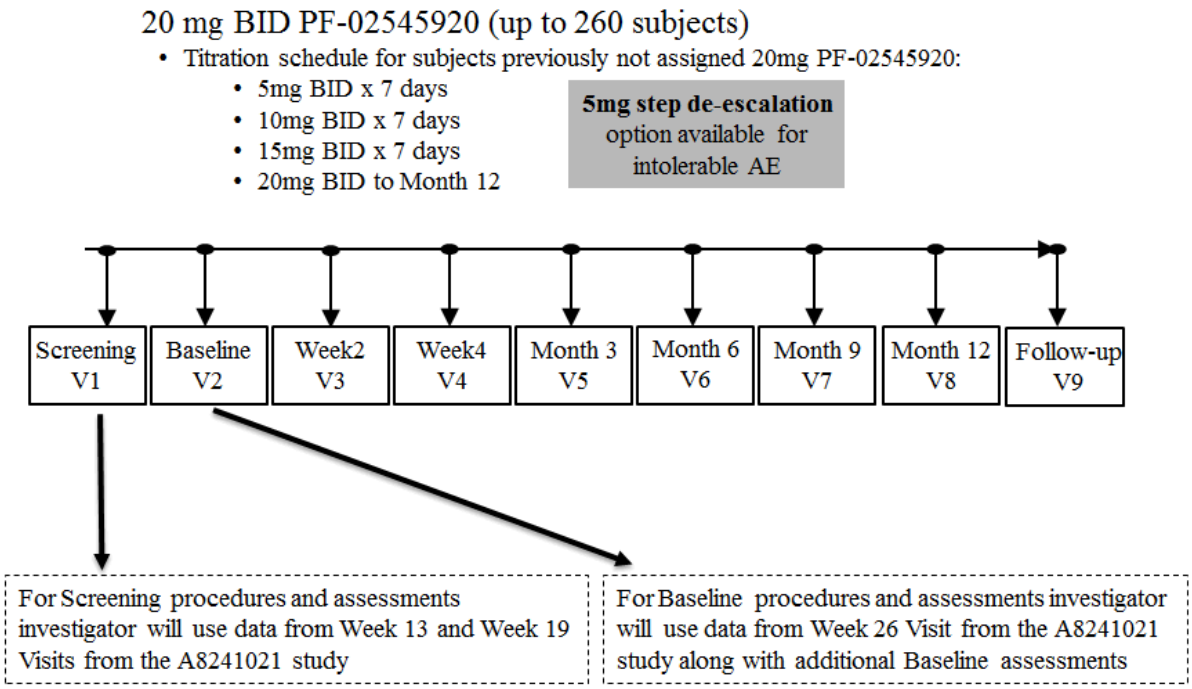
STUDY DESIGN

This study is a 12 month open label extension study, following study A8421021, with a single dose of 20 mg PF-02545920 BID for the treatment of motor impairment of subjects with HD. Subjects, who received 20 mg BID of PF-02545920 in the preceding study A8241021, will receive 20 mg BID of PF-02545920 in this study without any titration. A double blind titration scheme will be used to mitigate the potential risk of dystonia for those subjects who did not receive 20 mg in the first study (A8241021).


20 mg BID PF-02545920 (up to 260 subjects)
• Titration schedule for subjects previously not assigned 20mg PF-02545920:
• 5mg BID x 7 days
• 10mg BID x 7 days
• 15mg BID x 7 days
• 20mg BID to Month 12
5mg step de-escalation option available for intolerable AE
Screening V1
Baseline V2
Week2 V3
Week4 V4
Month 3 V5
Month 6 V6
Month 9 V7
Month 12 V8
Follow-up V9
For Screening procedures and assessments investigator will use data from Week 13 and Week 19 Visits from the A8241021 study
For Baseline procedures and assessments investigator will use data from Week 26 Visit from the A8241021 study along with additional Baseline assessments

SCHEDULE OF ACTIVITIES

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

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Visit Window			**Day (±3 days)[1]**		**Day (±7 days)[1]**				
Visit Identifier	**Screening[2]**	**Baseline[3]**	**Week 2**	**Week 4**	**Month 3**	**Month 6**	**Month 9**	**Month 12 /ET[4]**	**Follow up[5]**
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
Study Day		**Day 1**	**Day 14**	**Day 28**	**Day 91**	**Day 182**	**Day 273**	**Day 365**	**Day 372 to 379**
Informed Consent	X								
CCI	CCI								
File Record of Signed and Dated Pre-screening Checklist A[6]	X								
Complete Screening Checklist B for review of study A8241021 data[6]	X								
Review Inclusion/Exclusion Criteria	X	X							
CAG profile documentation		(X)[7]							
Demography		(X)[7]							
Review Medical History and Prior/Concomitant Medications		X							
Review Adverse Events (AE) & Changes since last visit (medical history, procedures, con. meds)			X	X	X	X	X	X	X
Height		(X)[7]							
Weight		(X)[8]				X		X	
Brief Physical Examination		(X)[8]				X		X	X
Brief Neurological Examination		(X)[8]				X		X	X
Electrocardiogram (ECG)[9]		(X)[8]			X	X	X	X	
Supine and Standing Blood Pressure and Pulse (orthostatic vitals); Body Temperature[10]		(X)[8]				X		X	

Visit Window			**Day (±3 days)[1]**		**Day (±7 days)[1]**				
Visit Identifier	**Screening[2]**	**Baseline[3]**	**Week 2**	**Week 4**	**Month 3**	**Month 6**	**Month 9**	**Month 12 /ET[4]**	**Follow up[5]**
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
Study Day		**Day 1**	**Day 14**	**Day 28**	**Day 91**	**Day 182**	**Day 273**	**Day 365**	**Day 372 to 379**
Sitting Blood Pressure and Pulse; Body Temperature (standard vital signs)[10]			X	X	X		X		X
Contraception Check		(X)[8]	X	X	X	X	X	X	
Laboratory tests:[11]									
Hematology[12]		(X)[8]	X[12]	X[12]	X	X	X	X	X[12]
Blood Chemistry		(X)[8]				X		X	
Serum Pregnancy Test		(X)[8]			X	X	X	X	
Urine Pregnancy Test		X							X
Serum FSH[13]		X							
Urinalysis		(X)[8]				X		X	
Urine drug screen[14]		X							
CCI									
Assessments:									
C-SSRS Since Last Visit		(X)[8]	X	X	X	X	X	X	X
CCI		[8] CCI							
CCI									

Visit Window			**Day (±3 days)[1]**		**Day (±7 days)[1]**				
Visit Identifier	**Screening[2]**	**Baseline[3]**	**Week 2**	**Week 4**	**Month 3**	**Month 6**	**Month 9**	**Month 12 /ET[4]**	**Follow up[5]**
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
Study Day		**Day 1**	**Day 14**	**Day 28**	**Day 91**	**Day 182**	**Day 273**	**Day 365**	**Day 372 to 379**
CCI									
ANC and WBC Review[17]	X	(X)[8]	X	X	X	X	X	X	X
Site Eligibility Review[6]	X	X							
Sponsor Eligibility Verification[18] and Documentation of Confirmation	X								
Randomization[19]		X							
CCI [20]									
CCI									
Dispense dosing diary		X							
Dispense study drug for outpatient dosing		X	X	X	X	X	X		
Subject instruction on outpatient dosing from blister packs/bottles, dosing diary use and reporting AEs and SAEs.		X							
Assess compliance based on observation of blister packs, pill counts, review dosing diary			X	X	X	X	X	X	
Collect dosing diary				X					

Footnotes:

1. All visits windows are relative to the V2 Baseline Day 1 visit date.
2. Screening visit will take place during the Week 19 Visit for study A8241021.
3. Baseline Day 1 activities will take place during Week 26 Visit for Study A8241021.
4. In case of Early Termination between Baseline and Day 14 (exclusive), only safety assessments will be performed (See STUDY PROCEDURES). If Early Termination occurs after Day 14 (inclusive), as many Month 12/ET assessments as possible should be completed.
5. Follow-up visit is to take place 7 to 14 days after the last dose on Month 12 (V8).
6. Site eligibility review: the site will review all laboratory test results, pregnancy test, ANC and WBC, drug test results, against I/E criteria. Checklists A and B will be provided to the site by the sponsor.
7. Data collected at Screening for Study A841021 will be used.
8. Assessment results collected at Week 26 for Study A8241021 will be used for Baseline Day 1 (V2).
9. Single 12-lead ECG will be recorded at Baseline Day 1 (V2) and collected at Month 3 (V5), Month 6 (V6), Month 9 (V7) and Month 12/ET (V8).
10. Vital signs to include blood pressure, pulse and oral or tympanic body temperature.
11. Samples for laboratory can be obtained without regard to fasting status.
12. Hematology samples will be collected only for ANC and WBC safety monitoring at Week 2 (V3), Week 4 (V4) and Follow-up (V9).
13. Serum FSH may be performed to confirm postmenopausal status for females who have been amenorrheic for at least 12 consecutive months.
14. Urine Drug screen may be performed at Baseline Day 1 (V2) and any time at the discretion of the investigator.
15. CCI [redacted].
16. CGI-S will be administered once at Baseline Day 1 (V2); CGI-I will be administered at Month 6 (V6) and Month 12 (V8) or Early Termination.
17. The site will perform and document ANC and WBC review at all visits for neutropenia safety monitoring. A source document worksheet will be provided by the sponsor to ensure this is documented and monitored carefully throughout the course of the study.
18. Sponsor Eligibility Verification process: The Sponsor will verify key elements of the study inclusion/exclusion criteria prior to randomization of each subject. All information related to subject eligibility, including, but not limited to, HD diagnosis and screening safety laboratory data, electrocardiograms, and Vital Sign results from study A8241021, should be entered in the subject eCRF and available for sponsor review. Investigators will be trained on the Screening Verification process, as part of the protocol training prior to study start.
19. Randomization code can be obtained by the clinical sites as soon as the sponsor has verified that the subject is eligible (2 business days reserved at the end of the Screening period).
20. CCI CCI [redacted].

Abbreviations: AE = adverse event; ANC = absolute neutrophil cell count; BP = blood pressure; CAG = cytosine adenine guanine codon for glutamine; [redacted] = [redacted]; CGI-S = Clinical Global Impression Severity Scale; CGI-I = Clinical Global Impression Improvement scale; C-SSRS = Columbia Suicide Severity Rating Scale; [redacted]: [redacted]; ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; FU = follow-up; [redacted] = [redacted] [redacted] = [redacted]; [redacted] = [redacted]; [redacted] = [redacted]; [redacted] = [redacted]; [redacted] = [redacted]; [redacted] = [redacted] [redacted]; [redacted] = [redacted]; TMS = Total Motor Score; SAE = serious adverse event; [redacted] = [redacted]; [redacted] = [redacted]; [redacted] = [redacted]; [redacted] = [redacted]; [redacted] = [redacted]; WBC = white blood cell

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1. INTRODUCTION

1.1. Mechanism of Action/Indication

PF-02545920 is a highly selective PDE10A inhibitor that is being developed for the symptomatic treatment of Huntington's disease (HD).

1.2. Background and Rationale

1.2.1. Drug Development and Study Rationale:

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.[1,2,3]

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,[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[5] and ultimately to neuronal death most prominent in the striatum. *Htt* gene alleles containing ≥36 CAG repeats are disease causing.[3]

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.[6]

Depending on the species, MSNs account for approximately 74% (humans) to more than 90% (rodents) of the striatal neuronal population.[7] 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.[8] 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.[8] 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[9,10] and by *in vivo* recordings from basal ganglia structures.[11,12,13,14] 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.[15]

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[16,17,18] and is highly enriched in the medium-sized spiny neurons of the striatum.[19,20,21,22] Reduced PDE10A mRNA and protein levels have been found in homogenates from the striatum of HD patients.[23] Results from a recent pilot PET imaging study with the PDE10A ligand [^{18}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. *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.[17-23,24] 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).[16,25,26] Inhibition of PDE10A has been found to modulate striatal signaling towards neuroprotective pathways,[16] to decrease neurodegenerative changes in the striatum of animal models of HD and to restore cAMP dependent CREB signaling.[27,28] The accumulated data strongly support targeting of the deficient cAMP and cGMP signaling[29,30] 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.[9,10,31]

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.[13]

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.[32] For this reason, the PDE10A inhibitor, PF-02545920, may offer HD patients amelioration of motor and cognitive symptoms, and potentially slow disease progression.

Summary of Benefit Risk Assessment

To date, PF-02545920 appears to be safe and well tolerated in more than 400 subjects (including healthy volunteers, subjects with schizophrenia and subjects with HD) (see Safety and Clinical Data) whether as a monotherapy or as an adjunctive treatment with antipsychotic medications. From these studies, the development of neutropenia and extrapyramidal symptoms (EPS) have emerged as potential, albeit infrequent, risks for the subjects, which have been mitigated by the inclusion of a titration regimen, together with a close monitoring plan for WBC/ANC (see Stopping Criteria) and an EPS monitoring and rescue plan (see Rescue Medications for the Management of Extrapyramidal Symptoms (akathisia, dystonia, tardive dyskinesia).

1.2.2. Safety and Clinical Data

To date, evaluation of PF-02545920 has been completed in 7 clinical studies, which are included in the 2014 Investigator Brochure.

- Protocols A8241001 and A8241008 were Phase 1 studies that evaluated the safety, tolerability, and pharmacokinetics of PF-02545920 in a total of 35 healthy subjects.

- Protocol A8241013 was a Phase 1 study that evaluated the effects of a single dose of PF-02545920 on regional glucose metabolism (PET) in the striatum and characterized the exposure-response relationship for PF-02545920 in 31 healthy subjects.

- Protocol A8241002 was a multiple dose Phase 1b study that further evaluated the safety, tolerability and pharmacokinetics of PF-02545920 in 40 subjects with stable symptoms of schizophrenia.

- Protocol A8241006 was the first Phase 2a study designed to evaluate the efficacy, safety, tolerability and pharmacokinetics of PF-0254920 in 35 subjects with an acute exacerbation of schizophrenia.

- Protocol A8241012 was a second Phase 2 study that evaluated the safety and efficacy of PF-02545920 in 259 subjects with schizophrenia, who were experiencing an acute exacerbation at the time of admission.

- Protocol A8241018 was a randomized, double blind, sponsor open, placebo controlled, Phase 1b study of the safety, tolerability and pharmacokinetics of PF-02545920 in 37 psychiatrically stable subjects with schizophrenia on a stable regimen of antipsychotics and other adjunctive psychotropic medications.

In 2 completed Phase 1 studies (**A8241001 and A8241008**), single oral doses of ≤30 mg of PF-02545920 were given to healthy subjects. PF-02545920 10 mg dose was well tolerated. Dose-related adverse events included mild sedation at doses of ≥15 mg and extrapyramidal symptoms (EPS) (including tremor and dystonic reactions) at doses ≥20 mg. At the 20 mg dose level, 1/11 subjects had a moderate episode of dystonia with onset 4 hours post-dose, and of approximately 3 hour duration. At the 30 mg dose level, 1/5 subjects had a moderate episode of dystonia with onset within 1 hour post-dose and of approximately 2 minute duration. Both episodes resolved spontaneously without requiring anticholinergic medication and did not recur.

In the completed Phase 1 PET study (**A8241013**), 31 healthy subjects were divided into two cohorts and received single oral doses of PF-02545920 (3 mg, 6 mg, or 15 mg) in two stages. In Stage 1, all subjects received a single oral dose of 6 mg PF-02545920 and a single dose of placebo in random order. In Stage 2, all subjects received 3 mg PF-0254920, 15 mg PF-02545920 and placebo in random order. In the first stage of the study, two mild adverse events (AEs) of dizziness and fatigue were reported in the 6 mg group. Most AEs reported during the second stage were mild in severity, with 1 moderate case of fatigue (PF-02545920 3 mg), 1 moderate headache (PF-02545920 3 mg), 1 moderate case of seborrhoeic dermatitis (PF-02545920 3 mg), and 1 severe case of somnolence (PF-02545920 15 mg).

In the completed multiple dose Phase 1 study (**A8241002**), a total of 40 subjects with chronic schizophrenia were randomized in the first multiple-dose study that evaluated the safety, tolerability, and pharmacokinetic parameters of PF-02545920. Subjects were randomized to 1 of 5 cohorts of PF-02545920 (5 to 40 mg Q12H) or placebo for 13 days. There were no deaths or serious adverse events (SAEs) reported during this study. The most frequently occurring treatment-emergent "all causality" AEs following multiple doses of PF-02545920 were central nervous system (CNS) related, which included sedation, dystonia, and dyskinesia. There were 17 subjects who experienced mild to moderate sedation occurring more often in the ≥20 mg BID dose groups. There were 8 subjects who experienced an AE of mild to severe dystonia, which was dose dependent and more frequent in the ≥20 mg BID dose groups. There were 6 subjects who experienced dyskinesia (1 in placebo [severe], 4 in the 15 mg PF-02545920 [mild], and 1 in the 30 mg PF-02545920 [moderate] treatment groups). All adverse events of dyskinesia were attributed to the protocol specified withdrawal of prior antipsychotic therapy.

Protocol **A8241006** was the first Phase 2 study that was planned to evaluate the efficacy, safety, tolerability and pharmacokinetics of PF-02545920 in a total of 54 subjects with an acute exacerbation of schizophrenia. This was a 3 week, double-blind, parallel-group, fixed-dose, placebo-controlled, multi-center, randomized study of PF-02545920 15 mg Q12H. This study was terminated prematurely to further investigate a potential safety concern of neutropenia. Six subjects (3 assigned to PF-02545920 and 3 assigned to placebo) had decreases in absolute neutrophil count that met the criteria of potential clinical concern. Five cases were classified as neutropenia and one as agranulocytosis. None of these subjects were symptomatic. The case of agranulocytosis rapidly resolved without sequelae. There have been no additional cases of agranulocytosis in subsequent completed and ongoing studies. After review of the cases an expert panel of hematologists concluded that further

studies should not pose an unacceptable risk to subjects with appropriate hematology monitoring. Based on the panel's recommendations, white blood cell (WBC) and absolute neutrophil count (ANC) exclusion criteria, local laboratory WBC and ANC monitoring, and WBC and ANC stopping criteria, were incorporated in the design of the next Phase 2 study (A8241012). Changes in white blood cell (WBC) counts were not reported in the single dose (A8241001) or multiple dose (A8241002) studies with PF-02545920. The most frequently reported AEs in PF-02545920 treated subjects in protocol A8241006 included dystonia, headache, and somnolence. The study results regarding the efficacy of PF-02545920 (15 mg Q12H) were inconclusive.

Protocol **A8241012** was the second Phase 2 study. The efficacy and safety of PF-02545920 in subjects with schizophrenia, who were experiencing an acute exacerbation, was evaluated in this double-blind, placebo-controlled, randomized multicenter study. Risperidone was used as an active control. Subjects were randomly assigned to 1 of 4 treatment groups in a 2:2:2:1 ratio, respectively: 1) PF-02545920 5 mg Q12H; 2) PF-02545920 15 mg Q12H (titrated); 3) placebo; and 4) risperidone 3 mg Q12H (titrated). A total of 258 subjects were randomized into the study, of which 74 subjects received PF-02545920 5 mg and 74 subjects received PF-02545920 15 mg, 36 subjects received risperidone 3 mg, and 74 subjects received placebo.

Two subjects died post-therapy (1 due to acute myocardial infarction and myocardium rupture and the other due to sudden cardiac death); both subjects were in the PF-02545920 5 mg group. Both occurred approximately 2.5 weeks after treatment with investigational drug was completed, after treatment with currently marketed medication was reinstituted; 1 subject died during the follow-up period and 1 subject died after completion of study participation. Autopsy reports attributed both deaths to myocardial infarction, and noted that both subjects had a history of cardiac disease and other cardiac risk factors. Per the investigators, the events were not related to study drug, concomitant medications, or study procedures, and internal medical safety review was in agreement. The SAEs observed in this study were predominately due to exacerbation of psychosis or schizophrenia symptoms, which is commonly observed in similar placebo-controlled trials in this study population. The most frequently reported treatment-related, treatment-emergent AEs across all treatment groups were headache, constipation, akathisia, nausea, sedation, neutropenia, somnolence, dizziness, and insomnia. Neutropenia was reported by subjects in all treatment groups. Severe treatment-emergent, treatment-related AEs of oculogyric crisis (PF-02545920 15 mg), akathisia (PF-02545920 15 mg), and exacerbation of schizophrenia (placebo) were reported by 1 subject each.

There were no trends for differences between treatment groups in absolute values or change from baseline of ECG parameters. No significant differences were observed between treatment groups for laboratory abnormalities.

The proportion of subjects triggering the subject stopping criteria for neutropenia did not differ substantively between the PF-02545920 5 mg (6 subjects), 15 mg (5 subjects), and placebo (5 subjects) treatment groups.

The overall dystonia incidence rate (includes dystonia, oromandibular dystonia and oculogyric crisis) was 1/74 in the PF-02545920 5 mg, 6/74 in the 15 mg treatment groups, 2/74 in the placebo group, and no subjects in the risperidone 3 mg group. Among the 6 subjects in the PF-02545920 15 mg group, 5 dystonia events occurred before Day 7, of which only 1 was reported as severe (oculogyric crisis). A single subject discontinued treatment in the study due to a dystonia AE. Dystonia AEs were successfully managed with as needed (prn) use of anticholinergic medication only, except in 1 case that required 4 days of treatment.

The 5 mg and 15 mg BID dose groups of PF-02545920 appeared to be generally well tolerated, with an overall tolerability profile comparable to risperidone. In general, there were few differences in AE frequency between the treatment groups, and most AEs were mild or moderate in severity. The most commonly occurring AEs with PF-02545920 were akathisia in both PF-02545920 groups, and dystonia and sedation/somnolence in the 15 mg group. The incidence rate of dystonia for the titrated 15 mg Q12H dose group in this study (8.1%) was substantially lower than the rate observed in a similar study (A8241006) population with a non-titrated 15 mg Q12H dose (43%) suggesting that titration reduced the risk for dystonia with this compound.

Although there were 14 SAEs in 12 subjects, all of them were judged to be non-treatment related by the investigator and the sponsor.

At the a priori specified level of significance of 0.1 (1-sided), it can be concluded from the primary analysis for the mean change from Baseline in the positive and negative syndrome scale (PANSS) total, that neither dose of PF-02545920 was different from placebo.

Study **A8241018** showed that overall PF-02545920 was safe and well tolerated in subjects with schizophrenia treated with adjunctive PF-02545920 titrated to 15 mg BID via the 3 approaches to titration. The most common AEs were somnolence, akathisia, dystonia, headache and extrapyramidal disorder. The majority of reported AEs were mild or moderate. Two subjects experienced severe AEs of oromandibular dystonia and myalgia (PF-02545920 treatment group). There were no deaths, SAEs, discontinuations, dose reductions, or temporary discontinuations of study medication due to AEs.

In prior studies with PF-02545920 (A8241006, A8241012), the incidence of dystonia was reduced by the incorporation of dose titration. In this study A8241018, dystonia and oromandibular dystonia were observed. The incidence rate of dystonia and oromandibular dystonia was lower in PF-02545920 treated subjects in Cohort 3 (14.2%) using the 7 day titration interval than in Cohorts 1 and 2 (33.4% in Cohort 1, 25.0% in Cohort 2) that used a shorter titration interval. Dystonia AEs responded well to “as needed” (PRN) use of anticholinergic medication treatment and resolved without interruption in study drug administration. No subjects required ongoing prophylactic treatment with anticholinergic medications, and no subjects were discontinued due to dystonia.

There were no notable changes from baseline in blood pressure (BP) or pulse rate in any treatment group or between the PF-02545920 and placebo groups. Two subjects were noted

to exhibit non-symptomatic orthostatic hypotension on routine assessments that were documented as AEs but not accompanied by lightheadedness and one subject exhibited non-symptomatic orthostatic changes in pulse rate that was documented as an AE but not accompanied by lightheadedness. There were no notable changes from baseline in ECG parameters or notable differences in mean ECG parameters between the PF-02545920 and placebo treatment groups. No ECG values were considered to be AEs. There were no clinically important trends in laboratory values during the study. There were no laboratory abnormalities reported as AEs.

As of August 2014 there are three active trials with PF-02545920, one in schizophrenia (A8241019), one in HD subjects (A8241016) and one in healthy volunteers (A8241017).

The proof-of-concept study in subjects with schizophrenia (**A8241019**) is a 12 week, randomized, outpatient, parallel group, double blind comparison of PF-02545920 5 mg, PF-02545920 15 mg, and placebo dosed BID in the adjunctive treatment of subjects with stable schizophrenia who have demonstrated a suboptimal response to a stable dose of antipsychotic monotherapy and other psychotropic medications.

Study **A8241017** is a Phase 1 open-label, single center, single oral dose, serial cohort study in healthy volunteers to establish the extent to which PF-02545920 occupies central PDE10A enzyme as assessed by *in vivo* PET scanning using the PDE10A radioligand [^{18}F]MNI-659.

Study **A8241016** is a Phase 2, double-blind, sequential treatment group, fixed dose, placebo-controlled, single center, randomized trial in subjects with a diagnosis of early HD. This study assesses the safety of PF-02545920 and its efficacy in improving motor, cognitive and behavioral deficits after 28 days of treatment. Subjects are randomized to PF-02545920 20 mg BID (titrated) or placebo (Cohort A), or to PF-02545920 5 mg BID or placebo (Cohort B), and are evaluated with several outcome measures including total motor score (TMS), executive function tasks, the Problem Behaviors Assessment for HD short form, and the Starkstein apathy scale.

As of August 2014, there have not been reports of new unexpected adverse events from the above ongoing studies and the available information suggests that the safety profile of PF-02545920 in subjects with HD should not be expected to be different than that observed in subjects with schizophrenia or healthy volunteers.

Complete information for PF-02545920 may be found in the SRSD, which for this study is the Investigator's Brochure.

1.2.3. Pharmacokinetics

Following single and multiple dose administration of PF-02545920, exposure of both parent and a pharmacologically active N-desmethyl metabolite (PF-01001252) increased with increases in dose in a nearly dose proportional manner. PF-02545920 absorption was rapid with median time to maximum plasma concentration (T_{max}) of approximately 1 hour post-dose. The mean terminal half-lives of PF-02545920 and PF-01001252 at steady state were approximately 11-13 hours and 8-12 hours, respectively.

To date, PF-02545920 has been evaluated in healthy subjects, subjects with chronic symptoms of schizophrenia, and subjects with acute exacerbation of schizophrenia. There was no significant difference in exposure across these populations. Steady state exposures of PF-02545920 and PF-01001252 are shown in Table 2.

Table 2. Steady State Exposures of PF-02545920 and PF-01001252 observed after Multiple Dosing in Subjects with Stable Schizophrenia (A8241002)

	PF-02545920	PF-01001252
PF-02545920 Dose = 20 mg Q12H for 13 days		
C_{max} (ng/mL)	327	66.1
AUC_{12} (ng*hr/mL)	1280	334

The major clearance pathway for PF-02545920 in humans is expected to be cytochrome P450 (CYP)-mediated hepatic metabolism, predominantly executed by CYP3A4. Additionally, the disposition of PF-02545920 does not appear to be modulated by p-glycoprotein (P-gp).

Both non-clinical data and clinical cerebrospinal fluid (CSF) data suggest equilibrium of unbound PF-02545920 concentration in plasma and CNS, therefore free plasma PF-02545920 concentration can be used as a surrogate of CNS target exposure with high confidence. Based on preclinical estimates of enzyme occupancy and observed PF-02549520 C_{max} values (Table 2), the 20 mg BID dose is projected to result in approximately 66% PDE10A occupancy at steady state C_{max} (Fu=0.0017). Similarly, the average enzyme occupancy at steady state over a 12 hr period is projected to be approximately 39% (Fu=0.0017) at 20 mg BID dosing. The *in vitro* IC_{50} for PF-02545920 on PDE10A inhibition was 0.18 nM, which corresponds to 42 ng/mL of total plasma PF-02545920 concentration, adjusted by molecular weight of 392 and free fraction of 0.0017.

1.2.4. Dose Selection Rationale

A single dose of 20 mg PF-02545920 (BID) will be studied to evaluate long-term safety and efficacy in subjects with HD. Based on the previous pre-clinical efficacy data and clinical safety data, a dose of 20 mg BID is estimated to produce the most robust PDE10A inhibition while still being well tolerated. The 20 mg BID dose is the maximum dose evaluated in the double blind Phase 2 Proof-Of-Concept Study (A8241021) in subjects with HD.

A titration scheme will be used for all subjects who did not receive the 20 mg BID dose in the previous study A8241021 in order to mitigate the potential risk of dystonia.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. 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.

CCI [redacted]:

- CCI [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

2.2. Endpoints

Primary Endpoint:

- 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).

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.
- 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.

CCI [redacted]:

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3. 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).

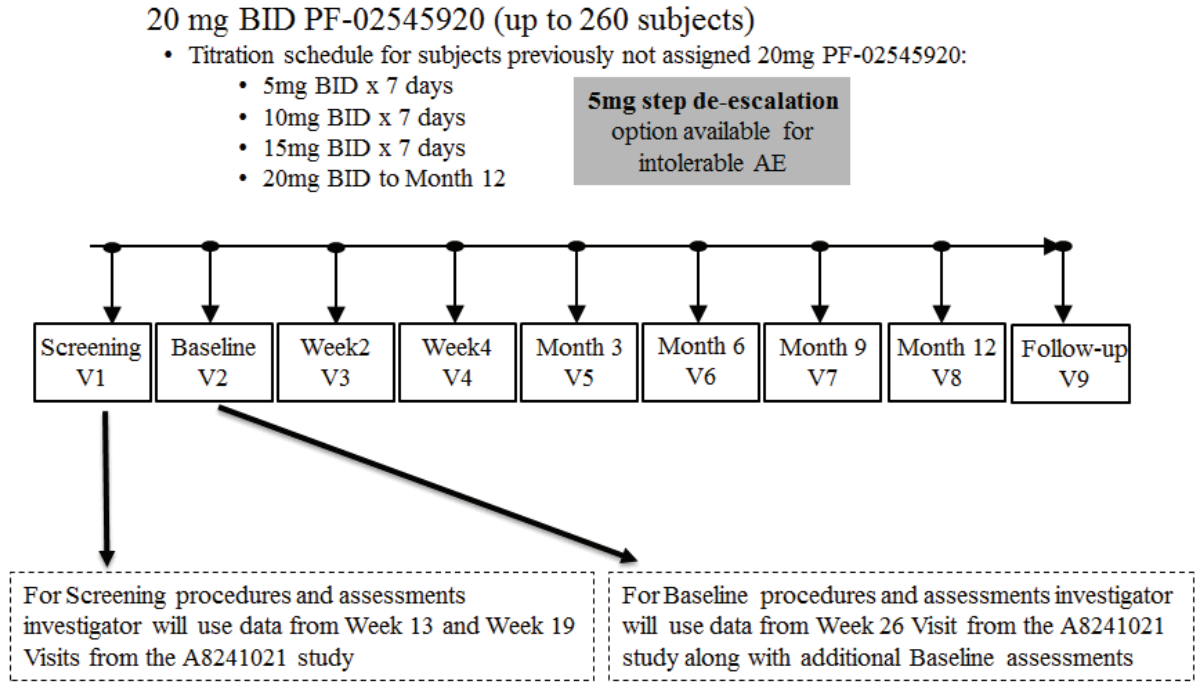
Subjects, who were assigned to the 20 mg PF-02545920 dose group in the preceding A8241021 study, will continue to receive 20 mg PF-02545920 in this study without any titration. All other subjects will be titrated to the 20 mg BID dose as follows: 5 mg BID for 7 days, 10 mg BID for 7 days, 15 mg BID for 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 (see Guidance on clinical management of subjects with acute extrapyramidal symptoms, Appendix 1).

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) CCI [redacted] (CCI).

Figure 1. Study Design Schematic



3.1. Stopping Criteria

White Blood Count (WBC) and Neutrophil (ANC) Monitoring:

WBC counts and differentials will be reviewed at Screening (V1) and Baseline Day 1 (V2) reviewed and performed at the following visits: Week 2 (V3), Week 4 (V4), Month 3 (V5), Month 6 (V6), Month 9 (V7), Month 12 (V8)/ET and Follow-up (V9). In the event that the ANC and/or WBC results are abnormal, the investigator (or a delegate) will contact the subject to inquire about potential symptoms. The lab results will be reviewed by the investigator (or delegate) as soon as possible once they are available, but no later than 2 business days after receipt of the lab results. The investigator must confirm and document that the results do not meet WBC/ANC stopping criteria listed below and that the subject can

continue to receive study medication. The Pfizer Medical Monitor and the Pfizer clinician should be contacted immediately if a subject meets any of the WBC/ANC stopping criteria. A separate source document worksheet will be provided to each site to assist in the monitoring of these criteria. See Neutropenia Assessment for a description of the minimal safety assessment for evaluating cases of neutropenia meeting any of the study stopping criteria described below.

3.1.1. Subject Stopping Criteria

- Subjects with WBC ≤3000 cells/mm^3 but ≥2000 cells/mm^3 and/or ANC ≤1500 cells/mm^3 but ≥1000 cells/mm^3 will have study treatment temporarily suspended and have three times per week WBC counts with differential until WBC ≥3000 cells/mm^3 and ANC ≥1500 cells/mm^3. Subjects who have at least 2 consecutive WBC or neutrophil findings meeting this criterion will be evaluated by a hematologist to determine the etiology of the adverse event and for medical management recommendations.

- Subjects will be discontinued from study participation if WBC ≤2000 cells/mm^3 and/or ANC ≤1000 cells/mm^3. Subjects who are discontinued or permanently suspended due to WBC or ANC findings will be evaluated by a hematologist to determine the etiology of the adverse event and for medical management recommendations.

3.1.2. Study Stopping Criteria

- The study will be stopped if any subject develops agranulocytosis, ie, ANC ≤500 cells/mm^3, which cannot be explained by other disease states or concurrent medications after medical assessment, including a hematology consultation. The data generated in the evaluation of events potentially meeting this stopping criterion will be reviewed by the independent External Data Monitoring Committee (E-DMC), which will make the final determination whether this criterion has been met. See Data Monitoring Committee for additional detail on DMC procedures.

4. SUBJECT SELECTION

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

4.1. Inclusion Criteria

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

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

1. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.

2. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

3. Subjects must have completed Study A8241021 and, in the opinion of the investigator and sponsor, have been compliant with the STUDY PROCEDURES, Lifestyle Guidelines and study treatment.

4. CCI [redacted].

5. Males or females between the age of 30 years and 66 years (inclusive).

6. Diagnosis of HD based on characteristic clinical findings, including presence of chorea, and genetic confirmation with the detection of an expansion of ≥36 CAG trinucleotide repeats in the huntingtin gene (*Htt*).

7. Male and female subjects of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for at least 28 days (90 days for males) after the last dose of assigned treatment.

   Female subjects who are not of childbearing potential (ie, meet at least 1 of the following criteria):

   - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
   - Have medically confirmed ovarian failure; or
   - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum follicle stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women.

4.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees directly involved in the conduct of the study.

2. Participation in study(ies) involving investigational drug(s) (Phases 1-4) other than PF-02545920 within the past 9 months before the current study begins and/or during study participation.

3. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

4. Evidence or history of:

    a. Clinically significant neurologic disorder other than Huntington's disease. This also includes subjects with previous history of epilepsy or seizures (except childhood febrile seizures), stroke, head injury with significant neurologic sequelae.

    b. Other severe acute psychiatric condition, mania and/or psychosis.

    c. For subjects who score ≥3 on the suicidal ideation item of the Problem Behaviors Assessment or answer "Yes" to the C-SSRS questions 4 or 5, a risk assessment should be done by a qualified mental health professional (eg, a psychiatrist or licensed PhD level clinical psychologist) to assess whether it is safe for the subject to participate in the study (See Suicidality Risk Assessment). In addition, subjects deemed by the investigator to be at significant risk of suicidal or violent behavior should be excluded. Attempted suicide or suicidal ideation with intention or plan, which required hospital admission and/or change of level of care within 15 months prior to Screening should be discussed with medical monitor or clinician before proceeding.

5. Evidence or history of any clinically significant conditions which affect one of the following systems and which were used as exclusion criteria in preceding A8241021 study:

    a. Renal.

    b. Endocrine.

    c. Pulmonary.

    d. Hematological.

    e. Gastrointestinal (including any condition possibly affecting drug absorption, eg, gastrectomy, gastric bypass).

    f. Immunological, including positivity for human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS).

    g. Severe allergic diseases (excluding untreated, asymptomatic, seasonal and environmental allergies at time of dosing).

    h. Any history of malignant tumors and treatment within the previous 15 months.

6. Subjects with:

    a. WBC ≤3500/mm^3 OR ANC ≤2000/mm^3 anytime in study A8241021 which were not approved as acceptable for enrollment in study A8241022 by the sponsor study clinician or sponsor medical monitor. These cases should be discussed with the sponsor medical monitor or clinician prior to submitting subject for an eligibility approval.

    b. History of neutropenia, including benign ethnic neutropenia, clozapine induced agranulocytosis or granulocytopenia.

    c. History of myeloproliferative disorders (primary myelofibrosis, polycythemia vera, essential thrombocythemia, chronic eosinophilic leukemia/hypereosinophilic syndrome, systemic mastocytosis).

7. Evidence or history of clinically significant cardiovascular disease, including:

    a. Uncontrolled hypertension (sitting or supine diastolic blood pressure >95 mmHg and/or sitting or supine systolic blood pressure >170 mmHg with or without treatment).

    b. Evidence of orthostatic symptoms (eg, dizziness upon standing) or systolic blood pressure (BP) drop ≥20 mm Hg or diastolic BP drop ≥10 mmHg from supine to standing assessment at screening.

    c. Any 12-lead ECG with repeated demonstration of QTc >450 msec or a QRS interval >120 msec.

    d. Coronary bypass surgery.

    e. History of myocardial infarction or ischemic heart disease.

    f. Heart failure.

    g. Non clinically significant ECG findings including sinus bradycardia and tachycardia will not exclude subjects from the study.

8. Subjects with laboratory test results reviewed at screening that deviate from the upper or lower limits of the reference range, as assessed by the study-specific laboratory and confirmed by a single repeat, if deemed necessary, except for non-clinically significant values, as determined by the investigator.

    a. AST or ALT must be ≤2 X upper limit of reference range.

    b. Total bilirubin must be within 1.5 X of the upper limit of reference range at screening; 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.

9. Subjects with 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.

10. Any positive urine drug screen documented during study A8241021 and not explained by subject's medication regimen.

11. Drugs or foods/food products which strongly inhibit CYP3A4 (including but not limited to atazanavir, amiodarone, cimetidine, clarithromycin, diltiazem, erythromycin, fluvoxamine, grapefruit, grapefruit juice, grapefruit-related citrus fruits/juices, indinavir, itraconazole, ketoconazole, mibefradil, nefazodone, nelfinavir, ritonavir, troleandomycin, and verapamil).

12. Drugs which significantly induce CYP3A4 (including but not limited to rifampin, rifapentine, rifabutin, phenytoin, carbamazepine, oxcarbazepine, phenobarbital, St. John's Wort).

13. Any history of deep brain stimulation (DBS).

14. Any history of surgical and experimental procedures aiming at improving HD symptoms including:

    a. Neural transplantation.

    b. Central nervous system lesions.

    c. Infusion of neurotrophic agents.

15. Any reported change in regular alcohol consumption since Baseline Day 1 (V2) of study A8241021, which raises clinical concern.

16. Any subject who is likely to be hospitalized (for any reason) during the study.

17. CCI [redacted]

18. CCI [redacted]

19. Unwilling or unable to comply with the Lifestyle guidelines described in this protocol (see Lifestyle Guidelines).

20. Pregnant female subjects; breastfeeding female subjects; male subjects with partners currently pregnant; male and female subjects of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days (90 days for males) after the last dose of investigational product.

21. Any drug-related SAE experienced during the Study A8241021 which were not approved as acceptable for enrollment in A8241022 study by the sponsor study clinician and sponsor medical monitor. These SAEs should be discussed with the sponsor clinician and sponsor medical monitor prior to submitting the subject for an eligibility approval.

4.3. Randomization Criteria

Once subjects have satisfied all selection criteria, they will be assigned a randomization number that will determine whether they will undergo blinded titration to 20 mg BID (subjects in the placebo and 5 mg BID arm in study A8241021) or continue the same dose (subjects already in the 20 mg BID arm in study A8241021) (See STUDY TREATMENTS).

4.4. Lifestyle Guidelines

4.4.1. Activity

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

4.4.2. Contraception

All male and female subjects who, in the opinion of the investigator, are biologically capable of having children and are sexually active must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days (90 days for males) after the last dose of investigational product. The investigator or his/her designee, in consultation with the subject, will confirm that the subject has selected the most appropriate method of contraception for the individual subject and his female partner from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet at least one of the selected methods of contraception. The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the schedule of activities (SOA) and document such conversation in the subject's chart. In addition, the investigator or his/her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected.

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

1. Established use of oral, inserted, injected, or implanted hormonal methods of contraception is allowed provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the post-vasectomy ejaculate.

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

All sexually active male subjects must agree to prevent potential transfer of and exposure to drug through semen to their partners by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for 90 days after the last dose.

4.4.3. Meals and Dietary Restrictions

Subjects will not be allowed to eat or drink grapefruit or grapefruit-related citrus fruits (eg, Seville oranges, pomelos) from the Screening visit through the Month 12 Visit (V8).

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 on the team SharePoint site.

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

The help desk number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigational site.

4.6. Rater Qualifications

Raters must demonstrate sufficient assessment experience as well as appropriate educational background and indication experience. Rater qualification will be documented as part of the overall rater qualification process.

Raters performing the following assessments will require certification or training by the sponsor designated vendor prior to rating in this study:

- UHDRS, [redacted], clinical global impression (CGI) [redacted] and C-SSRS.

Other efficacy and safety/screening scales outlined in the Schedule of Activities may require documentation of study specific training on these instruments before rating in the trial is permitted.

Vendor(s) designated by the sponsor will conduct rater qualification(s) and will provide written and signed documentation(s) about each rater's certification(s) and/or training(s). Recertification may be required and will be provided by the sponsor designated vendor(s) at periodic intervals during the study. A separate guideline will be developed to facilitate rater selection at the sites.

If possible, each subject will be interviewed and assessed throughout the study by the same rater. Reasons for rotation of approved raters should be documented in the site source documents.

5. STUDY TREATMENTS

All subjects who consent to participate will undergo screening procedures during the screening period. Informed consent should be obtained by Screening Visit, which is Week 19 of the A8241021 study, for subjects to participate in the open-label extension study. Subjects who meet enrollment criteria AND have received confirmation by the sponsor will be randomized to participate in the 12 month, open label study.

Subjects will be assigned to 20 mg BID dosing of PF-02545920 (with blind titration for subjects previously receiving 5 mg BID PF-02545920 or placebo in study A8241021).

Option for temporary or permanent blind de-escalation by 5 mg decrements will be available should the investigator consider the AE intolerable (see Guidance on clinical management of subjects with acute extrapyramidal symptoms - Appendix 1). Once AEs have resolved the principle investigator (PI) will have the option to resume escalation.

5.1. Allocation to Treatment

The investigator's knowledge of the treatment should not influence the decision to enroll a particular subject or affect the order in which subjects are enrolled.

Investigators will use an Interactive Response Technology (IRT) to assign a unique subject identification number to each subject who has signed the informed consent document (ICD). This identifying number will be retained throughout the duration of the study participation. Subject eligibility for participation in the study will be determined following the Screening assessments (V1). Once the subject is determined to be eligible for treatment, the investigator will obtain a randomization number and study medication assignment utilizing the IRT.

Subjects, who received PF-02545920 20 mg BID in the preceding A8241021 study, will continue to receive PF-02545920 20 mg BID in this study. Subjects, who previously received either PF-02545920 5 mg BID or placebo in the A8241021 study, will be titrated to PF-02545920 20 mg. The titration will start at 5 mg BID and the dose will be increased by 5 mg BID every 7 days, up to a 20 mg BID to be reached at Day 22, and maintained until Month 12 (V8). Subjects will take 4 tablets twice a day provided in blister packs from Baseline Day 1 (V2) to Week 4 (V4) and in bottles from Week 4 (V4) to Month 12 (V8). For subjects, who have been de-escalated from 20 mg BID to lower dose in the preceding study A8241021, the investigator should contact the sponsor study clinician and medical monitor to discuss titration scheme.

Table 3. Allocation to Study Treatments

Treatment Group	Study Treatment	Drug Administration	Duration
20 mg PF-02545920, Subjects receiving 20 mg PF-02545920 in the preceding A8241021 study	Days 1-365 Four 5 mg tablets of PF-02545920	Orally, BID	12 months (Days 1-365)
20 mg PF-02545920, All other subjects	Days 1-7 One 5 mg tablet of PF-02545920 Three placebo tablets for PF-02545920 Days 8-14 Two 5 mg tablets of PF-02545920 Two placebo tablets for PF-02545920 Days 15-21 Three 5 mg tablets of PF-02545920 One placebo tablet for PF-02545920 Days 22-365 Four 5 mg tablets of PF-02545920	Orally, BID	12 months (Days 1-365)

5.2. Breaking the Blind

All subjects will receive 20 mg PF-02545920 BID starting on Day 22. The initial titration period between Day 1 and Day 22 will be double blind.

The method for breaking the blind will be an electronic process via IRT. At the initiation of the study, the study site will be instructed on the method for breaking the blind. Blinding codes should only be broken in emergency situations for reasons of subject safety. The responsibility to break the treatment code in emergency situations resides with the investigator. Whenever possible, it is requested the investigator or sub-investigator consult with a member of the study team prior to breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the case report form (CRF)/data collection tool (DCT) and the Sponsor is to be notified.

5.3. Subject Compliance

Dosing compliance is documented in the accountability logs, the electronic Case Report Form (eCRF) and in the subject's dosing diary. On Day 1 subjects will be instructed on how to take their medication each day, twice a day, during outpatient dosing days. A dosing diary will be given to the subject for the first four weeks, with instructions on how to record daily times of study drug administration. The subject will bring the used and in-use medication blister cards and/or bottles back to the clinic at each visit. At each visit, a tablet count will be done by the research staff, and the subject will be questioned about any missed or extra doses taken. Checking blister packs and bottles will allow the site personnel to check on administration compliance.

A subject may be considered non-compliant if they have missed more that 20% of the required doses since the first dose.

Medication Compliance Formula:

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

For example, if the subject is required to take 4 tablets twice daily for exactly 12 months (365 days, 2,920 tablets prescribed) but according to the amount of drug returned the subject took 2280 tablets of study medication, percent compliance is calculated as follows:

$$\frac{2280}{2920} \times 100 = 78\%\ Compliance$$

Dosing record from Baseline to Week 4 should contain details of missed or lost doses for accurate compliance measurement. Compliance will be assessed by pill count after Week 4. If compliance is less than 80% or greater than 120% at any visit, the reason(s) must be noted. Subjects should not make up for missed doses. Missed dose(s) related to AEs should be discussed with the sponsor.

5.4. Drug Supplies

The study medication will be as follows:

Table 4. Drug Supplies

Dosage Forms	Compounds	Appearance
Active drug tablet 5 mg	PF-02545920	White to off white small round tablets
Placebo tablets for 5 mg PF-02545920	Placebo	White to off white small round tablets

5.4.1. Dosage Form(s) and Packaging

PF-02545920 will be supplied by the sponsor as tablets containing 5 mg of active drug. For treatment between Baseline Day 1 (V2) and Week 4 (V4), drug supplies will be packaged in blister packs with labels containing morning and evening administration and titration instructions. The tablet count per blister pack will be appropriate for the dosing regimen and treatment period. The blister pack also allows for an accurate blind de-escalation with 5 mg decrement, should the Principal Investigator assess that a subject requires a (temporary or permanent) dose adjustment due to intolerable AE(s) (See Appendix 1). The blister card will have column labels for each tablet (A, B, C, D) to facilitate giving direction to the subject. Once AEs have resolved the PI will have the option to resume escalation.

For treatment between Week 4 (V4) and Month 12 (V8), drug supplies will be packaged in high-density polyethylene (HDPE) bottles.

Pfizer will provide all study medication except for concomitant and rescue medications.

5.4.2. Preparation and Dispensing

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of the study drug.

The study medication will be dispensed using a drug management system at each visit from V2 to V7. Dispensing will be done by a qualified staff member via unique container numbers in either blister cards or bottles, in quantities appropriate for the study visit schedule. The subject should be instructed to maintain the product in the blister cards or bottles throughout the course of dosing and return the blister cards and/or bottles to the site at the next study visit.

5.5. Administration

Subjects will be instructed to take the study medication twice a day (BID), morning and evening, at approximately the same time of day throughout the study, and if possible (ideally) at least one hour prior to, or two hours after meals. Subjects will swallow the study medication whole, and will not manipulate or chew the medication prior to swallowing. Drug will be dispensed to the subject at each clinic visit starting at Baseline Day 1 (V2) and ending with Month 9 (V7).

Between clinic visits, subjects will be responsible for establishing a process for reliable outpatient dosing to ensure dosing compliance. To facilitate safety monitoring during the titration phase, a dosing diary will be supplied to the subject for the first four weeks and subjects will be instructed to record the time of each daily dose of study medication. Subjects will be instructed to bring the completed diary to Week 2 and Week 4 Visits, along with used and in-use blister packs containing the study medication. The study staff will use bottles to assess compliance after the Week 4 Visit.

If a subject misses a scheduled morning dose, that dose should be taken as soon as possible, but not later than 6 hours beyond the scheduled time of administration. If it is greater than 6 hours beyond the scheduled dose, the subject should be instructed to skip that dose and resume dosing at the next regularly scheduled time. Missed doses and reasons for missed doses should be recorded on the dosing diary.

5.6. Drug 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 recommended storage conditions (controlled room temperature between 15-25°C) and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original packaging or container and in accordance with the drug label. Storage conditions stated in the SRSD (Investigator Brochure) will be superseded by the storage conditions stated on the labeling.

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

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

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. Specific details regarding information the site should report for each excursion will be provided to the site. Receipt of materials, door opening and closing, and other routine handling operations where the product(s) are briefly out of labeled temperature range are not considered excursions. More specific details will be provided to the sites separately.

Site staff will instruct subjects on the storage requirements for medications they take home including how to report temperature excursions.

PF-02545920 must not be used outside the context of this protocol. Under no circumstances should the investigator or other site personnel supply PF-02545920 to other investigators, patients, or clinics, or allow supplies to be used other than directed by this protocol, without prior authorization from the sponsor. The investigator must maintain adequate records documenting the receipt, use, loss, or other disposition of investigational product(s). Pfizer may supply drug accountability forms that may be used, or may approve the use of an equivalent form. The form must identify the investigational product, including batch or code numbers, and account for its disposition on a subject by subject basis, including specific dates and quantities. Unused study drug, and unused or used study drug materials must be kept in a secure location for final accountability and reconciliation. At the end of the clinical study, Pfizer will provide instructions as to the disposition of any unused investigational product. The investigator must provide an explanation for any destroyed or missing study drug and/or study drug materials.

5.7. Drug Accountability

The investigator's site must maintain adequate records documenting the receipt, use, loss, or other disposition of the drug supplies. The subject will be instructed to return to all clinic visits with all (used and in-use) blister packs and/or bottles (and dosing diary at Week 2 and 4 Visits) for accountability and compliance check.

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

5.8. Concomitant Treatment(s)

All 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(s) at each clinic visit. Medications taken within 8 weeks prior to the Screening Visit or between Screening and Baseline Visits in study A8241022 will be documented as prior medications. Medications taken after the first dose of study medication in study A8241022 will be documented as concomitant medications. Additionally, history of all prior and current treatments indicated for HD at any time must be recorded. Concomitant medications include all vitamins, herbal remedies, nutritional supplements, over-the-counter, prescription medications, and prescription medical foods.

Antipsychotics, antidepressants and all permitted psychotropic medications need to be at stable doses for the duration of the study. Medication regimen stability is defined as maintaining the same dosage of medications except for minor adjustments to manage drug specific tolerability issues. Recognizing that physicians outside of the study may be managing the subject's background antipsychotic and other psychotropic medications,

changes of medications and/or doses should be discussed with the sponsor study clinician and medical monitor to determine subject disposition.

Stable administration of antidepressants will be allowed, with the exception of tricyclics and monoamino-oxidase inhibitors (MAOIs).

Prescription medical food (eg, Axona™) or prescription nutraceuticals marketed for HD (eg, creatine) or for movement disorders, which were prohibited during the study A8241021, are also prohibited in the study A8241022.

The use of tetrabenazine is prohibited at any time during the study period.

The use of amphetamine-like medications and stimulants is prohibited at any time during the study period.

Appendix 2 summarizes the drugs and classes of drugs allowed and prohibited as concomitant medications after the Screening visit (V1) and while on the study, until the end of the study Month 12 (V8), unless specified otherwise.

Acetaminophen/paracetamol may be used at doses of ≤1 g/day on an as needed basis. Limited use of non-prescription medications that are not believed to affect subject safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor's medical monitor.

5.9. Rescue Medication

The use of any rescue medication should be discussed with study sponsor medical monitor or clinician prior to administration if at all possible.

Use of all "prn" medications on an "as needed" basis should be avoided within 24 hours prior to each clinic visit to minimize potential effects on the assessment scales, unless withholding such treatment is judged by the investigator to present a safety risk for the subject.

5.9.1. Rescue Medications for Anxiety/agitation

Short acting benzodiazepines (whose median half-life is between 2 and 15 hours) may be given, and only as needed (prn), not as a standing dose.

5.9.2. Rescue Medication for Insomnia

Insomnia medications are permitted for the duration of the study only if it is determined to be clinically necessary by the investigator. Treatment for insomnia should be avoided within 24 hours prior to each clinic visit to minimize potential effects on the assessment scales.

5.9.3. Rescue Medications for the Management of Extrapyramidal Symptoms (akathisia, dystonia, tardive dyskinesia)

Subjects may receive treatment with anticholinergics for acute extrapyramidal symptoms (EPS) throughout the conduct of the study at doses within the respective approved dosing ranges by oral (preferred) or injectable administration; however, prophylactic or preventative treatment (eg, prescribed daily or routinely to prevent EPS) will not be permitted. Time and date documentation of the use of "as needed" ("prn") anticholinergics for the treatment of acute EPS must be directly linked to time and date adverse event documentation of the specific target EPS eg, dystonia, parkinsonism, akathisia. Additional guidance is presented in Appendix 1.

6. STUDY PROCEDURES

6.1. Screening

Screening Visit will take place on the same day as the Week 19 Visit for Study A8241021.

In preparation for the screening visit (prior to Week 19 for study A8241021), the investigator will assess subject eligibility for the open label study A8241022 using all data available from study A8241021, as described in detail in Section 7.4. Pre-screening Checklist A will be provided to assist the site in documenting this review.

The investigator will review available data for study A8241021 at Week 19 (changes in medical history, medical procedures, concomitant medications, compliance) and confirm continued eligibility by the PI prior to proceeding to informed consent documentation. Screening Checklist B will be provided to assist the site in documenting this review.

The following activities will be completed during the clinic visit:

- Obtain institutional review board/ethics committee (IRB/EC) approved written informed consent from the subject in accordance with local regulations before initiating any other screening procedures.
- Obtain informed consent. [redacted]
- Review overall subject eligibility (Section 7.4).
    - File Record of Signed and Dated Pre-screening Checklist A.
    - Complete Screening Checklist B for review of study A8241021 data.
    - Review inclusion/exclusion criteria.

- Obtain subject eight digit screening number from IRT.
- Submit information required to sponsor (or designee) for Sponsor Eligibility Verification Process, at least 2 business days prior to planned randomization, as instructed during protocol training (Section 7.5).
- To prepare for study participation the subject will be instructed on the Lifestyle Guidelines (Section 4.4) and concomitant medications restrictions required by protocol (Section 5.8). Ensure instructions for Lifestyle Guidelines are documented in the source documents.
- Remind the subject about the date of the next clinic visit at Baseline Day 1 (V2).

6.2. Study Period

6.2.1. Visit 2 - Baseline Day 1 (Randomization)

All visit windows will be relative to Baseline Day 1 (V2). The Baseline Day 1 (V2) will be performed on the same day as the Week 26 visit for study A8241021. Selected assessments from study A8241021 Week 26 clinic visit will be recorded and used for baseline, as specified below.

The following activities will be completed during the clinic visit

- Document Sponsor Eligibility Confirmation PRIOR to randomization.
- Review and document subject's medical history, medical procedures, concomitant medications (Section 7.3).
- Confirm continued subject eligibility (includes review of available data from Week 26 visit for study A8241021).
- Document the following data obtained at Screening for study A8241021:
  - Subject's number of CAG repeats obtained for A8241021 study to document continued eligibility (Section 7.2).
  - Demography data.
  - Height (centimeters).
- Record results of the following assessments captured at Week 26 for Study A8241021:
  - Weight (kilograms).
  - Brief physical examination (Section 7.7.1).

- Brief neurological examination (Section 7.7.3).
- Single 12-lead ECG (Section 7.7.7).
- Orthostatic vital signs (supine and standing blood pressure and pulse) and oral or tympanic body temperature (Section 7.7.2).
- Contraception check.
- Hematology (Section 7.7.4).
- Blood chemistry (Section 7.7.4).
- Serum pregnancy test for females of child bearing potential (sent to central lab) (Section 7.7.5).
- Urinalysis (Section 7.7.4).
- CCI [redacted]
- C-SSRS (since last visit) for suicidality risk assessment (Section 7.7.6 7.7.6.1).
- CCI [redacted] (Section 7.9.7).
- UHDRS Total Motor Score (TMS), CCI [redacted] CCI [redacted], CCI [redacted] CCI [redacted] (Section 7.9.1).
- CCI [redacted] (CCI [redacted] CCI [redacted]) (Section 7.9.2).
- CCI [redacted] (CCI [redacted]) (Section 7.9.3).
- CCI [redacted] (Section 7.9.4):
  - CCI [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

- CCI [redacted] (Section 7.9.5).
- CCI [redacted] (CCI [redacted]) CCI [redacted] (Section 7.9.9).
- Review of ANC and WBC for safety monitoring (Section 7.8).
- CCI [redacted] (Section 7.9.8).

The following assessments will be performed:

- Non-fasted blood sample may be collected for serum FSH (Section 7.7.4) (if requested by the investigator for female subjects, to confirm that FSH level is within the laboratory's reference range for postmenopausal women).
- Collect sample for urine pregnancy test (for females of child bearing potential) (Section 7.7.5).
- Urine drug screen may be performed, if deemed necessary by the investigator (Section 7.7.4).
- Administer Clinical Global Impression Severity (CGI-S) scale (Section 7.9.6).
- Obtain randomization number from selected automatic randomization system (IRT).
- Dispense dosing diary.
- Dispense study drug to subject for outpatient dosing.
- Provide instructions to subject for outpatient dosing, including storage, administration, dosing diary use.
- Provide instructions to subject on Adverse Event (AE) and Serious Adverse Event (SAE) collection and instructions for reporting such events to the investigator.
- Remind the subject about the date of the next clinic visit at Week 2 (V3) and also to bring to the visit all (used and in-use) blister packs and dosing diary.

6.2.2. Visit 3 – Week 2/Day 14 (±3 days)

The following activities will be completed during Week 2 visit (V3):

- Review adverse events since last visit.
- Review changes in the subject's medical history, concomitant medications, and medical procedures since last visit.

- Obtain vital signs (sitting blood pressure and pulse; oral or tympanic body temperature).
- Contraception check.
- Collect non-fasted blood sample for safety monitoring of ANC and WBC.
- Complete C-SSRS (since last visit) for suicidality risk assessment.
- Administer the UHDRS Total Motor Score (TMS).
- Review ANC and WBC for safety monitoring.
- Assess compliance based on observation of blister packs and review of dosing diary.
- Dispense study drug to subject for outpatient dosing, with instructions to return to next clinic visit with all (used and in-use) blister packs and dosing diary.
- Remind the subject about the date of the next scheduled Week 4 (V4).

6.2.3. Visit 4 – Week 4/Day 28 (±3 days)

The following activities will be completed during Week 4 visit (V4):

- Review adverse events since last visit.
- Review changes in the subject's medical history, concomitant medications, and medical procedures since last visit.
- Obtain vital signs (sitting blood pressure and pulse; oral or tympanic body temperature).
- Contraception check.
- Collect non-fasted blood sample for safety monitoring of ANC and WBC.
- CCI [redacted].
- Complete C-SSRS (since last visit) for suicidality risk assessment.
- Administer the UHDRS Total Motor Score (TMS).
- Review ANC and WBC for safety monitoring.
- Assess compliance based on observation of blister packs and review of dosing diary.
- Collect dosing diary.

- Dispense study drug to subject for outpatient dosing, with instructions to return to next clinic visit with all (used and in-use) blister packs and/or bottles.
- Remind the subject about the date of the next scheduled Month 3 visit (V5).

6.2.4. Visit 5 – Month 3/Day 91 (±7 days)

The following activities will be completed during Month 3 visit (V5):

- Review adverse events since last visit.
- Review changes in the subject's medical history, concomitant medications, and medical procedures since last visit.
- Obtain vital signs (sitting blood pressure and pulse; oral or tympanic body temperature).
- Obtain standard 12-lead ECG (may be repeated if clinically indicated).
- Contraception check.
- Collect non-fasted blood sample for Hematology.
- Serum pregnancy test for females of child bearing potential.
- CCI .
- Complete C-SSRS (since last visit) for suicidality risk assessment.
- Administer the UHDRS Total Motor Score (TMS).
- Review ANC and WBC for safety monitoring.
- Assess compliance based on counting of unused tablets in bottles.
- Dispense study drug to subject for outpatient dosing, with instructions to return to next clinic visit with all (used and in-use) bottles.
- Remind the subject about the date of the next scheduled Month 6 visit (V6).

6.2.5. Visit 6 –Month 6/ Day 182 (±7 days)

The following activities will be completed during Month 6 visit (V6):

- Review adverse events since last visit.
- Review changes in the subject's medical history, concomitant medications, and medical procedures since last visit.

- Obtain weight (kilograms).
- Perform brief physical examination.
- Perform brief neurological examination.
- Obtain standard 12-lead ECG (may be repeated if clinically indicated).
- Obtain orthostatic vital signs (supine and standing blood pressure and pulse) and oral or tympanic body temperature.
- Contraception check.
- Collect non-fasted blood sample for routine laboratory tests, including the following tests:
  - Hematology;
  - Blood chemistry;
  - Obtain serum sample for pregnancy test for females of child bearing potential (sent to central lab).
- Collect urine sample for urinalysis.
- CCI .
- Complete C-SSRS (since last visit) for suicidality risk assessment.
- CCI .
- Administer the UHDRS Total Motor Score (TMS), CCI (CCI), CCI (Section 7.9.1).
- CCI
- CCI (CCI).
- Complete CGI-I scale.
- CCI (CCI).
  - CCI (CCI);
  - CCI ;
  - CCI ;

- CCI ;
- CCI ;
- CCI .

- CCI .
- CCI CCI .
- Review ANC and WBC for safety monitoring.
- Assess compliance based on counting unused tablets in bottles.
- Dispense study drug to subject for outpatient dosing, with instructions to return to next clinic visit with all (used and in-use) bottles.
- Remind the subject about the date of the next scheduled Month 9 visit (V7).

CCI CCI :

- CCI .
- CCI .
- CCI (CCI CCI CCI).
- CCI .

6.2.6. Visit 7 – Month 9/Day 273 (±7 days)

The following activities will be completed during Month 9 visit (V7):

- Review adverse events since last visit.
- Review changes in the subject's medical history, concomitant medications, and medical procedures since last visit.
- Obtain vital signs (sitting blood pressure and pulse; oral or tympanic body temperature).
- Obtain standard 12-lead ECG (may be repeated if clinically indicated).
- Contraception check.

- Collect non-fasted blood sample for Hematology.
- Serum pregnancy test for females of child bearing potential.
- CCI .
- Complete C-SSRS (since last visit) for suicidality risk assessment.
- Administer the UHDRS Total Motor Score (TMS).
- Review ANC and WBC for safety monitoring.
- Assess compliance based on counting of unused tablets in bottles.
- Dispense study drug to subject for outpatient dosing, with instructions to return to next clinic visit with all (used and in-use) bottles.
- Remind the subject about the date of the next scheduled Month 12 visit (V8).

6.2.7. Visit 8 – Month 12/Day 365 (±7 days)

The following activities will be completed during Month 12 visit (V8):

- Review adverse events since last visit.
- Review changes in the subject's medical history, concomitant medications, and medical procedures since last visit.
- Obtain weight (kilograms).
- Perform brief physical examination.
- Perform brief neurological examination.
- Obtain standard 12-lead ECG (may be repeated if clinically indicated).
- Obtain orthostatic vital signs (supine and standing blood pressure and pulse) and oral or tympanic body temperature.
- Contraception check.
- Collect non-fasted blood sample for routine laboratory tests, including the following tests:
  - Hematology;
  - Blood chemistry;

  - Obtain serum sample for pregnancy test for females of child bearing potential (sent to central lab).

- Collect urine sample for urinalysis.
- CCI
- Complete C-SSRS (since last visit) for suicidality risk assessment.
- CCI .
- Administer the UHDRS Total Motor Score (TMS), CCI (CCI), CCI (Section 7.9.1).
- CCI .
- CCI (CCI).
- Complete CGI-I scale.
- CCI (CCI).
  - CCI (CCI);
  - CCI ;
  - CCI ;
  - CCI ;
  - CCI ;
  - CCI .
- CCI
- CCI (CCI)
- Review ANC and WBC for safety monitoring.
- Assess compliance based on counting unused tablets in bottles.
- Remind the subject about the date of the next scheduled Follow up visit (V9).

[redacted]:

- [redacted].
- [redacted].
- [redacted] ([redacted]).
- [redacted].

6.2.8. Early Termination Visit

Subjects who withdraw or are withdrawn from the study should undergo an early termination visit whenever possible, unless consent for participation is also withdrawn, in which case no further study related procedures should be performed (see Subject Withdrawal).

In case of Early Termination between Baseline Day 1 and Day 14 (exclusive), only safety assessments will be performed (no efficacy assessments). If Early Termination occurs after Day 14 (inclusive), as many Month 12 (V8) assessments as possible should be completed.

6.2.9. Unscheduled Visit

Unscheduled visits may be performed at any time during the study, whenever necessary to assess or to follow-up on adverse events (AE) or serious adverse events (SAE) at the subject's request, or as deemed necessary by the investigator. The following clinical evaluations should take place, as medically warranted in the judgment of the investigator:

- Physical examination.
- Neurological examination.
- 12-lead ECG, when clinically indicated to follow-up on any prior clinically significant ECG abnormalities.
- Vital signs (supine and standing).
- Laboratory safety assessments, when clinically indicated to follow-up on any prior clinically significant laboratory abnormality.
- Review study drug compliance and accountability (if applicable).
- Review and record adverse events (AE) and serious adverse events (SAE).
- Review of prior and concomitant medications.
- Subject education on how to maintain compliance.

6.3. Follow-up Visit (V9)

The Follow-up Visit will occur between Day 372 and Day 379.

During the visit the investigator will:

- Review adverse events since last visit.
- Review changes in the subject's medical history, concomitant medications, and medical procedures since last visit.
- Perform brief physical examination.
- Perform brief neurological exam.
- Obtain vital signs (sitting blood pressure and pulse; oral or tympanic body temperature).
- Collect non-fasted blood sample for safety monitoring of ANC and WBC.
- Urine pregnancy test.
- Complete C-SSRS (since last visit) for suicidality risk assessment.
- Review ANC and WBC for safety monitoring.

6.4. 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 the study site. To the extent possible, subjects withdrawing from the study early should undergo an Early Termination visit, as described in Section Early Termination Visit, unless consent is also withdrawn. Subjects removed from therapy for reasons of safety will continue to be followed for the collection of safety data until resolution or stabilization of any adverse events which resulted in study discontinuation.

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

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.

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 the subject to return all unused investigational product(s), request the subject to return for an early termination visit, if applicable, and follow-up with the subject regarding any unresolved adverse events (AEs).

Lost to Follow-Up: All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death. If investigator's use of 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 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 in the Schedule of Activities. However it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, which may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and wellbeing of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion. The sites should do their best to perform the assessments in the recommended order as listed in Section 6 to maximize the likelihood to secure data for the primary and secondary endpoints.

7.1. Review of Inclusion/Exclusion Criteria

All inclusion and exclusion criteria must be carefully reviewed and compared against the screening data from the subject. Protocol deviations related to subject eligibility are of particular concern and will be specifically monitored for by the sponsor Inclusion/Exclusion criteria verification process, described below in Section 7.5.

7.2. CAG Profiling Documentation

At Baseline Day 1 (V2), the investigator should document the genetic profile of CAG repeats, as recorded for study A8241021. A critical feature of this criterion is the required documentation of a CAG repeat expansion ≥36. A cut-off of CAG repeats ≥36 was selected based on the carrier probability of becoming symptomatic.

7.3. Medical History/Prior Medications/Procedures

At Baseline Day 1 (V2), the investigator should make all reasonable efforts to obtain an accurate and complete medical history and history of prior medication use (at least 8 weeks prior to Screening) when evaluating whether a subject is eligible for the study. Dominant hand, potential color blindness, level of education, should also be documented, due to their relevance with task performance (CCI, CCI). If a subject's medical history is unclear or information pertaining to a critical variable is conflicting, every reasonable step to secure accurate information 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.

7.4. Site Eligibility Review

Pre-screening Activities

Investigator will assess subject eligibility for the open label study A8241022 using all data available from study A8241021. First review of data will be performed and documented (Pre-screening Checklist A provided by the sponsor) prior to Screening Visit for this study A8241022 (Week 19 Visit for study A8241021).

If subject meets the pre-screening requirements after this initial review, the second review will be performed and documented (Screening Checklist B provided by the sponsor) after completion of Week 19 Visit for study A8241021. All data from Week 19 visit for Study A8241021 will be used for eligibility review, including but not limited to changes in medical history, medical procedures, concomitant medications, compliance.

Site Eligibility Review

The site will review and document eligibility for the subject and provide documentation to the sponsor for the eligibility verification Process described below in Section 7.5. The site will review all laboratory test results, pregnancy test, ANC and WBC, drug test results, against I/E criteria.

7.5. Sponsor Eligibility Verification Process

Sponsor eligibility verification and documentation of completion is required for each subject. The sponsor or designee will verify all critical elements of the screening and enrollment process and will provide written authorization (eg, e-mail) concurring with the investigator assessment that the subject is eligible for enrollment into the study prior to Baseline Day 1 (V2). Such approval will be contingent upon the subject still meeting all eligibility criteria for randomization at Baseline Day 1 (V2). The key elements to be reviewed by the sponsor may include HD diagnostic criteria, CAG repeats, medical history, concomitant medications, and selected screening safety assessments including out of range laboratory results, abnormal ECGs, and abnormal vital signs. Full instructions on the Screening Verification process will be provided as part of site training. It is critical that the sponsor be provided with all requested data at least 2 business days in advance of any scheduled Baseline Day 1 (V2).

7.6. Blood Volume

Total blood sampling volume for the individual subjects is approximately 112 mL. The actual times of blood sampling may change but the total blood volume collected will not increase. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 30 consecutive days and the IRB/EC is notified of the blood collection.

Table 5. Blood Volume

Sample Type	Blood Sample Volume (mL)	Number of Sampling Times									Total Volume (mL)
		Screening	Bsl	V3	V4	V5	V6	V7	V8	FU	
Routine lab tests [1]	7		(1)			1	1	1	1		35
Safety lab monitoring (ANC/WBC)	7			1	1					1	21
Serum Pregnancy test [2]	3		(1)			1	1	1	1		15
Serum FSH [2]	5		1								5
CCI [redacted]	[redacted]		([redacted])		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		CCI [redacted]
TOTAL											112

1. Includes hematology and blood chemistry.
2. Female only.
3. Numbers in parentheses will be collected only if missed or abnormal in study A8241021.

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

7.7. Safety Assessments

7.7.1. Brief Physical Examination

The brief physical examination will be performed to assess the subject's health during the study and for any potential changes in physical status (including weight), as determined by

the investigator during the study. Brief physical examinations will be performed by a study physician or a trained study nurse.

The brief physical examination will be focused on general appearance, the cardiovascular, pulmonary, abdominal exams, as well as towards any subject reported symptoms. Examination of other systems to explore reports of AEs should be conducted as needed by the investigator.

The results of the brief physical examination from Week 26 Visit for study A8241021 will be reviewed at Baseline Day 1 (V2). The brief physical examination will be performed at Month 6 (V6), at Month 12 (V8) or early termination, at Follow-up (V9) and during any unplanned visit as necessary for follow-up of AEs.

The physical examination will be documented in the source documents, and any clinically significant changes from baseline will be captured as an AE.

7.7.2. 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.

Qualified staff members will perform blood pressure measurement. Blood pressure will be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mmHg. If possible, blood pressure measurements will be taken from the same arm (opposite to the arm that is used for blood sample collection and preferably the dominant arm). If there is a clinically important change in blood pressure from the previous recording, measurements will be repeated immediately to confirm the change.

All scheduled blood pressure, and pulse measurements should be performed after the subject has rested quietly for at least 5 minutes. The same size blood pressure cuff, which has been properly sized, will be used to measure blood pressure each time. The use of automatic devices for measuring BP and pulse rate are acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. Blood pressure and pulse rate should be obtained prior to the nominal time of the blood collection.

The procedure for collecting orthostatic blood pressure, and pulse will be to 1) assess blood pressure after subject remains in supine position for a minimum of 5 minutes; 2) ask the subject to stand up for ~2 minutes; 3) assess blood pressure, and pulse immediately at the end of the two minutes, while the subject remains in standing position.

Orthostatic hypotension is defined as a decrease of ≥20 mm Hg for systolic blood pressure or ≥10 mm Hg for diastolic blood pressure after 2 minutes of 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.

Common symptoms include dizziness, lightheadedness, blurred vision, weakness, fatigue, nausea, palpitations, and headache. Less common symptoms include syncope, dyspnea, chest pain, and neck and shoulder pain.

If a subject has orthostatic symptoms suggestive of, but does not have documented orthostatic hypotension, repeated measurements of supine/standing blood pressure should be obtained, if possible in triplicate. 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).

Body temperature will be measured either by placing a digital thermometer under the tongue for at least 30 seconds or by measuring tympanic temperature. The temperature will be reported in degree Celsius.

7.7.3. Brief Neurological Examination

The brief neurological exam will consist of assessments of the cranial nerves, motor function, deep tendon reflexes, sensory exam, coordination and gait. The exam should be recorded or performed to the extent needed to assess the subject for any potential changes in neurological status, as determined by the investigator, at Baseline Day 1 (V2), Month 6 (V6), Month 12 (V8) and Follow up (V9), or Early Termination, and during any unplanned visit, as necessary for follow-up of AEs.

The brief neurological examination results will not be recorded in the case report form (CRF). All the neurological examination results must be recorded on the source documents, which will be monitored at the study site. Abnormal neurological examination results deemed to be clinically significant and occurring after randomization will be captured as an AE.

7.7.4. Laboratory Tests

The screening/safety laboratory tests (hematology, chemistry, and urinalysis) may be obtained without regard to fasting status.

Table 6. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count [a] Total neutrophils (Abs)[a] Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN/urea Creatinine Glucose HbA1c *(for diabetics only)* Calcium Phosphorus Magnesium Creatine kinase Sodium Potassium Chloride Total CO2 (Bicarbonate) ALT AST LDH Total Bilirubin Alkaline phosphatase Uric acid Albumin Total protein	Color Appearance Specific Gravity pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Microscopy [c]	FSH [d] Urine drug screen [e] Urine pregnancy (hCG) [f] Serum beta hCG [f]
Additional Hematology [a]	Additional Chemistry [b]		
WBC count [a] Total neutrophils (Abs)[a]	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT PT/INR		

[a] See Section 3.1 for the stopping criteria and related procedures for repeat WBC and neutrophil count assessments.

[b] Additional testing for potential Hy's Law cases only.

[c] Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.

[d] At Baseline Day 1 (V2), investigator may request FSH to confirm postmenopausal status for females who have been amenorrheic for at least 12 consecutive months.

[e] At Baseline Day 1 (V2) and at any time at the discretion of the investigator.

[f] Women of childbearing potential: A serum pregnancy test result will be recorded at Baseline Day 1 (V2) and serum pregnancy test will be performed at Month 3 (V5), Month 6 (V6), Month 9 (V7) and Month 12 (V8) or early termination. A urine pregnancy test will be performed at Baseline Day 1 (V2) and at Follow-up (V9). *Note*: At Baseline Day 1 (V2) both serum AND urine pregnancy tests will be performed or recorded (urine test for immediate readout and serum test for confirmation by central lab).

Minimum requirements for drug screening includes: phencyclidine (PCP), cocaine, cannabinoids, opiates/barbiturates, amphetamines, methadone and methylenedioxy methyamphetamine (MDMA, known as ecstasy).

7.7.5. Pregnancy Testing

For female subjects of childbearing potential, a serum pregnancy test for human chorionic gonadotropin (β-hCG), with sensitivity of at least 25 mIU/mL will be reviewed at Baseline Day 1 (V2) and performed at Month 3 (V5) Month 6 (V6), Month 9 (V7), Month 12 (V8) or early termination. Urine pregnancy test will be performed at Baseline Day 1 (V2) and at follow-up (V9). At Baseline Day 1 (V2) serum pregnancy test result will be recorded from study A8241021 Week 26 Visit. The urine test is done for immediate readout while the serum test is performed for confirmation by central lab.

Qualitative urine pregnancy tests must be sensitive to at least 25 mIU/mL. Qualitative urine point-of-service pregnancy tests are to be conducted with the test kit provided or approved by the sponsor and in accord with instructions provided in its package insert. Results from urine dipstick will be obtained prior to dosing. A documented negative urine pregnancy result is required before the subject may receive the investigational product on Baseline Day 1 (V2). Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected, to confirm the subject has not become pregnant during the study). Pregnancy tests may also be repeated as per request of IRB/ECs or if required by local regulations. Subjects who have missed a menstrual period or who show an indeterminant or positive result on the qualitative point-of-service urine test may not further progress in the study until pregnancy is ruled out using further diagnostic testing (eg, a negative quantitative serum pregnancy test conducted at a certified laboratory). A positive urine pregnancy test should be followed by a serum β-hCG for confirmation. The sponsor should be immediately notified and the study drug should be withheld until the serum β-hCG test results are available. In the case of a positive serum β-hCG test, the subject will be immediately withdrawn from study medication but may remain in the study. The outcome of the pregnancy will be followed according to relevant sponsor's processes.

7.7.6. Assessment of Suicidal Ideation and Behavior (SIB)

7.7.6.1. Columbia Suicide Severity Rating Scale

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.

If at any visit from baseline on, there are "YES" answers on items 4, 5 or on any behavioral question of the C-SSRS, a risk assessment should be done by a qualified clinician/qualified medical health practitioner to determine whether it is safe for the subject to continue to participate in the trial (see Suicidality Risk Assessment). A suicidality narrative should be constructed for subjects who have undergone any post-baseline risk assessment, using information from the C-SSRS, prior screening and baseline information, the clinician assessment and the narrative guide. Subjects who answer "YES" on items 4, 5 or on any

behavioral question of the C-SSRS on more than one occasion during a trial should be discontinued from the trial.

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

7.7.6.2. Suicidality Risk Assessment

At Screening, all subjects must be assessed for potential suicidality; data from study A8241021 will be used including the most recent assessments at Week 19 Visit for study A8241021. Subjects felt to have significant suicidal ideation with actual plan and intent or suicidal behavior, must be evaluated by a clinician/qualified medical health practitioner (MHP) skilled in the evaluation of suicidality in the target population by virtue of training or experience (eg, psychiatrist, psychiatrist/licensed clinical psychologist, or neurologist experienced in assessing suicidality) who will determine if it is safe for the subject to participate in the trial. If determined not to be safe, the subject will be excluded. Specific criteria that indicate a need for such an assessment are:

- Any history of serious or recurrent suicidal behavior.
- Previous history of suicide behaviors in the past 10 years (a "YES" answer to any of the suicidal behavior items of the C-SSRS with the behavior occurring in the past 10 years).
- Suicide ideation 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") – See Columbia Suicide Severity Rating Scale.
- Suicide ideation with actual intent and/or plan in the past year ([redacted]).
- In the investigator's judgment a risk assessment or exclusion is warranted.

In the United States, a qualified MHP is a psychiatrist or licensed PhD level clinical psychologist. In other countries, a qualified MHP has appropriate training in the assessment of suicide risk, according to local clinical practice standards and regulations, and would normally evaluate the risk for suicide in a subject.

7.7.7. Electrocardiogram (ECG)

ECGs should be collected at times specified in the STUDY PROCEDURES Section of this protocol. Single 12-lead ECGs will be recorded or collected at on Baseline Day 1 (V2),

Month 3 (V5), Month 6 (V6), Month 9 (V7), 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, PR interval, QRS interval, QT interval, and QTc interval, and assessment of rhythm and morphology. If necessary (eg, suspected QTc prolongation), a manual reading of the ECG data will be performed.

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

All ECGs will also be centrally read. Instructions for transmission of ECGs to the vendor will be provided in the ECG vendor manual.

7.8. Special Safety Assessment

7.8.1. ANC and WBC 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 Stopping Criteria) for the subject to continue in the study. A separate source document will be provided to each site to assist in monitoring these criteria.

7.8.2. 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.

7.9. CCI

7.9.1. Unified Huntington's Disease Assessment Scale (UHDRS) – TMS, CCI , CCI

In this study four subscales of the UHDRS will be administered to the subject by a trained certified rater from the site investigational staff (clinician): the Total Motor Score (TMS), CCI 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.[33] 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.[34] The components of the full UHDRS assess motor function, cognition, behavior and functional abilities.

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.

CCI

CCI [redacted]

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

7.9.2. CCI [redacted]
(CCI [redacted]**)**

CCI [redacted]

CCI

7.9.4. CCI

CCI

7.9.4.1. CCI

CCI

CCI

7.9.4.3. CCI (CCI)

CCI

CCI

7.9.4.4. CCI (CCI)

CCI

7.9.4.5. CCI (CCI)

CCI

7.9.4.6. CCI (CCI)

CCI

CCI

7.9.5. CCI

CCI

7.9.5.1. CCI [redacted] (CCI [redacted])

CCI [redacted]

7.9.5.2. CCI [redacted] (CCI [redacted])

CCI [redacted]

7.9.5.3. CCI [redacted] (CCI [redacted])

CCI [redacted]

7.9.5.4. CCI [redacted]

CCI [redacted]

CCI

[redacted]

7.9.6. 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.[65]

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).

7.9.7. CCI

CCI

[redacted]

CCI [redacted]

7.9.8. CCI [redacted] (CCI [redacted])

CCI [redacted]

1. CCI [redacted]
2. [redacted]
3. [redacted]

CCI [redacted]

CCI [redacted]

CCI

CCI : CCI
CCI

7.9.9. CCI (CCI) CCI
CCI

7.10. CCI

7.10.1. CCI (CCI)
CCI

CCI [redacted]

- CCI [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

7.10.2. CCI [redacted]

CCI [redacted]

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

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

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

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

8.2. Reporting Period

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

AEs (serious and nonserious) should be recorded on the Case Report Form (CRF) from the time the subject has taken at least 1 dose of study treatment through the last subject visit.

8.3. Definition of an Adverse Event

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

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

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

- Drug overdose;
- Drug withdrawal;

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

8.4. Medication Errors

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

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

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

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

8.5. Abnormal Test Findings

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

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or

- Test result is considered to be an AE by the investigator or sponsor.

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

8.6. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

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

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

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

8.6.1. Protocol-Specified Serious Adverse Events

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

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases)[77] and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who

present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin value ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 X ULN or not available;

- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

    - For subjects with preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 X ULN, or ≥8 X ULN (whichever is smaller).

    Concurrent with

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

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

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time, should be considered potential Hy's law cases[77] irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a

tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

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

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

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

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

8.8. Severity Assessment

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

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

8.9. Causality Assessment

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

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

8.10. Exposure During Pregnancy

For investigational products and for marketed products, an exposure during pregnancy occurs if:

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

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

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

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

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

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

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

- Spontaneous abortion includes miscarriage and missed abortion;

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

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnant Partner Release of

Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

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

An occupational exposure is reported to safety within 24 hours of Investigator's awareness, using the SAE Report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a Case Report Form (CRF), however a copy of the completed SAE Report form is maintained in the study master file.

8.12. Withdrawal Due to Adverse Events (See Also Section on Subject Withdrawal)

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

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

8.13. Eliciting Adverse Event Information

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

8.14. Reporting Requirements

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

8.14.1. Serious Adverse Event Reporting Requirements

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

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

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the

investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

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

8.14.2. Nonserious Adverse Event Reporting Requirements

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

8.14.3. Sponsor Reporting Requirements to Regulatory Authorities

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

9. DATA ANALYSIS/STATISTICAL METHODS

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

9.1. Sample Size Determination

This is an open-label extension study. Subjects who complete the A8241021 study and are deemed eligible for this study per inclusion/exclusion criteria will be given the opportunity to enroll in this open label study. It is estimated that up to 260 subjects may participate in this extension study.

9.2. Efficacy Analysis

All endpoints will be evaluated over the Full Analysis Set (FAS), which is the set of subjects who have an extension study baseline efficacy evaluation, 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.

9.2.1. Analysis of Primary Endpoint

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), 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).

Adverse events will be coded for analysis with 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.

Safety analyses will be performed on the safety population, which includes all subjects who received at least 1 dose of study medication during the open-label period.

Further information about the safety analysis can be found in Section 9.5.

9.2.2. 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 95% confidence interval will be provided to summarize results for the baseline and change from baseline values by visit. A two-sided, paired *t*-tests at the 5% level of significance will also be used to summarize results. 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.

Missing values will be imputed using last observation carried forward (LOCF) approach. Sensitivity analysis of the secondary variables using only observed cases (no imputation) will be performed to support the robustness of the conclusions drawn from the LOCF approach.

Exploratory analysis: The mean rates of change of TMS and TMC during the double-blind period (Week 0-26) will be compared with the mean rates of change in the open label period. A two-sided, paired t-tests at the 5% level of significance will be used to summarize results.

Data for efficacy endpoints will be tested for normality assumption. If normality assumption is substantial violated, appropriate variable transformations or non-parametric tests may be performed.

9.3. CCI [redacted]

CCI [redacted]

9.4. CCI [redacted]

CCI [redacted]

[redacted]

[redacted].

CCI

[redacted]

9.5. Safety Analysis

Adverse events, ECGs, blood pressure, pulse rate and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. Any clinical laboratory, ECG, BP, and PR abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Physical examination and neurologic examination information collected during the course of the study will not be captured for inclusion into the study database, unless otherwise noted. However, any untoward findings identified on physical and/or neurologic examinations conducted after the administration of the first dose of study medication will be captured as an adverse event, if those findings meet the definition of an adverse event. Demographic data collected at Screening will be included in the study database. C-SSRS responses will be mapped onto the C-CASA scale, and the frequency distribution of the C-CASA scores (pre-dose/post-dose) will be reported. No hypotheses associated with the C-SSRS or C-CASA scales will be tested.

9.5.1. Electrocardiogram (ECG) Analysis

Changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, PR interval and QRS interval will be summarized by treatment and time. The number (%) of subjects with maximum post-dose QTc values and maximum increases from baseline in the following categories will be tabulated by treatment:

Table 7. Safety QTc

	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.

9.6. Interim Analysis

No interim analysis will be performed in the study.

9.7. Data Monitoring Committee

This study will use an External Data Monitoring Committee (E-DMC).

An independent unblinded External DMC consisting of experts in movement disorder, hematology/clinical trial safety monitoring, and statistics will evaluate the safety of the trial on an ongoing basis. Further detail on the composition and responsibility of the Data Monitoring Committee is outlined in a separate DMC charter. The E-DMC will make recommendations related to the study continuation based on their safety review as described in the PDE10 program level DMC Charter. For purposes of internal decision-making, an Executive Steering Committee (ESC) may be identified to liaise with the E-DMC to review E-DMC recommendations. No members of the ESC will be involved in the day to day conduct of the study. The results of the DMC review will not be shared with the study team, except for the key outcome ("Stop for unacceptable safety findings", or "Continue"). Further detail on the composition and responsibility of the E-DMC and ESC will be outlined in a separate DMC charter.

The program level external DMC was established in May 2013 for all PDE10 studies. The DMC charter gets amended for addition of each new interventional protocol with PF-02545920. The E-DMC meets on a regular basis and will evaluate this trial safety as soon as possible after the first approximately 20 subjects have completed Month 6 (V6), and then periodically at least twice a year thereafter. The sponsor may request an *ad hoc* meeting earlier, and/or more frequent review of safety data by the E-DMC, should potential safety signals of concern arise from blinded medical review of adverse events and other safety data by the Pfizer medical monitor. The timing of the E-DMC reviews may also be slightly adjusted to align with scheduled safety analysis for other studies, as specified in the DMC Charter. More information on the frequency of the E-DMC reviews will be included in the DMC Charter.

The E-DMC will be responsible for external monitoring of the safety of subjects in the study according to the charter. Prior to every scheduled E-DMC safety review the E-DMC members will receive an unblinded data package that will include all available safety data. Additionally, serious adverse event (SAE) case reports and drug related discontinuations will be communicated to the E-DMC on an ongoing basis, as soon as the sponsor is notified. 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

During study conduct, Pfizer or its agent will conduct periodic monitoring visits 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.

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

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

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

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

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator’s site as well as at Pfizer and clearly

identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), 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 (IRB)/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 legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996),[78] and the Declaration of Helsinki (World Medical Association, 1996 and 2008).[79]

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

12.3. Subject Information and Consent

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

When study data is compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify study subjects. The study site will maintain a confidential list of subjects who participated in the study linking their numerical code to the subject's actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data consistent with applicable privacy laws.

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

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

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

The investigator will make the determination during the consent process whether the subject with HD does or does not have the requisite decision-making capacity to provide informed consent. Such a determination should be made based on any local standards and requirements for determination of decision making capacity, and based on the clinical judgment and experience of the investigator in conducting research in this population.

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

12.4. Subject Recruitment

Subject recruitment efforts are not required for this study because this is an extension study.

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

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

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of subjects have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as the Last Subject Last Visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-02545920 at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within approximately 30 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), www.pfizer.com, and/or the European Clinical Trials Database (EudraCT), and other public registries in accordance with applicable local laws/regulations.

www.clinicaltrials.gov

Pfizer posts clinical trial Basic Results on www.clinicaltrials.gov for all Pfizer-sponsored interventional studies that evaluate the safety and/or efficacy of a Pfizer product.

The timing of the posting depends on whether the Pfizer product is approved for marketing in any country at the time the study is completed:

- For studies involving products applicable under the US Food and Drug Administration Amendments Act of 2007 (FDAAA), ie, Food and Drug Administration (FDA)-approved products, Pfizer posts results within 1 year of the

primary completion date (PCD). For studies involving products approved in any country, but not FDA approved, Pfizer posts results 1 year from last subject last visit (LSLV);

- For studies involving products that are not yet approved in any country, Pfizer posts the results of already-completed studies within 30 days of US regulatory approval, or 1 year after the first ex-US regulatory approval of the product (if only submitted for approval ex-US);

- For studies involving products whose drug development is discontinued before approval, Pfizer posts the results within 1 year of discontinuation of the program (if there are no plans for outlicensing, or within 2 years if outlicensing plans have not completed).

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

www.pfizer.com

Pfizer posts clinical trial results on www.pfizer.com for all Pfizer-sponsored interventional studies in patients that assess the safety and/or efficacy of an FDA-approved Pfizer product with a LSLV on or after 27-Sep-2007 for which Basic Results were posted on www.clinicaltrials.gov.

EudraCT

Pfizer posts clinical trial results on EudraCT in accordance with Commission Guideline 2012/C 302/03 *Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006* for studies with centers in the European Economic Area and with LSLV on or after 01-May-2004, regardless of the marketing status of the compound.

15.2. Publications by Investigators

Pfizer has no objection to publication by an investigator of any information collected or generated by the investigator, whether or not the results are favorable to the investigational drug. 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 before it is submitted or otherwise disclosed.

The investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent

action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information (other than the study results themselves) before disclosure.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all centers. 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.

16. REFERENCES

1. Warby, S. C., Graham, R.K., Hayden, M.R. in *GeneReviews™ [Internet]*. (ed Adam MP Pagon RA, Bird TD, et al.) (University of Washington, Seattle; 1993-2014, 1998 Oct 23, Updated 2010 Apr 22).

2. Vonsattel, J. P., Keller, C. & Cortes Ramirez, E. P. Huntington's disease - neuropathology. *Handbook of clinical neurology* **100**, 83-100, doi:10.1016/B978-0-444-52014-2.00004-5 (2011).

3. Fahn, S., Jankovic, J. & Hallett, M. in *Principles and Practice of Movement Disorders (Second Edition)* (ed Stanley FahnJoseph JankovicMark Hallett) 311-334 (W.B. Saunders, 2011).

4. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. *Cell* **72**, 971-983 (1993).

5. Vonsattel, J. P. & DiFiglia, M. Huntington disease. *Journal of neuropathology and experimental neurology* **57**, 369-384 (1998).

6. Myers, R. H. *et al.* Factors associated with slow progression in Huntington's disease. *Archives of neurology* **48**, 800-804 (1991).

7. Groves, P. M. A theory of the functional organization of the neostriatum and the neostriatal control of voluntary movement. *Brain research* **286**, 109-132 (1983).

8. Lawrence, A. D., Sahakian, B. J. & Robbins, T. W. Cognitive functions and corticostriatal circuits: insights from Huntington's disease. *Trends in cognitive sciences* **2**, 379-388 (1998).

9. Beaumont, V. cGMP-hydrolyzing PDEs are Therapeutics Targets for Huntington's Disease. *2012 HD Therapeutics Conference* (2012).

10. Kleiman, R. J. *et al.* cGMP Phosphodiesterase inhibitors rescue deficits in synaptic plasticity and medium spiny neuron excitability in transgenic Huntington's Disease mouse models. *SFN 2011* (2011).

11. Heikkinen, T. *et al.* Characterization of neurophysiological and behavioral changes, MRI brain volumetry and 1H MRS in zQ175 knock-in mouse model of Huntington's disease. *PloS one* **7**, e50717, doi:10.1371/journal.pone.0050717 (2012).

12. Miller, B. R., Walker, A. G., Barton, S. J. & Rebec, G. V. Dysregulated Neuronal Activity Patterns Implicate Corticostriatal Circuit Dysfunction in Multiple Rodent Models of Huntington's Disease. *Frontiers in systems neuroscience* **5**, 26, doi:10.3389/fnsys.2011.00026 (2011).

13. Zhong, S. *et al.* in *2012 SFN.*

14. Menalled, L. B. *et al.* Comprehensive behavioral and molecular characterization of a new knock-in mouse model of Huntington's disease: zQ175. *PloS one* **7**, e49838, doi:10.1371/journal.pone.0049838 (2012).

15. Wolf, R. C. *et al.* Altered frontostriatal coupling in pre-manifest Huntington's disease: effects of increasing cognitive load. *European journal of neurology : the official journal of the European Federation of Neurological Societies* **15**, 1180-1190, doi:10.1111/j.1468-1331.2008.02253.x (2008).

16. Kleiman, R. J. *et al.* Chronic suppression of phosphodiesterase 10A alters striatal expression of genes responsible for neurotransmitter synthesis, neurotransmission, and signaling pathways implicated in Huntington's disease. *The Journal of pharmacology and experimental therapeutics* **336**, 64-76, doi:10.1124/jpet.110.173294 (2011).

17. Schmidt, C. J. *et al.* Preclinical characterization of selective phosphodiesterase 10A inhibitors: a new therapeutic approach to the treatment of schizophrenia. *The Journal of pharmacology and experimental therapeutics* **325**, 681-690, doi:10.1124/jpet.107.132910 (2008).

18. Strick, C. A. *et al.* Alterations in gene regulation following inhibition of the striatum-enriched phosphodiesterase, PDE10A. *Neuropharmacology* **58**, 444-451, doi:10.1016/j.neuropharm.2009.09.008 (2010).

19. Soderling, S. H., Bayuga, S. J. & Beavo, J. A. Isolation and characterization of a dual-substrate phosphodiesterase gene family: PDE10A. *Proceedings of the National Academy of Sciences of the United States of America* **96**, 7071-7076 (1999).

20. Coskran, T. M. *et al.* Immunohistochemical localization of phosphodiesterase 10A in multiple mammalian species. *The journal of histochemistry and cytochemistry : official journal of the Histochemistry Society* **54**, 1205-1213, doi:10.1369/jhc.6A6930.2006 (2006).

21. Fujishige, K. *et al.* Cloning and characterization of a novel human phosphodiesterase that hydrolyzes both cAMP and cGMP (PDE10A). *The Journal of biological chemistry* **274**, 18438-18445 (1999).

22. Fujishige, K., Kotera, J. & Omori, K. Striatum- and testis-specific phosphodiesterase PDE10A isolation and characterization of a rat PDE10A. *European journal of biochemistry / FEBS* **266**, 1118-1127 (1999).

23. Hebb, A. L., Robertson, H. A. & Denovan-Wright, E. M. Striatal phosphodiesterase mRNA and protein levels are reduced in Huntington's disease transgenic mice prior to the onset of motor symptoms. *Neuroscience* **123**, 967-981 (2004).

24. Lione, L. A. *et al.* Selective discrimination learning impairments in mice expressing the human Huntington's disease mutation. *The Journal of neuroscience : the official journal of the Society for Neuroscience* **19**, 10428-10437 (1999).

25. Steffan, J. S. *et al.* The Huntington's disease protein interacts with p53 and CREB-binding protein and represses transcription. *Proceedings of the National Academy of Sciences of the United States of America* **97**, 6763-6768,

26. Lonze, B. E. & Ginty, D. D. Function and regulation of CREB family transcription factors in the nervous system. *Neuron* **35**, 605-623 (2002).

27. Giampa, C. *et al.* Inhibition of the striatal specific phosphodiesterase PDE10A ameliorates striatal and cortical pathology in R6/2 mouse model of Huntington's disease. *PloS one* **5**, e13417, doi:10.1371/journal.pone.0013417 (2010).

28. Giampa, C. *et al.* Phosphodiesterase 10 inhibition reduces striatal excitotoxicity in the quinolinic acid model of Huntington's disease. *Neurobiology of disease* **34**, 450-456, doi:10.1016/j.nbd.2009.02.014 (2009).

29. Cramer, H., Kohler, J., Oepen, G., Schomburg, G. & Schroter, E. Huntington's chorea--measurements of somatostatin, substance P and cyclic nucleotides in the cerebrospinal fluid. *Journal of neurology* **225**, 183-187 (1981).

30. Giralt, A. *et al.* PDE10 inhibition increases GluA1 and CREB phosphorylation and improves spatial and recognition memories in a Huntington's disease mouse model. *Hippocampus* **23**, 684-695, doi:10.1002/hipo.22128 (2013).

31. Schmidt, C. J. in *2012 Huntington's Disease Therapeutics Conference.* (CHDI Foundation).

32. Zaleska, M. M. in *2013 HD Therapeutics Conference.* (CHDI Foundation).

33. Posner, K. *et al.* The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *The American journal of psychiatry* **168**, 1266-1277, doi:10.1176/appi.ajp.2011.10111704 (2011).

34. Tabrizi, S. J. *et al.* Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: analysis of 24 month observational data. *The Lancet. Neurology* **11**, 42-53, doi:10.1016/S1474-4422(11)70263-0 (2012).

35. CCI [redacted] CCI [redacted] (CCI).

36. CCI [redacted] (CCI).

37. CCI
CCI (CCI).

38. CCI
CCI (CCI).

39. CCI
CCI (CCI).

40. CCI
CCI (CCI).

41. CCI
(CCI).

42. CCI
(CCI).

43. Smith, A. D. (ed Los Angeles: Western Psychological Services.) (Western Psychological Services, Los Angeles, 1991).

44. Unified Huntington's Disease Rating Scale: reliability and consistency. Huntington Study Group. *Movement disorders : official journal of the Movement Disorder Society* **11**, 136-142, doi:10.1002/mds.870110204 (1996).

45. CCI. (CCI).

46. CCI
CCI (CCI).

47. CCI
CCI (CCI).

48. Walker, F. O. Huntington's disease. *Lancet* **369**, 218-228, doi:10.1016/S0140-6736(07)60111-1 (2007).

49. Tabrizi, S. J. *et al.* Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. *The Lancet. Neurology* **8**, 791-801, doi:10.1016/S1474-4422(09)70170-X (2009).

50. Tabrizi, S. J. *et al.* Biological and clinical changes in premanifest and early stage Huntington's disease in the TRACK-HD study: the 12-month longitudinal analysis. *The Lancet. Neurology* **10**, 31-42, doi:10.1016/S1474-4422(10)70276-3 (2011).

51. CCI
CCI
(CCI).

52. CCI
CCI
(CCI).

53. CCI
(CCI).

54. CCI
(CCI).

55. de Yebenes, J. G. TRACK and attack Huntington's disease. *The Lancet. Neurology* **10**, 21-22, doi:10.1016/S1474-4422(10)70307-0 (2011).

56. CCI
CCI
(CCI).

57. CCI

58. CCI
CCI
(CCI).

59. CCI
CCI
(CCI).

60. CCI
CCI
(CCI).

61. CCI
CCI
CCI
(CCI).

62. CCI
(CCI).

63. CCI
(CCI).

64. CCI [redacted] (CCI).

65. Guy, W. in *U.S. Department of Health, Education, and Welfare ed. National Institute of Mental Health (U.S.). Psychopharmacology Research Branch. Division of Extramural Research Programs* (U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs, 1976).

66. CCI [redacted] (CCI).

67. Levy, R. & Dubois, B. Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. *Cerebral cortex* **16**, 916-928, doi:10.1093/cercor/bhj043 (2006).

68. Thompson, J. C. *et al.* Longitudinal evaluation of neuropsychiatric symptoms in Huntington's disease. *The Journal of neuropsychiatry and clinical neurosciences* **24**, 53-60, doi:10.1176/appi.neuropsych.11030057 (2012).

69. Marin, R. S. Apathy: a neuropsychiatric syndrome. *The Journal of neuropsychiatry and clinical neurosciences* **3**, 243-254 (1991).

70. Tabrizi, S. J. *et al.* Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. *The Lancet. Neurology* **12**, 637-649, doi:10.1016/S1474-4422(13)70088-7 (2013).

71. CCI [redacted] CCI [redacted] (CCI).

72. CCI [redacted] (CCI).

73. CCI [redacted] CCI [redacted] (CCI).

74. CCI [redacted] (CCI).

75. Poudel, G. R. *et al.* in *ACNS-2012 Australasian Cognitive Neuroscience Conference.*

76. CCI [redacted] CCI [redacted] (CCI [redacted]).

77. Temple, R. Hy's law: predicting serious hepatotoxicity. *Pharmacoepidemiology and drug safety* **15**, 241-243, doi:10.1002/pds.1211 (2006).

78. Council for International Organizations of Medical, S. International ethical guidelines for biomedical research involving human subjects. *Bulletin of medical ethics*, 17-23 (2002).

79. Williams, J. R. The Declaration of Helsinki and public health. *Bulletin of the World Health Organization* **86**, 650-652 (2008).

Appendix 1. Guidance on Clinical Management of Subjects with Acute Extrapyramidal Symptoms - EPS (reported AE of dystonia, akathisia, tardive dyskinesia)

Safety Profile of PF-02545920

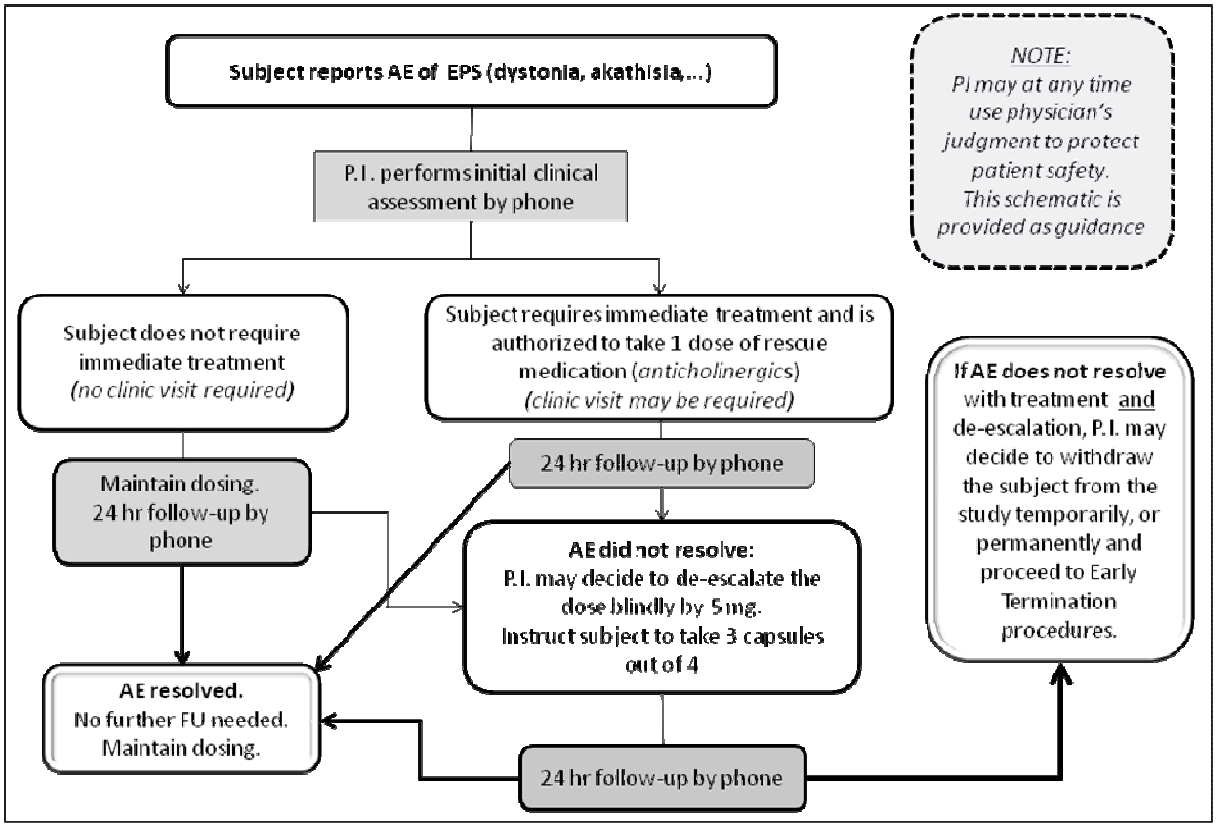
In a healthy volunteer study with PF-02545920, a rate of 6-8% of dystonia was observed at 15 mg with titration. One subject out of 24 schizophrenic subjects experienced dystonia after multiple doses of 20 mg without titration. In the 28 day study in schizophrenic subjects (A8241012), one subject was discontinued due to dystonia (20 mg titrated). Study A8241018 showed that overall PF-02545920 was safe and well tolerated in psychiatrically stable subjects with schizophrenia on a stable regimen of antipsychotic and other adjunctive psychotropic medications treated with PF-02545920 titrated to 15 mg BID. 4 AEs of dystonia were observed (3 mild, 1 moderate), 2 AEs of oromandibular dystonia (1 mild, 1 severe) and 5 AEs of EPS (4 mild).

Based on the safety profile of PF-02545920 established with prior completed studies, it is predicted that 10% or less of the subjects on a titrated dose of 20 mg of PF-02545920 may experience this type and severity of AE requiring clinical management and intervention (in a cohort of N=75, this rate of occurrence would correspond to 7 or 8 subjects in the 20 mg dose group).

Prior studies in healthy volunteers show that dystonia due to administration of PF-0545920 responds to a single administration of anticholinergics within 24 hours. As a result it is recommended to perform a follow-up visit with the subject to re-evaluate symptoms within 24 hours from the onset (see latest Investigator Brochure).

As described in STUDY TREATMENTS, the dosing of four tablets (5 mg each) allows for de-escalation with a 5 mg decrement, should the Principal Investigator assess that a subject requires a dose adjustment (temporary or permanent) due to intolerable AE. For example, a subject may be instructed to take only three tablets instead of four tablets for a total dose of 15 mg rather than the full 20 mg dose. Any subsequent dose reduction will proceed in a similar manner. Once AEs have resolved the PI will have the option to resume escalation.

Figure 2. Guidance for Clinical Management of EPS



Appendix 2. Drugs and Classes of Drugs Allowed and Prohibited as Concomitant Medications

Summary of drugs and classes of drugs allowed and prohibited as concomitant medications after the Screening visit (V1) and while on the study, until the end of the study Month 12 (V8), unless specified otherwise.

The use of any rescue medication should be discussed with study sponsor medical monitor or clinician prior to administration if at all possible.

"prn" (as needed) is defined as no more than three times per week.

Drug/Class	As Needed Use	Chronic Use
Antihypertensive drugs		
ACE Inhibitors	N	Y
Aldosterone receptor antagonists	N	Y
Alpha 2 agonist antihypertensives (clonidine, guanabenz, guanfacine, methyldopa)	N	N
Angiotensin II receptor antagonists	N	Y
Beta Blockers	N	Y
Calcium channel blockers (except verapamil, diltiazem)	N	Y
Guanadrel	N	N
Guanethidine	N	N
Ketanserin	N	N
Metyrosine	N	N
CNS acting drugs		
Anorexics	N	N
Anticholinergics	Y (rescue)	N
Anticonvulsants *(except valproic acid and lamotrigine)*	N	N
Antidepressants *(except tricyclic antidepressants (TCA) and MAOIs)*	N	Y
Antiemetics with dopamine antagonist activity	N	N
Anti-Parkinson medications (including levodopa, levodopa-carbidopa, dopamine receptor agonists -eg, pramipexole, ropinirole, apomorphine-, MAOIs, amantadine)	N	N
Antipsychotics *(except clozapine, see below)*	N	Y
Benzodiazepines *(only short acting benzodiazepines allowed as rescue therapy)*	Y (rescue)	Y
Clozapine	N	N
Lamotrigine	N	Y
Lithium	N	N
Narcotics/opioid / analgesics	Y (prn)	N
Nonbenzodiazepines hypnotics	Y	Y
Promethazine	N	N
Psychostimulants	N	N
Tetrabenazine	N	N
Valproic acid	N	Y
CYP3A4 inducers and inhibitors		
Atazanavir	N	N
Amiodarone	N	N
Cimetidine	N	N

Drug/Class	As Needed Use	Chronic Use
Carbamazepine	N	N
Clarithromycin	N	N
Diltiazem	N	N
Erythromycin	N	N
Fluvoxamine	N	N
Grapefruit, grapefruit juice, pomelos, related fruits	N	N
Indinavir	N	N
Itraconazole	N	N
Ketoconazole	N	N
Mibefradil	N	N
Nefazodone	N	N
Nelfinavir	N	N
Oxcarbazepine	N	N
Phenobarbital	N	N
Phenytoin	N	N
Rifabutin	N	N
Rifampin	N	N
Rifapentine	N	N
Ritonavir	N	N
Saint John's Wort *(Hypericum perforatum)*	N	N
Troleandomycin	N	N
Verapamil	N	N
Miscellaneous Drugs		
Anticoagulants *(except aspirin, clopidogrel)*	N	N
Antihistamines, sedating *(except diphenhydramine)*	Y (24 hr)	N
Antihistamines, non-*sedating (loratadine, ceftazidine, fexofenadine)*	Y	Y
Asthma drugs (inhaled)	Y	Y
Contraceptives (oral and injectable)	Y	Y
Cough/Cold preparations *(except those containing diphenhydramine)*	Y	N
Herbals	N	N
Hormones *(except estrogen replacement therapy)*	N	N
Insulin	N	N
Nonsteroidal anti-inflammatory drugs (NSAIDS)	Y	Y
Nutraceuticals, prescription and non-prescription	N	N
Proton pump inhibitors	Y	Y
Steroids (inhaled, topical, ophthalmic only)	Y	Y
Thyroid Hormone Replacement Therapy	N	Y
Tryptophan	N	N