CLINICAL PROTOCOL

A PHASE 3, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL-GROUP, FLEXIBLE-DOSE, 27-WEEK TRIAL TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF TAVAPADON AS ADJUNCTIVE THERAPY FOR PARKINSON'S DISEASE IN LEVODOPA-TREATED ADULTS WITH MOTOR FLUCTUATIONS (TEMPO-3 TRIAL)

Protocol Number: CVL-751-PD-003

Compound: Tavapadon (CVL-751)

Trial Phase: 3

Short Title: Flexible-Dose, Adjunctive Therapy Trial in Adults With Parkinson's Disease With Motor Fluctuations

Sponsor Name: Cerevel Therapeutics, LLC

Legal Registered Address: 222 Jacobs Street, Suite 200, Cambridge, MA 02141 USA

Regulatory Agency Identifier Number

Regulatory Agency File	Identifying #
IND	118,647
EudraCT	2019-002951-40

Version 4.0: 06 Jul 2023
Version 3.0: 03 Sep 2021
Version 2.0: 29 Jun 2020
Original Version 1.0: 07 Oct 2019

MEDICAL MONITOR NAME AND CONTACT INFORMATION ARE PROVIDED IN THE TRIAL OPERATIONS MANUAL.

Sponsor Signatories:

[redacted]

10JUL2023
Date

10 JUL 2023
Date

10 JUL 2023
Date

PROTOCOL VERSION 4.0 SUMMARY OF CHANGES TABLE

Document History	
Document:	**Date (Day-Month-Year)**
Version 4.0	06 Jul 2023
Version 3.0	03 Sep 2021
Version 2.0	29 Jun 2020
Original Protocol Version 1.0	07 Oct 2019

Amendment: Protocol Version 4.0 (06 Jul 2023)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment: The overall rationale for this amendment is to add eye examinations as an additional trial assessment to monitor for the new potential risk of increased intraocular pressure across the Phase 3 tavapadon protocols.

Section # and Name	**Description of Change**	**Brief Rationale**
1.3 Schedule of Assessments	Added eye examination assessment Added footnotes “w” and “x” to clarify the assessment and follow-up frequency Removed footnote “b” allowing remote visits if the subject cannot attend the clinic visit in person due to restrictions related to COVID-19 Note, footnote order has shifted as a result of these changes.	To monitor for increased intraocular pressure Remote visits are no longer needed as COVID-19 restrictions have ended
7.3 Individual Subject Discontinuation	Removed reference to in-home visits	Remote visits are no longer needed as COVID-19 restrictions have ended
8.3.8 Eye Examinations	Added new section for eye examinations and guidance for follow-up	To monitor for increased intraocular pressure

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Sponsor Name: Cerevel Therapeutics, LLC

Name of Investigational Medicinal Product: Tavapadon

Protocol Title: A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Flexible-Dose, 27-Week Trial to Evaluate the Efficacy, Safety, and Tolerability of Tavapadon as Adjunctive Therapy for Parkinson's Disease in Levodopa-Treated Adults With Motor Fluctuations (TEMPO-3 Trial)

Short Title: Flexible-Dose, Adjunctive Therapy Trial in Adults With Parkinson's Disease With Motor Fluctuations

IND Number: 118,647

EudraCT Number: 2019-002951-40

Trial Phase: 3

Indication: Parkinson's disease

Rationale: Tavapadon (PF-06649751, CVL-751) is a partial agonist of the dopamine D1-like receptors (D1Rs), with high specificity for the D1 and D5 receptor subtypes (D1/D5), which is being developed as a treatment for Parkinson's disease (PD). The efficacy, safety, and tolerability of tavapadon in Phase 1b and 2 trials support its potential as the first partial agonist therapy in an important new dopamine receptor-selective mechanism for treatment of PD symptoms. By targeting the D1R subtype, tavapadon aims to improve motor control symptoms while minimizing adverse events (AEs) that may be mechanistically linked to D2/D3 dopamine receptor agonists (notably, dose-limiting hypotension, impulse control disorders, sleep disorders, and, potentially, some forms of hallucinations). This trial is designed to further define and confirm the magnitude of efficacy and the risk/benefit profile of tavapadon over the target dose range of 5 to 15 mg once daily (QD).

Objectives and Endpoints:

The objectives and efficacy, safety, and pharmacokinetic (PK) endpoints of the trial are summarized in Table 1.

Table 1 Objectives and Endpoints

Objectives	Endpoints
Efficacy	
Primary • To assess the effect of tavapadon on the change from baseline in total daily hours of "on" time without troublesome dyskinesia in L-Dopa-treated subjects with PD who are experiencing motor fluctuations Secondary • To assess the effect of tavapadon on the change from baseline in total daily hours of "off" time in L-Dopa treated subjects with PD who are experiencing motor fluctuations	Primary Efficacy Endpoint • Change from baseline to endpoint the total "on" time without troublesome dyskinesia based on the 2-day average of the self-completed home diary for motor functional status (Hauser diary) Key Secondary Efficacy Endpoint • Change from baseline to endpoint in total daily "off" time based on the 2-day average of the self-completed home diary for motor function status (Hauser diary) Secondary Efficacy Endpoints (at all time points) • Change from baseline in the total "on" time without troublesome dyskinesia based on the 2-day average of the self-completed home diary for motor function status (Hauser diary) • Change from baseline in the total "off" time without troublesome dyskinesia based on the 2-day average of the self-completed home diary for motor function status (Hauser diary) • Change from baseline in the MDS-UPDRS Part I score • Change from baseline in the MDS-UPDRS Part II score • Change from baseline in the MDS-UPDRS Part III score Other Endpoints • Change from baseline in the PDQ-39 score • Change from baseline in the EQ-5D-5L index and VAS scores
Safety and Tolerability	
• To assess the safety and tolerability of tavapadon in L-Dopa-treated subjects with PD who are experiencing motor fluctuations	• QUIP-RS • ESS • C-SSRS • Nature, frequency, and temporality of TEAEs, including abuse-related AEs and AEs related to MHIs • Clinical laboratory evaluations • Vital signs • Physical examinations • ECGs

Table 1 Objectives and Endpoints

Objectives	Endpoints
Pharmacokinetic	
• To evaluate the PK of tavapadon in this population	Plasma concentrations of tavapadon and its metabolite (if required) at baseline (Day 1) and at Weeks 5, 11, 14, 22, and 27

Abbreviations: AE = adverse event, C-SSRS = Columbia-Suicide Severity Rating Scale, ECG = electrocardiogram, EQ-5D-5L = EuroQol 5 Dimension 5 Level, ESS = Epworth Sleepiness Scale, L-Dopa = levodopa, MDS-UPDRS = Movement Disorder Society-Unified Parkinson's Disease Rating Scale, MHIs = medication handling irregularities, PD = Parkinson's disease, PDQ-39 = 39-Item Parkinson's Disease Rating Scale, PK = pharmacokinetic, QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale, TEAE = treatment-emergent adverse event, VAS = visual analog scale.

Overall Design: This is a prospective, Phase 3, multicenter, multinational, randomized, double-blind, placebo-controlled, parallel-group, 27-week trial to evaluate the efficacy, safety, tolerability, and PK of tavapadon as adjunctive therapy to levodopa (L-Dopa) in male and female subjects aged 40 to 80 years who have a diagnosis of PD (consistent with the UK Parkinson's Disease Society Brain Bank diagnostic criteria); a modified Hoehn and Yahr score of 2, 2.5, or 3 in the "on" state; a minimum of 2½ hours of "off" time on 2 consecutive days; and a good response to L-Dopa in the judgment of the investigator. The trial will include a Screening Period (maximum of 4 weeks), a 27-week Treatment Period, and a 4-week Safety Follow-up Period.

Each subject will participate in the trial for up to approximately 35 weeks, including screening (up to 4 weeks), treatment (27 weeks), and posttreatment safety follow up (4 weeks). Subjects who complete through Week 27 of the trial may have the opportunity to enter an open-label extension trial (Protocol CVL-751-PD-004).

Disclosure Statement: This is a parallel-group trial to evaluate the efficacy, safety, tolerability, and PK of flexible doses of tavapadon and placebo in subjects with advanced PD. Treatment assignments will be blinded to the investigators and other trial site personnel, the subjects, and all sponsor personnel who are involved in the conduct of the trial (including trial monitoring, data management, and data analysis).

Number of Subjects: A total of 368 subjects are planned to be randomized into 2 treatment groups (184 subjects per treatment group).

Key Entry Criteria: Male and female subjects aged 40 to 80 years who have a diagnosis of PD (consistent with the UK Parkinson's Disease Society Brain Bank diagnostic criteria), a modified Hoehn and Yahr score of 2, 2.5, or 3 in the "on" state, a minimum of 2½ hours of "off" time on 2 consecutive days, and a good response to L-Dopa in the judgment of the investigator will be enrolled.

Intervention Groups, Trial Treatments, and Duration: Subjects will be randomized in a 1:1 ratio to receive tavapadon 5 to 15 mg QD or placebo QD. The planned duration of treatment is 27 weeks, including the Dose Titration, Dose Adjustment, and Maintenance Phases. The IMPs will be taken orally.

Interim Analysis Review Committee: Given that the assumptions for the sample size were based on a preliminary study using a different dosing schedule, it is unknown if these assumptions are appropriate for this study as designed. To this end, an interim analysis of the primary efficacy endpoint will be included to assess the adequacy of the overall sample size relative to achieving the study objectives. This analysis will be conducted by an independent Interim Analysis Review Committee (IARC), which may make a recommendation to increase the overall sample size up to a maximum of 528 subjects. Full details and rules for the IARC and planned interim analysis will be provided in a separate IARC charter and in the statistical analysis plan.

Statistical Methods

Sample Size Estimation**:** A sample size of 184 subjects per group (total, 368 subjects) will provide at least 90% power to detect a change in the primary outcome measure (change from baseline in "on" time without troublesome dyskinesia) of 1 hour with a standard deviation of 2.5, a 2-sided alpha level = 0.049, and assuming a 27% dropout rate.

In the event of higher than anticipated early terminations due to COVID-19 or other reasons, Cerevel may extend enrollment in order to maintain the planned statistical power.

Efficacy Analyses: The analysis of the primary and each secondary endpoint will include the comparison of tavapadon versus placebo. The hypothesis testing will be done in hierarchical order from the primary endpoint onward. To control for any potential inflation of Type I error that may be incurred from the interim analysis, the primary hypothesis will be tested at an α level of 0.049 (2-sided) to ensure that the overall Type I error rate is below 0.05. Subsequent testing in the secondary endpoints will be conducted at an α level of 0.05 (2-sided).

The primary endpoint (change from baseline to endpoint in "on" time without troublesome dyskinesia) will be analyzed using a Mixed Model for Repeated Measures (MMRM) on the modified intent-to-treat (mITT) population. This estimand will be based on the 2-day average of the self-completed Hauser diary from each postbaseline visit. A hypothetical strategy will be used to address the intercurrent events of discontinuation or use of prohibited medications with the data post intercurrent events treated as censored. The baseline value will be included as a covariate, and the treatment group (tavapadon or placebo), visit, and interaction between treatment group and visit will be included as fixed factors in the MMRM. The difference between tavapadon versus placebo at endpoint will be estimated based on the least square means (LSMeans) from the MMRM.

The key secondary endpoint (change from baseline to endpoint in "off" time) and other continuous secondary endpoints (as listed in Table 1) will be analyzed in a similar manner to the primary endpoint. Categorical endpoints will be analyzed on the mITT population using the SAS® GLIMMIX procedure for binomial data with logit link. This generalized linear mixed model analysis will include response data from each

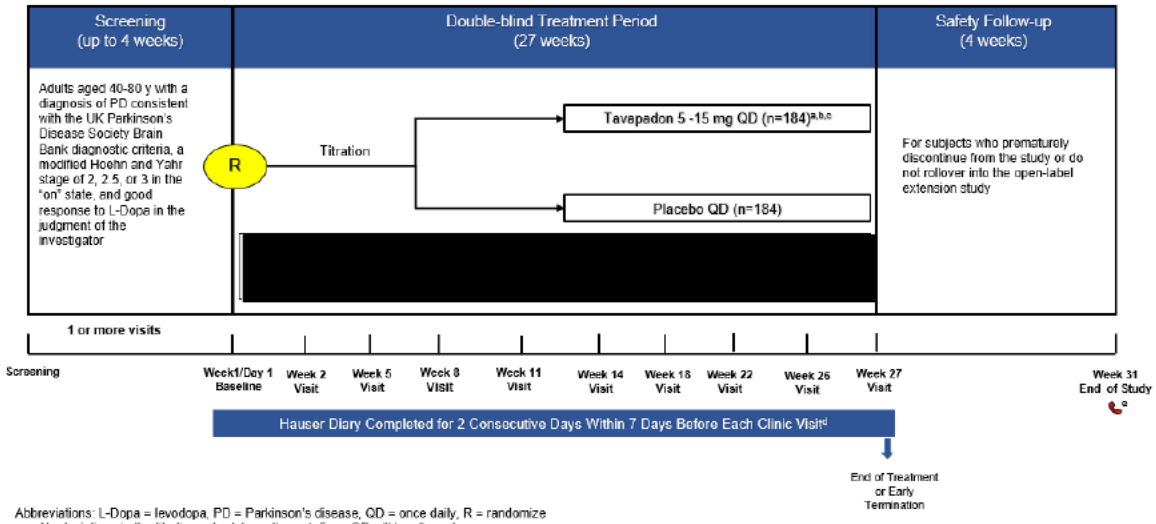
postbaseline visit that occurs before discontinuation of treatment or addition of rescue medication through endpoint. The model will include the treatment group, visit, and interaction between treatment group and visit. An unstructured covariance structure will be used for the repeated measures. If the model fails to converge with the unstructured covariance structure, the heterogeneous Toeplitz structure or further reduced covariance structure may be used.

Safety Analyses: Treatment-emergent adverse events (TEAEs) will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by treatment group, system organ class, and preferred term. Additional summaries by seriousness, severity, relationship to IMP, and dose at the time of onset will also be prepared. Other safety endpoints (as listed in Table 1) will be summarized with descriptive statistics. Abuse potential will be assessed through active monitoring of events subject to additional monitoring (ESAMs; ie, TEAEs related to abuse potential and TEAEs related to medication handling irregularities [MHIs]).

1.2 Schema

The trial design is depicted in Figure 1.

Figure 1 Trial Schematic



Abbreviations: L-Dopa = levodopa, PD = Parkinson's disease, QD = once daily, R = randomize

a. No deviations in the titration schedule up through 5 mg QD will be allowed.
b. The dose will be adjusted over the range of 5 to 15 mg QD based on individual subject tolerability.
c. Subjects will receive the highest tolerated dose that is achieved during the Dose Adjustment Phase (5, 10, or 15 mg QD) for the duration of the subsequent 13-week Maintenance Phase. No dose adjustments will be allowed during the Maintenance Phase.
d. The change from baseline to endpoint in the total "on" time without troublesome dyskinesia based on the 2-day average of the self-completed motor home diary (Hauser diary) is the primary endpoint.
e. Adverse events and concomitant medications will be recorded. Nonserious adverse events will be followed through Week 31. Serious adverse events will be followed to resolution.

1.3 Schedule of Assessments

The Schedule of Assessments for the trial is shown in Table 2. At each clinic visit, the assessments that are listed under "efficacy and other endpoint assessments" should be completed first, in the order listed, followed by the safety assessments, in the order listed.

Table 2 Schedule of Assessments

Trial Period:	Screen	Baseline	Treatment									Safety Follow-up[a]
Trial Week:	**-4 to -1**	**1**	**2**	**5**	**8**	**11**	**14**	**18**	**22**	**26**	**27[b]**	**31**
Trial Day:	**-31 to -1**	**1**	**14±3**	**35±3**	**56±3**	**77±3**	**98±3**	**126±3**	**154±3**	**182±3**	**189±3**	**217±3**
Visit/Contact:	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11 (EOT/ET)**	**Telephone[c]**
Entrance and History												
Informed consent[d]	X											
Eligibility criteria	X	X										
Demography	X											
Psychiatric history[e]	←----------→											
Medical history[e]	←----------→											
Alcohol/illicit drug use inquiry	X											
Modified Hoehn and Yahr stage	X						X			X	X	
MoCA	X											
Randomization		X										
Efficacy and Other Endpoint Assessments												
Hauser diary training video and on/off time concordance testing[f]	X											
Dispense Hauser diary[g]	X	X	X	X	X	X	X	X	X	X	X	
Collect/review Hauser diary[g]		X	X	X	X	X	X	X	X	X	X	
MDS-UPDRS[h]	X	X		X	X	X	X	X	X	X	X	
PDQ-39		X								X	X	
EQ-5D-5L		X					X			X	X	
Safety Assessments												
ESS		X	X	X	X	X	X	X	X	X	X	
QUIP-RS		X	X	X	X	X	X	X	X	X	X	

Table 2 Schedule of Assessments

Trial Period:	Screen	Baseline	Treatment									Safety Follow-up[a]
Trial Week:	-4 to -1	1	2	5	8	11	14	18	22	26	27[b]	31
Trial Day:	-31 to -1	1	14±3	35±3	56±3	77±3	98±3	126±3	154±3	182±3	189±3	217±3
Visit/Contact:	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11 (EOT/ET)	Telephone[c]
C-SSRS[i]	X	X	X	X	X	X	X	X	X	X	X	
Physical/neurological examination[j]	X										X	
Weight	X	X									X	
Vital signs[k]	X	X	X	X	X	X	X	X	X	X	X	
Single 12-lead ECG[l]	X	X		X		X	X		X		X	
One set of triplicate ECGs prior to first dose of IMP[m]		X										
[redacted]						X[w]					X[x]	
Prior/concomitant medications	←----------										----------→	
Adverse events[n]		←----------									----------→	
Laboratory[o]												
Safety laboratory blood sample	X	X				X			X		X	
Prolactin level		X[v]									X[v]	
Serology (HIV, HbsAg, and HCV)	X											
Dipstick urinalysis[p]	X	X				X			X		X	
Serum pregnancy test[q]	X											
Urine dipstick pregnancy test[q]		←----------									----------→	
Urine drug screen[r]	X	←----------									----------→	
Plasma PK sample[s]		X		X		X	X		X		X	
Future biospecimen research blood sample[t]		X										

Table 2 Schedule of Assessments

Trial Period:	Screen	Baseline	Treatment									Safety Follow-up[a]
Trial Week:	**-4 to -1**	**1**	**2**	**5**	**8**	**11**	**14**	**18**	**22**	**26**	**27[b]**	**31**
Trial Day:	**-31 to -1**	**1**	**14±3**	**35±3**	**56±3**	**77±3**	**98±3**	**126±3**	**154±3**	**182±3**	**189±3**	**217±3**
Visit/Contact:	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11 (EOT/ET)**	**Telephone[c]**
IMP Administration and Compliance[u]												
Dispense IMP		X	X	X	X	X	X	X	X	X		
Assess IMP compliance			X	X	X	X	X	X	X	X	X	

Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale, ECG = electrocardiogram, eCRF = electronic case report form, EQ-5D-5L = EuroQol 5 Dimension 5 Level, ESS = Epworth Sleepiness Scale, EOT = end of treatment, ET = early termination, HbsAg = hepatitis B surface antigen, HCV = hepatitis C virus, HIV = human immunodeficiency virus, IMP = investigational medicinal product, [redacted] L-Dopa = levodopa, MDS-UPDRS = Movement Disorder Society – Unified Parkinson's Disease Rating Scale, MoCA = Montreal Cognitive Assessment, PDQ-39 = 39-Item Parkinson's Disease Questionnaire, PK = pharmacokinetic, QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale.

a. Subjects who prematurely discontinue from the trial or who are not eligible for or choose not to participate in the open-label extension trial (Protocol CVL-751-PD-004) are to participate in the 4-week Safety Follow-Up Period. Subjects who proceed into the open-label extension trial will go directly into that trial and will not complete the Safety Follow-up Period.
b. The assessments scheduled for the Week 27 visit are to be performed for any subject who prematurely discontinues from the trial.
c. Contact with subjects via telephone call or other means of communication to check on their status.
d. Informed consent must be obtained before any trial-related procedures are performed.
e. Medical occurrences that begin before the start of IMP dosing but after obtaining informed consent will be recorded as medical and/or psychiatric history.
f. Subjects and investigators (or qualified designees) will independently complete concordance testing. Full details and requirements for the conduct and successful completion of concordance testing are provided in the appropriate protocol-specific manual.
g. Subjects will record entries for 24 hours on 2 consecutive days within the 7 days before randomization at the Baseline Visit, after diary training and concordance testing has occurred. Subject will record entries for 24 hours on 2 consecutive days within the 7 days before each postbaseline clinic visit.
h. MDS-UPDRS Parts I, II, and III should be conducted approximately 2 to 3 hours after the last dose of L-Dopa on that day.
i. The "Baseline/Screening" C-SSRS form will be completed at the Screening Visit to determine eligibility. The "Since Last Visit" C-SSRS form will be completed at the Baseline Visit to ensure that the subject continues to qualify for the trial and at all visits after the Baseline Visit.
j. Full physical and neurological examinations should be completed at the Screening Visit and at Week 27. The physical examination should include height at the Screening Visit only. Physical and/or neurological examinations can be done at any time point during the trial at the investigator's discretion.
k. Duplicate measurements of blood pressure and heart rate will be obtained supine (after 5 minutes of rest) and 1 measurement of blood pressure and heart rate will be obtained on standing (2 minutes after rising from supine to standing).
l. The postdose ECG will be obtained at ~1 hour after administration of the first dose of IMP at the Baseline Visit just prior to the time of collection of the PK blood sample. ECGs at all postbaseline visits will be obtained just prior to the time of collection of the PK blood sample.
m. A triplicate set of ECGs is 3 consecutive ECGs collected 1 to 2 minutes apart over a 5-minute period.

n. All adverse events that are observed by trial personnel or volunteered by the subject in response to open-ended questioning will be recorded from the first dose of IMP through the end of the Safety Follow-up Period. Serious adverse events will be followed until resolution.
o. Individual sites may require subjects to have COVID-19 testing done prior to randomization. COVID-19 testing may be performed after randomization per the principal investigator's discretion.
p. Dipstick urinalysis results are not to be recorded on the eCRFs; any clinically significant abnormality should be captured as an adverse event.
q. For women of childbearing potential only. All positive urine dipstick pregnancy tests must be confirmed by a serum test. Pregnancy tests can be performed at any time during the trial at the discretion of the investigator. Female subjects with exclusively the same sex partners may not be required to have pregnancy tests per investigator discretion; confirmation with the medical monitor is required.
r. A urine drug screen is required at screening (see exclusion criteria for exclusions based on the urine drug screen) and may be obtained at other times, at investigator discretion, if use of prohibited drugs is suspected.
s. PK samples will be collected ~1 hour after administration of the first dose (Day 1) and at the clinic visits at the end of Weeks 5, 11, 14, 22, and 27 just after ECG acquisition at each time point. The date and time of the most recent dose, the dose amount, and the time of the blood draw will be recorded.
t. Future biospecimen research sample is optional and is to only be collected if signed consent is obtained from the subject.
u. The first dose of IMP (at the Baseline Visit) will be taken in the clinic; all other doses will be taken on an outpatient basis. Subjects will be instructed to bring their IMP to each clinic visit. Compliance will be assessed through self-reporting by the subject and by tablet count.
v. Prolactin results will be blinded.

2 INTRODUCTION

2.1 Trial Rationale

Tavapadon (PF-06649751, CVL-751) is a partial agonist of the dopamine D1-like receptors (D1Rs), with high specificity for the D1 and D5 receptor subtypes (D1/D5), which is being developed as a treatment for Parkinson's disease (PD). Efforts to develop selective D1R agonists have been ongoing for decades, in part, because of their clear potential to produce robust efficacy through selective stimulation of the direct pathway. Mechanistic evidence also suggests that selective and partial activation of D1Rs may avoid some of the limiting side effects of the D2/3 agonist or dopamine replacement therapies.

The efficacy, safety, and tolerability of tavapadon in Phase 1b and 2 trials support its potential as the first partial agonist therapy in an important new dopamine receptor-selective mechanism for treatment of PD symptoms. By targeting the D1R subtype, tavapadon aims to improve motor control symptoms while minimizing adverse events (AEs) that may be mechanistically linked to D2/D3 dopamine receptor agonists (notably, dose-limiting hypotension, impulse control disorders, sleep disorders, and, potentially, some forms of hallucinations).

This prospective, Phase 3, multicenter, multinational, randomized, double-blind, placebo-controlled, parallel-group, 27-week trial will evaluate the efficacy, safety, tolerability, and pharmacokinetics (PK) of flexible doses of tavapadon (5 mg to 15 mg once daily [QD]) as adjunctive therapy for PD in levodopa (L-Dopa)-treated adults with motor fluctuations to further define and confirm the magnitude of efficacy and risk/benefit profile of this target dose range.

2.2 Background

Parkinson's disease is a chronic, progressive and disabling neurodegenerative disease. The number of individuals with PD aged 50 and older was between 4.1 and 4.6 million in 2005 in the 10 most populous nations in the world[*] combined and is projected to double to between 8.7 and 9.3 million by 2030 (Dorsey et al, 2007). The incidence is approximately 20 per 100,000 persons per year, increases with advancing age (65 years and older) to up to >100 per 100,000 (Twelves et al, 2003), and is reported to be 1.4% at age 55 years and 4.3% at 85 years and older (de Rijk et al, 1995).

The specific etiology of PD remains unclear, but there are continued advances in understanding the possible underlying mechanisms and causative factors. A more complete understanding of basal ganglia function, the neuropathologic and neurochemical abnormalities in PD, and genetic forms of parkinsonism provide hope that disease-modifying therapeutic approaches can be identified. However, there remains significant current and future need for improved symptomatic therapies.

[*] China, India, United States, Indonesia, Brazil, Pakistan, Bangladesh, Russia, Nigeria, and Japan.

It is generally recognized that the primary degeneration in PD involves basal ganglia and its projections. The underlying pathology indicates a loss of dopaminergic neurons in the substantia nigra, and neuronal loss in the locus coeruleus and the nucleus raphe. Dopamine acts on 5 receptor subtypes to facilitate controlled movement, and insufficient activation of these receptors is established as the primary cause of motor control deficits in PD. The dopamine receptor subtypes have distinct localization and primary signaling cascades and are commonly divided into 2 groups based on their function. The D1-like family includes the D1 and D5 subtypes, which are localized on a "direct" striatal motor control pathway and which stimulate cellular activity by increasing intracellular cyclic adenosine monophosphate (cAMP) levels. The D2-like family includes the D2, D3, and D4 subtypes, which are localized to an "indirect" motor control pathway and which decrease intracellular cAMP when activated. The degenerative character of the disease is accompanied by intracellular deposits of Lewy bodies and by microglia-activation. Basic research currently suggests that oxidative injury to specific neurons in the basal ganglia may be at least one of the underlying causes of "idiopathic parkinsonism," apart from other factors, such as genetic changes.

The major clinical diagnostic features of PD include tremor, rigidity of skeletal muscles, bradykinesia, impairment of postural reflexes (also referred to as parkinsonism), and gait disturbances. Additional symptoms include many other motor features and nonmotor features, including psychiatric, sensory, and autonomic changes. Patients may or may not require therapy in the early stages of PD, which typically presents with fewer and less severe symptoms, and may still be able to work. Unfortunately, disease progression is inevitable and, within 1 to 3 years of diagnosis, nearly all patients will require therapy. Continued disease progression, in conjunction with common medication-related side effects, usually leads to individualized optimization of therapy in an effort to manage the increasing symptoms and common medication-related side effects. Despite these efforts, a majority of patients experience significant worsening of symptoms and reduced quality of life and independence and will leave the workforce within 5 years of diagnosis (Jasinska-Myga et al, 2012). No proven disease-modifying treatments for PD are currently available. Management options for PD consist mainly of dopaminergic drugs and, in a limited number of patients, deep brain stimulation.

L-Dopa (the metabolic precursor of dopamine) therapy provides increased dopamine levels in a transient and pulsatile fashion and affords rapid improvement of motor symptoms. However, prolonged use of L-Dopa leads to the development of motor complications in most patients. These include motor fluctuations, which are an alternation between "on" periods when motor symptoms are well controlled and "off" periods when motor symptoms are poorly controlled. An additional type of motor complication is the occurrence of dyskinesia or abnormal involuntary movements (Marconi et al, 1994; Vijayakumar and Jankovic, 2016). Troublesome motor complications from L-Dopa therapy can lead to substantial impairment, negative impacts on activities of daily living, and decreased quality of life.

Agents that preferentially activate the dopamine D2 and D3 receptor subtypes (D2/D3R), such as pramipexole, ropinirole, and rotigotine, are also approved for the symptomatic

treatment of PD (Stocchi et al, 2016). These agents generally exhibit less frequent motor complications than L-Dopa but are not as effective for controlling motor symptoms (Connolly and Lang, 2014; Rizek et al, 2016; Dietrichs and Odin, 2017). D2/D3-preferring agonists are also associated with an increased incidence of specific adverse effects, including somnolence, hypotension, compulsive behaviors, and hallucinations, particularly in the elderly (Stowe et al, 2008).

Selegiline, rasagiline, and safinamide are monoamine oxidase B (MAO-B) inhibitors, which block one pathway of dopamine degradation and improve motor symptoms of PD in some settings (Connolly and Lang, 2014; Binde et al, 2018). Of these, only rasagiline is approved in the United States and Europe as a monotherapy treatment, and available indirect evidence suggests that this class is less efficacious than D2/3 agonists (Stowe et al, 2008; Zhuo et al, 2017).

Despite available treatment approaches, the chronic and progressive nature of PD continues to result in significant burden and impact on quality of life and day-to-day functioning for patients (Drutyte et al, 2014). There are significant unmet medical needs throughout the stages of PD, from improving motor control in patients with early-stage disease who have not yet begun dopamine replacement therapy, to increasing daily "on" time without troublesome dyskinesias while adequately controlling motor symptoms in patients with moderate-to-advanced disease who are receiving available therapies (patients with motor fluctuations). Patients and their families are anxious for testing of new therapeutic mechanisms that can provide strong and lasting control of the symptoms of PD and that can minimize some of the known side effects of existing therapeutic options, such as dose-limiting dyskinesias, daytime sleepiness, and impulsivity. Completed Phase 1b and 2 trials have demonstrated that tavapadon can provide improved control of motor symptoms in both early and more advanced stages of PD, with an acceptable safety profile.

2.3 Benefit/Risk Assessment

In a Phase 1b trial in subjects with PD with motor fluctuations (Trial B7601009), increasing benefit on motor symptoms was observed with increased tavapadon dose, with magnitudes of change on the Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III scores well above the changes that are recognized as clinically meaningful (>3-point decrease from baseline; Horváth et al, 2015) and significantly better than for placebo. Sustained effects of tavapadon on tremor (as shown by the MDS-UPDRS Part III scores that were lower than at baseline for up to 12 hours after dosing) were also observed in a second Phase 1b trial in subjects with PD with motor fluctuations (Trial B7601005).

In a Phase 2 trial of tavapadon in L-Dopa-treated subjects with PD who were experiencing motor fluctuations (Trial B7601003), analysis of the change from baseline in average daily "on" time without troublesome dyskinesia showed that the magnitude of benefit of tavapadon 15 mg QD, relative to placebo, was approximately 1 hour at Week 10. Although the difference from placebo did not achieve statistical significance

due to the small sample size, this difference is considered clinically meaningful (Hauser et al, 2011; Hauser et al, 2014).

Motor symptoms were significantly more improved with tavapadon monotherapy than with placebo in a Phase 2, placebo-controlled, 15-week, flexible-dose trial in subjects with early PD (Trial B7601011), as assessed by the change from baseline to Week 15 in the MDS-UPDRS Part III total score (least square mean [LSMean] change from baseline = -9.0 for tavapadon and -4.3 for placebo; difference from placebo = -4.8; p=0.041). The difference between tavapadon and placebo in the change from baseline to Week 15 in the MDS-UPDRS Parts II and III combined score was also statistically significant (LSMean change from baseline = -11.2 for tavapadon and -5.4 for placebo; difference from placebo: -5.9; p=0.020). The magnitude of the placebo-adjusted treatment difference in improvement from baseline in the MDS-UPDRS Part III score met the threshold for a clinically meaningful change (>3-point decrease from baseline; Horváth et al, 2015), as did the magnitude of the placebo-adjusted treatment difference in improvement from baseline in the MDS-UPDRS Parts II and III combined score (>4.9-point decrease from baseline; Makkos et al, 2018).

The safety results across all clinical trials demonstrate that tavapadon was generally well tolerated up to a titrated dose of 15 mg QD in subjects with PD, either as monotherapy (early PD) or as adjunctive treatment with a stable dose of L-Dopa (advanced PD). A dose-dependent increase in the frequencies of nausea and headache was observed across all trials. Nausea, vomiting, dyskinesia, fall, fatigue, sleep disorder, and tremors were the most common AEs leading to discontinuation of tavapadon. The appearance of nausea, orthostatic blood pressure changes, and fatigue is often related to the speed of titration with dopamine receptor agonists (historically with D2 agents) and may be mitigated by a slower titration method.

No notable differences in laboratory abnormalities, electrocardiogram (ECG) parameters, or suicidality assessments were observed between tavapadon and placebo. Multidose cohorts in Phase 1 trials in healthy volunteers and subjects with PD (including subjects with PD who were treated at doses of up to 25 mg QD of tavapadon) did not suggest that tavapadon prolonged the QT interval corrected for heart rate by Fridericia's formula (QTcF). Trials of longer treatment duration suggest a tavapadon dose-related decrease from baseline in systolic and/or diastolic parameters, with some cases of asymptomatic hypotension. This finding is common with dopamine D2 agonists and is prevalent in the population of patients with PD whether treatment naïve or treated with L-Dopa.

Taken together, the current data suggest an appropriate benefit-risk ratio for further evaluation of tavapadon in Phase 3 clinical trials at doses up to 15 mg QD. Additional information about the known and expected benefits, risks, and AEs of tavapadon is provided in the Investigator's Brochure.

In response to the COVID-19 pandemic, Cerevel has performed a risk assessment of this trial and the investigator of each individual trial site and has implemented measures throughout the protocol, which prioritizes trial participant safety and data validity.

3 OBJECTIVES AND ENDPOINTS

The trial objectives and endpoints are summarized in Table 3.

Table 3 Objectives and Endpoints

Objectives	Endpoints
Efficacy	
Primary • To assess the effect of tavapadon on the change from baseline in total daily hours of "on" time without troublesome dyskinesia in L-Dopa-treated subjects with PD who are experiencing motor fluctuations Secondary • To assess the effect of tavapadon on the change from baseline in total daily hours of "off" time in L-Dopa treated subjects with PD who are experiencing motor fluctuations	Primary Efficacy Endpoint • Change from baseline to endpoint the total "on" time without troublesome dyskinesia based on the 2-day average of the self-completed home diary for motor function status (Hauser diary) Key Secondary Efficacy Endpoint • Change from baseline to endpoint in total daily "off" time based on the 2-day average of the self-completed home diary for motor function status (Hauser diary) Secondary Efficacy Endpoints (at all time points) • Change from baseline in the total "on" time without troublesome dyskinesia based on the 2-day average of the self-completed home diary for motor function status (Hauser diary) • Change from baseline in the total "off" time without troublesome dyskinesia based on the 2-day average of the self-completed home diary for motor function status (Hauser diary) • Change from baseline in the MDS-UPDRS Part I score • Change from baseline in the MDS-UPDRS Part II score • Change from baseline in the MDS-UPDRS Part III score Other Endpoints • Change from baseline in the PDQ-39 score • Change from baseline in the EQ-5D-5L index and VAS scores
Safety and Tolerability	
• To assess the safety and tolerability of tavapadon in L-Dopa-treated subjects with PD who are experiencing motor fluctuations	• QUIP-RS • ESS • C-SSRS • Nature, frequency, and temporality of TEAEs, including abuse-related AEs and AEs related to MHIs • Clinical laboratory evaluations • Vital signs • Physical examinations • ECGs

Table 3 Objectives and Endpoints

Objectives	Endpoints
Pharmacokinetic	
• To evaluate the PK of tavapadon in this population	Plasma concentrations of tavapadon and its metabolite (if required) at baseline (Day 1) and at Weeks 5, 11, 14, 22, and 27

Abbreviations: AE = adverse event, C-SSRS = Columbia-Suicide Severity Rating Scale, ECG = electrocardiogram, EQ-5D-5L = EuroQol 5 Dimension 5 Level, ESS = Epworth Sleepiness Scale, L-Dopa = levodopa, MDS-UPDRS = Movement Disorder Society-Unified Parkinson's Disease Rating Scale, MHIs = medication handling irregularities, PD = Parkinson's disease, PDQ-39 = 39-Item Parkinson's Disease Rating Scale, PK = pharmacokinetic, QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale, TEAEs = treatment-emergent adverse events, VAS = visual analog scale.

4 TRIAL DESIGN

4.1 Overall Design

This is a prospective, Phase 3, multicenter, multinational, randomized, double-blind, placebo-controlled, parallel-group, 27-week trial to evaluate the efficacy, safety, tolerability, and PK of tavapadon as adjunctive therapy to levodopa (L-Dopa) in male and female subjects aged 40 to 80 years who have a diagnosis of PD (consistent with the UK Parkinson's Disease Society Brain Bank diagnostic criteria); a modified Hoehn and Yahr score of 2, 2.5, or 3 in the "on" state; a minimum of 2½ hours of "off" time on 2 consecutive days; and a good response to L-Dopa in the judgment of the investigator. The trial will include a Screening Period (maximum of 4 weeks), a 27-week Treatment Period, and a 4-week Safety Follow-up Period (Figure 1). Each subject will participate in the trial for up to approximately 35 weeks.

4.1.1 Screening/Baseline Period

Subjects who provide written informed consent will be screened for eligibility during the Screening Period. During the Screening Period, subjects will be trained in the use of the home diary (Hauser diary), and subjects and investigators (or qualified designee) will independently complete concordance testing on the Hauser diary (full details and requirements for conduct and successful completion of concordance testing are provided in the appropriated protocol-specific manual). Subjects who successfully meet the concordance testing criteria will complete the Hauser diary on at least 2 consecutive days (24-hour periods) within the 7 days before the Baseline Visit.

Subjects whose diary shows a minimum of 2½ hours of "off" time on each of the 2 days and who continue to satisfy the trial eligibility criteria at the Baseline Visit will be randomized in a 1:1 ratio to receive:

- Tavapadon ranging from 5 to 15 mg QD
- Placebo QD

4.1.2 Treatment Period

The dose of tavapadon will be gradually titrated to 15 mg QD in all subjects over the first 14 weeks of the trial during the Dose Titration and Dose Adjustment Phases unless prevented by intolerance. A reduction in dose (from 15 mg QD to 10 mg QD or from 10 mg QD to 5 mg QD) will be allowed based on individual subject tolerability. Subjects who require a dose reduction may be rechallenged with the higher dose, at the discretion of the investigator, to address symptomatic needs.

The titration schedule, as shown in Table 4, will be used for all subjects who are randomized to receive tavapadon. Subjects will take 3 tablets of IMP, either all tavapadon tablets, all placebo tablets, or a combination of tavapadon and placebo tablets, throughout the trial to maintain the trial blind.

Table 4 Tavapadon and Placebo Dosing Schedule

Trial Day	Titration Step	Blinded Treatment Assignment
[redacted]		
[redacted] **Maintenance Phase**[c]		
[redacted]	[redacted]	Maximum tolerated tavapadon dose (5-15 mg) or placebo QD

Abbreviation: QD = once daily.

a. No deviations in the titration schedule up through 5 mg QD[redacted] will be allowed.

b. The dose will be adjusted over the range of 5 to 15 mg[redacted] based on individual subject tolerability.

c. Subjects will receive the highest tolerated dose level that is achieved during the Dose Adjustment Phase. No adjustment in the tavapadon dose will be allowed during the Maintenance Phase.

No deviations in the titration schedule up through [redacted] (5 mg QD) will be allowed. Titration of tavapadon should be guided by absence of tolerability issues that are reported as AEs and that are of sufficient severity resulting in significant dysfunction or distress to the subject. Any questions regarding tolerability issues and titration should be directed to the medical monitor before adjustments are initiated. The dose of tavapadon will be gradually titrated to the [redacted] dose (15 mg QD) in all subjects, as shown Table 4, unless prevented by intolerance.

Subjects who are unable to achieve or tolerate the [redacted] dose (15 mg QD) may receive the [redacted] dose (10 mg QD). Subjects who cannot achieve or tolerate the [redacted] dose (10 mg QD) may receive the [redacted] dose (5 mg QD). Subjects who cannot achieve or tolerate the [redacted] dose (5 mg QD) will be discontinued from the trial. Subjects who require a dose reduction may be rechallenged with a higher dose to address symptomatic needs after at least 7 days at the lower dose during the Dose Adjustment Phase.

Subjects will receive the highest tolerated dose level that is achieved during the Dose Adjustment Phase for the duration of the subsequent 13-week Maintenance Phase. Adjustments in the dose of tavapadon will not be allowed during the Maintenance Phase. Subjects who cannot tolerate their maintenance dose will be discontinued from the trial.

The first dose of IMP will be taken at the trial site at the Baseline Visit; all other doses will be taken on an outpatient basis. Assessments will be conducted in the clinic at the end of Weeks 2, 5, 8, 11, 14, 18, 22, 26, and 27. Subjects will complete the Hauser diary on 2 consecutive days within the 7 days before each scheduled postbaseline clinic visit. Blood samples for PK will be collected after administration of the first dose on Day 1 (~1 hour after dosing) and at the Weeks 5, 11, 14, 22, and 27 clinic visits.

4.1.3 Safety Follow-up Period

Subjects who complete through Week 27 of the trial may have the opportunity to enter an open-label extension trial (Protocol CVL-751-PD-004). Subjects who are ineligible or elect not to enter the open-label trial will be contacted by telephone at 4 weeks after discontinuation of trial treatment (either after completing the full 27-week treatment period or upon premature discontinuation from the trial).

4.2 Scientific Rationale for Trial Design

The randomized, double-blind, placebo-controlled, parallel-group trial design is widely accepted as one that minimizes the risk of bias and that is appropriate for evaluating the effects of a trial treatment in indications in which use of a placebo is ethical (US FDA, 2001). Randomization reduces bias in the assignment of subjects to a treatment group, the double-blind design prevents differential treatment and assessments, and the placebo-controlled design controls for all potential influences on the actual or apparent course of the disease other than those arising from the pharmacologic action of the drug.

The Hauser diary (Hauser et al, 2000) assesses patient-defined clinical status over a period of time and provides a tool for assessment of the change in “off” time and “on”

time with troublesome dyskinesia (which is a more accurate reflection of clinical response than "off" time alone. The minimum clinically important difference (smallest change that is meaningful to patients) for a reduction in "off" time (key secondary efficacy endpoint) has been reported to be 1.0 hour (Hauser et al, 2011; Hauser et al, 2014).

The MDS-UPDRS is a comprehensive assessment that is designed to monitor the burden and extent of PD across the longitudinal disease course and provides a clinical endpoint in therapy trials (Goetz et al, 2008).

The safety endpoints, including physical and neurological examinations, vital signs, ECGs, laboratory evaluations, and AEs, are those commonly used to assess the safety and tolerability of trial treatments. The Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale (QUIP-RS) is a global screening instrument that assesses impulsive control disorders (ICDs) and related disorders (punding, hobbyism, and dopamine dysregulation syndrome) in patients with PD (Weintraub et al, 2012), and the Epworth Sleepiness Scale (ESS) is a scale that is intended to measure daytime sleepiness (Johns, 1991). The Columbia-Suicide Severity Rating Scale (C-SSRS) is commonly used for stringent monitoring of suicidality in clinical trials of neurological compounds (Posner et al, 2011).

4.3 Justification for Dose

Patients with PD prioritize robust motor control as a key attribute of a desirable symptomatic therapeutic. In the small, Phase 2, flexible-dose, 15-week trial of tavapadon in early PD (Trial B7601011), subjects gradually increased their dose of tavapadon at weekly intervals, as tolerated, during the initial 9-week dose optimization period until their parkinsonian symptoms were optimally controlled. The target dose range was 3 to 15 mg QD; however, a maintenance dose of <3 mg may have been selected, based on clinical response. Of the 26 subjects who were randomized to tavapadon and who reached the 6-week maintenance dosing phase, 73% required doses of 5 to 15 mg QD to achieve optimized motor control based on clinical judgement. Reduction from baseline in motor symptoms of >10 points on the MDS-UPDRS Part III score primarily occurred in subjects who received doses of >5 mg QD of tavapadon, with robust separation from placebo treatment achieved at doses >7 mg QD (-6.9 placebo-adjusted treatment difference), whereas a dose of 3 mg QD consistently produced reductions of <10 points from baseline on the MDS-UPDRS Part III score. These data suggest that doses <5 mg QD are unlikely to deliver clinically meaningful benefit over placebo in motor symptom control to most patients with PD.

In a Phase 1 multiple-dose trial in subjects with PD (Trial B7601005), tavapadon exposure increased with an increase in dose over the dose range of 5 to 15 mg; however, the increase in mean area under the plasma concentration-time curve over the dosing interval (24 hours; AUC_{tau}) and in mean maximum observed plasma concentration (C_{max}) was less than dose proportional between the 15 and 25 mg doses. This is consistent with the known moderate-to-low solubility of tavapadon at the pH of the gastrointestinal track

(pH 6.5), which likely limited absorption. Therefore, doses >15 mg are not likely to provide meaningful increases in tavapadon exposure and may eventually lead to an exposure plateau. In this same trial, doses of 25 mg QD produced markedly greater rates of gastrointestinal AEs as compared with doses of 15 mg QD. Nausea and vomiting were reported in 8 of 19 and 4 of 19, respectively, of the subjects who received 25 mg QD doses of tavapadon, whereas nausea and vomiting were reported in 3 of 11 and 1 of 11, respectively, of the subjects who received 15 mg QD doses of tavapadon. The safety and pharmacokinetic data from this Phase 1 trial suggest that doses >15 mg QD are unlikely to have an optimal risk/benefit profile for patients with PD.

Taken together, these findings suggest that an optimal dose range of tavapadon for the treatment of PD may reasonably be between 5 and 15 mg QD for the individual patient, based on symptomatic needs and tolerability thresholds.

4.4 Definition of Completed Subject

Subjects will be considered to have completed this trial once they complete the assessments that are scheduled at the Week 27 visit.

4.5 End of Trial Definition

The end of the trial is defined as the date of the last visit (including phone contact) of the last subject in the trial globally.

5 TRIAL POPULATION

Prospective approval of protocol deviations to the recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Subjects are eligible to be included in the trial only if all of the following criteria apply:

General and Administrative	
1.	Male and female subjects aged 40 to 80 years, inclusive, at the time of signing the ICF.
2.	Sexually active men or women of childbearing potential must agree to use acceptable (at minimum) or highly effective birth control, as defined in Section 10.4 (Appendix 4), or remain abstinent during the trial and for 4 weeks after the last dose of trial treatment.
3.	Subjects who are capable of giving signed informed consent as described in Section 10.1.3 (Appendix 1), which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
4.	Subjects who are able, in the opinion of the investigator, to understand the nature of the trial and comply with protocol requirements, including the prescribed dosage regimens, scheduled visits, laboratory tests, and other trial procedures.

Parkinson's Disease Diagnosis	
5.	Subjects with a diagnosis of PD that is consistent with the UK Parkinson's Disease Society Brain Bank diagnostic criteria. Note: Subjects having more than one affected relative (Step 2 UK Parkinson's Disease Society Brain Bank exclusion criterion) but meeting all other criteria consistent with the UK criteria will be considered to have met eligibility criteria for a diagnosis of PD (Litvan et al, 2003; Massano and Bhatia, 2012). Note: Motor asymmetry may or may not be present at the time of Screening, and is not an explicit requirement for inclusion, as long as the subject meets the UK Parkinson's Disease Society Brain Bank diagnostic criteria based on medical history or physical examination.
6.	Subjects with modified Hoehn and Yahr stage 2, 2.5, or 3 in the "on" state.
7.	Subjects with a good response to L-Dopa in the judgment of the investigator. Note: Subjects using levodopa/carbidopa intestinal gel are not eligible to participate in the trial.
8.	Subjects who return a completed self-reported home diary for motor function status (Hauser diary) during the screening period (after diary training and concordance testing has occurred), with recordings for 2 consecutive days (ie, 2 consecutive 24-hour periods) showing at least 2½ hours of "off" time on each of the 2 days.
Concomitant Parkinson's Disease Medications	
9.	Subjects who are on a stable dose of L-Dopa for at least 4 weeks prior to screening and are taking a minimum total daily dose of 400 mg divided in at least 4 doses per day of standard carbidopa/levodopa or divided in at least 3 doses per day of extended-release carbidopa/levodopa capsules. The carbidopa/levodopa dose and frequency must be maintained for the duration of the trial. Standard or extended-release levodopa/benserazide is allowed as an alternative to levodopa/carbidopa, where available. The minimum dose and frequency requirements for levodopa still apply.
10.	Prior and concurrent use of COMT inhibitors, MAO-B inhibitors, amantadine, istradefylline, or anticholinergic drugs is permitted if use was initiated >90 days before the Baseline Visit and the dosage will remain stable for the duration of the trial (ie, no change in the COMT, MAO-B inhibitor, amantadine, istradefylline, or anticholinergic dose is permitted during the trial).

Abbreviations: COMT = catechol-O-methyl transferase, ICF = informed consent form, IMP = investigational medicinal product, L-Dopa = levodopa, MAO-B = monoamine oxidase inhibitor B, PD = Parkinson's disease.

5.2 Exclusion Criteria

Subjects are excluded from the trial if any of the following criteria apply:

Parkinson's Disease Diagnosis	
1.	Subjects with a history or clinical features consistent with essential tremor, atypical or secondary parkinsonian syndrome (including, but not limited to, progressive supranuclear palsy, multiple system atrophy, cortico-basal degeneration, or drug-induced or poststroke parkinsonism).
2.	Subjects with a history of nonresponse or insufficient response to L-Dopa at therapeutic dosages.
3.	Subjects who have had previous surgical intervention (eg, deep brain stimulation) for PD or for whom such a procedure is planned or anticipated during the trial period.

Medical History	
4.	Subjects with an acute or chronic, clinically significant medical or psychiatric condition, cognitive impairment, or laboratory abnormality that might increase the risk associated with trial participation or administration of trial treatment or interfere with the interpretation of the trial results or that, in the judgment of the investigator, would make the subject inappropriate for entry into this trial. Medical conditions that are minor or well controlled may be considered acceptable if the condition does not expose the subject to an undue risk of a significant AE or interfere with the assessments of safety or efficacy during the course of the trial. Subjects with symptoms of anxiety or depression that are not debilitating and that are stable or adequately controlled with non-prohibited medication are considered acceptable. The medical monitor should be contacted in any instance where the investigator is uncertain regarding the stability of a subject's medical conditions(s) and the potential impact of the condition(s) on trial participation.
5.	Subjects with a history or current diagnosis of a clinically significant impulse control disorder (Disruptive, Impulse Control, and Conduct Disorder per DSM-5) (American Psychiatric Association, 2013).
6.	Subjects with the presence of or history of brain tumor, hospitalization for severe head trauma, epilepsy (as defined by the International League Against Epilepsy), or seizures.
7.	Subjects with a history of psychosis or hallucinations within the previous 12 months.
8.	Subjects who answer "yes" on the C-SSRS Suicidal Ideation Item 4 or Item 5 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan, or Active Suicidal Ideation with Specific Plan and Intent) and whose most recent episode meeting the criteria for C-SSRS Item 4 or Item 5 occurred within the last 6 months, **OR** Subjects who answer "yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) and whose most recent episode meeting the criteria for any of these 5 C-SSRS Suicidal Behavior Items occurred within the last 2 years, **OR** Subjects who, in the opinion of the investigator, present a serious risk of suicide.
9.	Subjects with substance abuse or dependence disorder, including alcohol, benzodiazepines, and opioids, but excluding nicotine, within the past 6 months (180 days).
10.	Subjects with dementia or cognitive impairment that, in the judgement of the investigator, would exclude the subject from understanding the ICF or participating in the trial.
11.	Subjects with any condition that could possibly affect drug absorption, including bowel resections, bariatric weight loss surgery, or gastrectomy (this does not include gastric banding).
12.	Subjects who have a positive result for HIV antibodies, HbsAg, or HCV antibodies at screening. Note: Subjects who were previously infected with hepatitis C but have been successfully treated (defined as a sustained virologic response or undetectable hepatitis C viral RNA levels at 12 or more weeks after the end of treatment) may be enrolled after discussion with the medical monitor.

13.	Subjects with a history of malignancy other than: • Non-metastatic basal or squamous cell carcinoma of the skin or carcinoma in situ that was surgically removed in total >1 year before signing the ICF and had not recurred • Another type of malignancy that had been in remission for ≥5 years before signing the ICF and had not recurred
14.	Subjects with a history of myocardial infarction with residual atrial, nodal, or ventricular arrhythmias that are not controlled with medical and/or surgical intervention; second- or third-degree atrioventricular block; sick sinus syndrome; severe or unstable angina; or congestive heart failure within the last 12 months. A recent (≤12 months) history of myocardial infarction with secondary arrhythmias is exclusionary regardless of the therapeutic control.
15.	Subjects with a history of neuroleptic malignant syndrome.
16.	Female subjects who are breastfeeding and/or who have a positive pregnancy test result prior to receiving IMP.
Prior or Concomitant Medications	
17.	Subjects who are currently receiving moderate or strong CYP3A4 inducers or CYP3A4 inhibitors (except for topical administration).
18.	Subjects with a positive urine drug screen for illicit drugs are excluded and may not be retested or rescreened. Subjects with a positive urine drug screen resulting from use of marijuana (any THC-containing product), prescription, or over-the-counter medications or products that, in the investigator's documented opinion, do not signal a clinical condition that would impact the safety of the subject or interpretation of the trial results may continue evaluation for the trial following consultation and approval by the medical monitor.
19.	Subjects who are using prohibited medications prior to randomization (as listed in Table 6) or who would be likely to require the use of prohibited concomitant medications during the trial (as listed in Table 7).
Screening Assessments	
20.	Subjects with a MoCA score <26.
21.	Subjects with a supine blood pressure ≥160 mmHg (systolic) or ≥100 mmHg (diastolic) at screening. The average of two supine measurements will be used to assess eligibility.
22.	Subjects with clinically significant orthostatic hypotension (eg, syncope).
23.	Subjects with a 12-lead ECG demonstrating a QTcF interval >450 msec At screening: • If the QTcF interval is >450 msec on the machine reading, the ECG should be repeated with 2 additional recordings. Based on the QTcF intervals that are reported by the central service, a subject will be excluded if the QTcF interval is >450 msec on 2 or more of the 3 ECG recordings, unless due to ventricular pacing. At baseline: • If the QTcF interval is >450 msec on the machine readings, consult the medical monitor to determine whether the subject remains eligible to be randomized while awaiting the readings from the central service.
24.	Subjects with moderate or severe renal impairment (creatinine clearance as estimated by Cockcroft-Gault formula <30 mL/min or on dialysis).

25.	Subjects with any of the following abnormalities in clinical laboratory tests at the Screening Visit, as assessed by the central laboratory and confirmed by a single repeat measurement, if deemed necessary: • AST or ALT ≥3 × ULN. • Total bilirubin ≥1.5 × ULN. Subjects with a history of Gilbert's syndrome may be eligible provided they have a value <ULN for direct bilirubin.
26.	Subjects with other abnormal laboratory test results, vital sign results, or ECG findings unless, in the judgment of the investigator, the findings are not medically significant and would not impact the safety of the subjects or the interpretation of the trial results. The medical monitor should be contacted to discuss individual cases, as needed. Tests with exclusionary results should be repeated to ensure reproducibility of the abnormality before excluding a subject based on the criteria provided in the protocol. For medically significant or exclusory abnormal ECGs results, 2 additional ECG recordings should be collected, to ensure reproducibility of the abnormality, and the 3 ECG recordings read by the central service to confirm the abnormality before excluding a subject.
Other	
27.	Subjects who previously participated in any tavapadon trial, including this trial, and received IMP.
28.	Subjects who received treatment with any other investigational drug within 60 days before signing the ICF.
29.	Any subject who, in the opinion of the sponsor, investigator, or medical monitor, should not participate in the trial.

Abbreviations: AE = adverse event, ALT = alanine aminotransferase, AST = aspartate aminotransferase, C-SSRS = Columbia-Suicide Severity Rating Scale, CYP = cytochrome P450, DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, ECG = electrocardiogram, HbsAg = hepatitis B surface antigen, HCV = hepatitis C virus, HIV = human immunodeficiency virus, ICF = informed consent form, IMP = investigational medicinal product, L-Dopa = levodopa, MoCA = Montreal Cognitive Assessment, PD = Parkinson's disease, QTcF = QT interval as corrected for heart rate by Fridericia's formula, THC = tetrahydrocannabinol, ULN = upper limit of normal.

5.3 Lifestyle Considerations

Subjects should take the IMP at approximately the same time each day (in the morning at ~24-hour intervals), with or without food. No lifestyle restrictions will be imposed.

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but who are not subsequently randomized to treatment in the clinical trial. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

Individuals who do not meet the criteria for participation in this trial (screen failure) at screening may be rescreened once at the discretion of the investigator and after consultation with the sponsor unless screen failure is due to a positive urine drug screen for illicit substances other than tetrahydrocannabinol (THC) (Section 5.2). Subjects who

have a positive urine drug screen for THC at screening may be rescreened once and randomized into the trial if the repeat urine drug screen is negative for THC, and the subject agrees to abstain from THC use throughout the duration of the trial. Rescreened subjects will be assigned a new subject number.

6 TRIAL TREATMENTS

Trial treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) that is intended to be administered to a trial subject according to the trial protocol. Investigational medicinal product (IMP) refers to a pharmaceutical form of any active substance or placebo that is being tested in this clinical trial.

6.1 Trial Intervention(s) Administered

Tavapadon or matching placebo will be administered orally once daily for up to 27 weeks (Table 5).

Table 5 Investigational Medicinal Products Administered

ARM Name	**Tavapadon 5-15 mg QD**	**Placebo QD**
Type	Drug	Matching drug
Dose Formulation	Tablet	Matching tablet
Unit Dose Strength(s)	[redacted]	0 mg
Dosage Level(s)	5 mg	0 mg
Route of Administration	Oral	Oral
Sourcing	Cerevel Therapeutics	Cerevel Therapeutics
Packaging and Labeling	Blister cards labeled according to local regulations	Blister cards labeled according to local regulations
Former Name(s)	PF-06649751, CVL-751	--

6.2 Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit (original shipment and/or moving of IMP supply from one office or facility to another within the sites network) for all IMP received and any discrepancies are reported and resolved before use of the IMP.

Only subjects who are enrolled in the trial may receive IMP and only authorized site staff may supply or administer IMP. All IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized site staff.

The investigator is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused IMPs are provided in the appropriate protocol-specific manuals.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Subject Assignment to Treatment

All subjects will be centrally randomized in a 1:1 ratio to 2 treatment arms (tavapadon 5 to 15 mg QD or placebo) at the Baseline Visit via an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS), according to a computer-generated randomization scheme. Subjects will be sequentially assigned to the next available randomization number and will receive the IMP that corresponds to that randomization number. Once a randomization number has been assigned, it will not be reassigned.

The telephone number and call-in directions for the IVRS and/or the log-in information for and directions for the IWRS will be provided to each trial site before the trial is initiated.

6.3.2 Blinding

The tavapadon and placebo tablets will be identical in appearance and will be packaged in identically appearing blister cards. All subjects will take 3 tablets once daily of IMP during the Treatment Period, either all tavapadon tablets, all placebo tablets, or a combination of tavapadon and placebo tablets. Tablets will be packaged to allow dosage adjustments (as shown in Table 4) to be made without breaking the trial blind.

Treatment assignments will be blinded to the investigators and other trial site personnel, the subjects, and all sponsor personnel who are involved in the conduct of the trial (including trial monitoring, data management, and data analysis). Access to the treatment codes will be restricted to personnel who are responsible for generating and maintaining the randomization code, packaging the IMPs, operating the IVRS/IWRS, analyzing the PK blood samples, or reporting serious adverse events (SAEs) or adverse events of special interest (AESI) to regulatory agencies.

At the initiation of the trial, investigators and site personnel will be instructed on the method for breaking the blind. The IVRS/IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of the treatment assignment for an individual subject is warranted. Subject safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor before unblinding a subject's treatment assignment unless this could delay emergency treatment of the subject. The sponsor must be notified within 24 hours after breaking the blind for a trial subject.

Documentation of breaking the blind should be recorded in the subject's medical record and electronic case report forms (eCRFs), with the reason for breaking the blind, the date

and time the blind was broken, and the names of the personnel involved. Once the blind is broken for a subject, treatment with the IMP may not be reinitiated for that subject.

6.4 Trial Treatment Compliance

All IMP will be dispensed by responsible trial personnel. Subjects will be counseled on the importance of taking the IMP as directed (once daily in the morning, with or without food) at each clinic visit and will be instructed to bring all used and unused blister cards to each clinic visit. Accountability and compliance (as assessed through self-reporting by the subject and by tablet count at each clinic visit) will be documented in the subject's trial records. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

If poor compliance is encountered (eg, multiple missed doses resulting in <80% overall compliance at any point in the trial), discontinuation of the subject from the trial should be considered. Subjects who habitually miss visits or habitually attend visits outside of the protocol-defined visit window are also defined as noncompliant and should be considered for discontinuation. The medical monitor should be contacted if the investigator is uncertain whether a subject's lack of compliance merits discontinuation from the trial.

6.5 Concomitant Therapy

6.5.1 Prior and Concomitant Medications

The investigator will record all medications and therapies (including vaccines, over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that are used by the subject from 30 days before the informed consent form (ICF) is signed through the end of the 4-week Safety Follow-up Period (Week 31 or early termination). The investigator will also record all medications and therapies taken or received by a subject for treatment of an AE or that cause an AE through Week 31 or early termination.

The medication, indication, dose, frequency, route, and start and end dates will be recorded in the eCRFs for each concomitant medication, and the therapy, indication, and start and end dates will be recorded in the eCRFs for any concomitant therapy. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

All subjects should be counselled on the importance of taking background medications as prescribed.

6.5.2 Allowed Medications Before and During the Trial

Subjects must be on a stable dose of L-Dopa for at least 4 weeks prior to screening and be taking a minimum total daily dose of 400 mg divided in at least 4 doses per day of standard carbidopa/levodopa or divided in at least 3 doses per day of extended-release carbidopa/levodopa capsules. Subjects must continue taking the carbidopa/levodopa at

the same dose and frequency for the duration of the trial. No adjustment in the dose of frequency of carbidopa/levodopa is permitted during the study.

Standard or extended-release levodopa/benserazide is allowed as an alternative to levodopa/carbidopa, where available.

6.5.3 Prohibited Medications Before the Trial

Subjects must agree to discontinue use of all prohibited medications in accordance with predefined washout periods, as shown in Table 6.

Table 6 List of Medications Prohibited Before the Trial

	Medication	Washout Period
1.	Moderate or strong CYP3A4 inducers or CYP3A4 inhibitors (refer to Section 10.6 [Appendix 6] for examples), except for topical administration	--
2.	Levodopa inhalation powder	>7 days before Baseline Visit
3.	Dopamine agonists, including apomorphine	>14 days before Baseline Visit
4.	Varenicline	>14 days before Baseline Visit
5.	Nonselective MAO inhibitors, methyldopa, reserpine, or tricyclic antidepressants	>2 months before Screening Visit
6.	Dopamine antagonists, such as neuroleptics/antipsychotics (eg, phenothiazines, butyrophenones, thioxanthenes), including haloperidol, trimethobenzamide, or domperidone for nausea/vomiting, metoclopramide, and quetiapine for insomnia	>14 days before Baseline Visit
7.	Atypical antipsychotics, mood stabilizers (lithium or anticonvulsants), or prescription stimulants (amphetamine derivatives, methylphenidate, bupropion, phentermine, phenylpropanolamine modafinil, mazindol) Note: use of certain anticonvulsants (eg, pregabalin) for medical reasons unrelated to seizures or psychiatric mood stabilization may be allowed after discussion with and approval by the medical monitor.	>14 days before Baseline Visit (1 full cycle for long-acting depot antipsychotics)
8.	Sedatives, hypnotics, antidepressants, or anxiolytics	No washout is required if dose has been stable for >90 days before the Baseline Visit; washout of >14 days if dosing was started or dose was changed ≤90 days before the Baseline Visit.
9.	COMT inhibitors, MAO-B inhibitors, amantadine, istradefylline, or anticholinergic drugs if use was initiated ≤90 days before the Baseline Visit	>14 days before Baseline Visit
10.	Other investigational medications	>60 days before Screening Visit

Abbreviations: COMT = catechol-O-methyl transferase, CYP = cytochrome P450, ICF = informed consent, MAO = monoamine oxidase.
-- Not applicable. Any prior use is prohibited.

6.5.4 Prohibited Medications During the Trial

The concomitant medications that are prohibited during the trial are listed in Table 7.

The medical monitor should be contacted regarding the appropriateness of a subject's continued participation in the trial in the event that initiation of therapy with a prohibited concomitant medication is deemed necessary, in the investigator's opinion, for the treatment of a treatment-emergent adverse event (TEAE).

Table 7 List of Medications Prohibited During the Trial

	Medication
1.	Sedatives, hypnotics, antidepressants, and anxiolytics (unless dose has been stable for >90 days before the Baseline Visit and will remain stable for the duration of the treatment phase) Note: Short-term use of lorazepam (up to 4 mg/day), or its equivalent, for TEAEs of anxiety or insomnia may be permitted following consultation with and approval by the medical monitor, but may not be taken within 12 hours prior to efficacy assessments during clinic visits. Use should be discontinued upon TEAE resolution.
2.	Atypical antipsychotics
3.	Dopamine antagonists, such as neuroleptics/antipsychotics (eg, phenothiazines, butyrophenones, thioxanthenes), including: a. Haloperidol b. Trimethobenzamide or domperidone (for nausea/vomiting) c. Metoclopramide d. Quetiapine (for insomnia)
4.	COMT inhibitors, MAO-B inhibitors, amantadine, istradefylline, or anticholinergic drugs (unless use was initiated >90 days before the Baseline Visit and dose will remain stable for the duration of the treatment phase) Note: Short-term use of scopolamine for TEAEs of nausea may be permitted following consultation with and approval by the medical monitor, but may not be taken within 12 hours prior to efficacy assessments during clinic visits. Use should be discontinued upon TEAE resolution.
5.	Levodopa inhalation powder
6.	Dopamine agonists, including apomorphine
7.	Methyldopa
8.	Moderate or strong CYP3A4 inducers[a] (refer to Section 10.6 [Appendix 6] for examples)
9.	Moderate or strong CYP3A4 inhibitors[a] (refer to Section 10.6 [Appendix 6] for examples)
10.	Mood stabilizers a. Anticonvulsants b. Lithium Note: Use of certain anticonvulsants (eg, pregabalin) for medical reasons unrelated to seizures or psychiatric mood stabilization may be allowed after discussion with and approval by the medical monitor.
11.	Nonselective MAO inhibitors
12.	Prescription stimulants a. Amphetamine derivatives b. Bupropion c. Mazindol d. Methylphenidate e. Modafinil f. Phentermine g. Phenylpropanolamine
13.	Reserpine
14.	Tricyclic antidepressants

15.	Varenicline
16.	Zonisamide
17.	Other investigational medications

Abbreviations: COMT = catechol-O-methyl transferase, CYP = cytochrome P450, MAO = monoamine oxidase; TEAE = treatment-emergent adverse event.
a. Except for topical administration.

6.5.5 Dose Modification

The dose of tavapadon will be gradually titrated to 15 mg QD in all subjects, as shown in Table 4, unless prevented by intolerance, and then maintained for the duration of the trial. Procedures for dose modifications are provided in Section 4.1.2.

Dose modifications will be achieved by issuing new IMP blister cards with the adjusted dose to the subject such that the subject continues to take 3 tablets once daily. The IMP will be packaged in a manner that will allow dose modifications to be made without unblinding the trial.

6.6 Intervention after the End of the Trial

Subjects who complete through Week 27 of the trial may have the opportunity to receive open-label treatment with tavapadon in an open-label extension trial (Protocol CVL-751-PD-004). Subjects who are ineligible or elect not to enter the open-label extension trial will resume treatment with available antiparkinsonian medications at the discretion of and as determined by their physician.

7 DISCONTINUATION OF TRIAL INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Entire Trial

If the sponsor terminates or suspends the trial for any reason, prompt notification will be given to investigators, Institutional Review Boards/Independent Ethics Committees (IRBs/IECs), and regulatory authorities in accordance with regulatory requirements.

7.2 Discontinuation of Individual Site

Participation of an individual trial site may be discontinued by the sponsor, the investigator, or the IRB/IEC if judged to be necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP). The investigator will notify the sponsor promptly if the trial is terminated by the investigator or the IRB/IEC at the site.

7.3 Individual Subject Discontinuation

After treatment assignment, a subject may stop treatment permanently for a variety of reasons. Treatment discontinuation may be initiated by a subject who is not satisfied with

treatment or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other issues, as determined by the investigator.

A subject may discontinue the IMP for any of the following reasons:

- Adverse event
- Death
- Worsening of PD symptoms to such an extent that, in the judgment of the investigator, the subject requires additional anti-PD medications
- Treatment with prohibited concomitant medications
- Noncompliance with study schedule
- Noncompliance with study drug
- Withdrawal by subject
- Pregnancy
- Physician decision

If a subject discontinues the IMP due to an AE, the investigator or other trial personnel will make every effort to follow the event until it has resolved or stabilized.

All subjects have the right to withdraw consent for further participation in the trial at any time without prejudice. Subjects cannot withdraw consent for use of data that have already been collected as part of the trial but can withdraw consent for future participation. The investigator can also discontinue a subject from the trial at any time if medically necessary. Unless the subject provides written withdrawal of consent or there is other written documentation by the investigator confirming the subject's verbal intent to completely withdraw from the trial, subjects should be followed for all protocol-specified evaluations and assessments, if possible.

Complete withdrawal of consent requires a subject to refuse of ALL of the following methods of follow-up:

- Participation in all follow-up procedures specified in the protocol (whether in-clinic or by telephone)
- Participation in a subset of protocol specified follow-up procedures (by a frequency schedule and method, as agreed by subject and staff)
- Contact of the subject by trial personnel, even if only by telephone, to assess current medical condition, and obtain necessary medical or laboratory reports relevant to the trial's objectives
- Contact of an alternative person(s) who has been designated in source records as being available to discuss the subject's medical condition, even if only by telephone, mail, or e-mail (eg, family, spouse, partner, legal representative [as defined per local regulations], friend, neighbor, or physician)

- Access to medical information from alternative sources (eg, hospital/clinic medical records, referring doctor's notes, public records, dialysis, transplantation or vital registries, social media sources)

Withdrawal of consent is a critical trial event and, therefore, should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a subject's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the subject and the integrity of the trial. A subject may initially express the desire to interrupt, modify, or discontinue administration of the IMP, which is not equivalent to a complete withdrawal of consent for further participation. A subject may, however, indicate that further trial participation is creating a burden on his or her work, school, or social schedule. Therefore, the investigator should determine if the subject can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated. Only subjects who withdraw their permission for all of the above methods of follow-up are considered to have completely withdrawn their consent to participate in the trial.

Details on the withdrawal of consent for the optional banked biospecimen sample are provided in the separate ICF for that sample.

7.4 Lost to Follow up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by trial site personnel.

The following actions must be taken if a subject fails to return to the clinic for a required trial visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the trial.
- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the trial.

8 TRIAL ASSESSMENTS AND PROCEDURES

Trial procedures and their timing are summarized in the Schedule of Assessments (Table 2). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue trial intervention.

Adherence to the trial design requirements, including those specified in the Schedule of Assessments, is essential and required for trial conduct.

8.1 Screening and Baseline Assessments

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. Data collected as part of the screening process may be submitted to sponsor/clinical research organization (CRO) in order to facilitate eligibility assessment. Protocol waivers or exemptions are not allowed. The investigator will maintain a screening log to record details of all subjects who are screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures that are conducted as part of the subject's routine clinical management (eg, blood count) and that are obtained before the ICF is signed may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the Schedule of Assessments (Table 2).

As part of the screening procedures, the investigator will assess the severity of each subject's PD symptoms using the modified Hoehn and Yahr scale (Hoehn and Yahr, 1967; Goetz et al, 2004) on which:

Stage	Definition
1 =	Unilateral involvement only
1.5 =	Unilateral and axial involvement
2 =	Bilateral involvement without impairment of balance
2.5 =	Mild bilateral disease with recovery on pull test
3 =	Mild to moderate bilateral disease; some postural instability; physically independent
4 =	Severe disability; still able to walk or stand unassisted
5 =	Wheelchair bound or bedridden unless added

Subjects must have a modified Hoehn and Yahr stage of 2, 2.5, or 3 for inclusion in the trial.

The investigator will also administer the Montreal Cognitive Assessment (MoCA) to detect the subject's level of cognitive impairment (Nasreddine et al, 2005). The MoCA is administered over approximately 10 minutes to gauge areas of language, visuospatial ability, memory, recall, and abstract thinking. The total possible score is 30, with any score greater than 25 considered normal. Scores of 25 or less are considered to be an

indication of some form of cognitive impairment. Subjects with a MoCA score <26 will not be eligible for the trial.

8.2 Efficacy Assessments

The planned time points for efficacy assessments are shown in the Schedule of Assessments (Table 2). At each clinic visit, efficacy assessments should be completed first, followed by the safety assessments.

8.2.1 Hauser Diary

The Hauser diary assesses patient-defined motor function status over a period and provides a tool for assessment of change in "off" time and "on" time with troublesome dyskinesia (Hauser et al, 2000). The Hauser diary asks patients to rate their mobility for each 30-minute period and to record their status for the majority of the period in 1 of 5 categories as: "on" time without dyskinesia, "on" time with nontroublesome dyskinesia, "on" time with troublesome dyskinesia, "off" time, or asleep.

During the Screening Period, subjects will be trained in the use of the home diary (Hauser diary), and subjects and investigators (or qualified designee) will independently complete concordance testing on the Hauser diary (full details and requirements for conduct and successful completion of concordance testing are provided in the appropriated protocol-specific manual). Subjects who successfully meet the concordance testing criteria will complete the Hauser diary at home on at least 2 consecutive days (24-hour periods) within the 7 days before the Baseline Visit.

Subjects will record diary entries at home at 30-minute intervals for 24 hours on 2 consecutive days within the 7 days before randomization at the Baseline Visit and at 30-minute intervals for 24 hours on 2 consecutive days within the 7 days before each postbaseline clinic visit.

8.2.2 Movement Disorder Society-Unified Parkinson's Disease Rating Scale

The MDS-UPDRS (Goetz et al, 2008) is a multidimensional scale that assesses the motor and nonmotor impacts of PD across 4 parts. The scale is completed using a combination of physician and patient assessments and a collection of information from the patient or caregiver:

- Part I, nonmotor aspects of experiences of daily living, comprises 13 items, 6 of which are rated by the physician (Part IA) and 7 of which are rated by the patient (Part IB).
- Part II, motor aspects of experiences of daily living, comprises 13 items that are rated by the patient. The 13 items in Part II and the 7 items in Part IB constitute the patient questionnaire portion of the MDS-UPDRS.

- Part III, motor examination, comprises 18 items that are assessed by the investigator (resulting in 33 scores by location and lateralization).
- Part IV, motor complications, comprises 6 item (3 items for dyskinesia and 3 items for fluctuation) and requires the physician to use historical and objective information to assess dyskinesia and motor fluctuations.

Each item is rated on a scale from 0 to 4 on which 0 = normal, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe.

The same individual should perform the ratings for an individual subject throughout the course of the trial. The postbaseline MDS-UPDRS assessments Parts I, II, and III should be conducted approximately 2 to 3 hours after the last dose of L-Dopa on the day of the clinic visit.

8.2.3 39-Item Parkinson's Disease Questionnaire

The 39-item Parkinson's Disease Questionnaire (PDQ-39) is the most thoroughly validated and extensively used self-report measure for the assessment of health-related quality of life in people with PD. The questionnaire measures 39 items, which assess 8 domains of health: mobility (10 items), activities of daily living (6 items), emotional well-being (6 items), stigma (4 items), social support (3 items), cognitions (4 items), communication (3 items), and bodily discomfort (3 items) (Peto et al, 1998). Each item is scored on the following scale: 0=never, 1=occasionally, 2=sometimes, 3=often, and 4=always. Items in each subscale and the total scale can be summarized into an index and transformed linearly to a scale from 0 (perfect health as assessed by the measure) to 100 (worst health as assessed by the measure).

8.2.4 EuroQol 5 Dimension 5 Level

The EuroQol 5 Dimension 5 Level (EQ-5D-5L) is a patient-reported outcome that measures health in 5 dimensions. It is a widely used survey instrument for measuring economic preferences for health states, is applicable to a wide variety of health conditions and treatments, and provides a simple descriptive profile and a single index value for health status (Herdman et al, 2011). The EQ-5D-5L consists of a descriptive system and a visual analog scale (VAS).

The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The patient is asked to indicate his or her health state by ticking the box next to the most appropriate statement in each of the 5 dimensions. This decision results if a 1-digit number that expresses the level that was selected for that dimension. The digits for the 5 dimensions are combined into a 5-digit number that describes the patient's health state.

The EQ-5D-5L VAS records the patient's self-rated health on a vertical VAS on which the endpoints are labeled "the best health quality that you can imagine" and " the worst

health quality that you can imagine." The VAS can be used as a quantitative measure of health outcome that reflects the patient's own judgment.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Assessments (Table 2).

Safety assessments should be performed after all efficacy assessments have been completed. Assessments should be performed in the following order:

- Epworth Sleepiness Scale (ESS)
- Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale (QUIP-RS)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Physical and neurological examinations
- Vital signs
- Electrocardiograms
- Blood specimen collection
- Other procedures (eg, concomitant medications, AEs): all other procedures may be obtained before or after blood specimen collection

8.3.1 Epworth Sleepiness Scale

The ESS is a scale that is intended to measure daytime sleepiness (Johns, 1991). It assesses the likelihood of dozing off or falling asleep in the following common situations: sitting and reading, sitting inactive in a public place (eg, in a meeting, theater, dinner event), as a passenger in a car for an hour or more without stopping for a break, lying down to rest when circumstances permit, sitting and talking to someone, sitting quietly after a meal without alcohol, and in a car while stopped for a few minutes in traffic or at a light. Each situation is rated as 0=would never nod off, 1=slight chance of nodding off, 2=moderate chance of nodding off, or 3=high chance of nodding off. A score ≥10 indicates that the patient may need to get more sleep, improve sleep practices, or seek medical attention to determine why he or she is sleepy.

8.3.2 Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale

The QUIP-RS is a global screening instrument that assesses ICDs and related disorders (punding, hobbyism, and dopamine dysregulation syndrome) in patients with PD

(Weintraub et al, 2012). The QUIP-RS has 4 primary questions that pertain to commonly reported thoughts, urges/desires, and behaviors associated with ICDs, each of which is applied to 4 ICDs (compulsive gambling, buying, eating, sexual behavior) and 3 related disorders (medication use, punding, and hobbyism).

The QUIP-RS uses a 5-point Likert scale (score 0–4 for each question) to gauge the frequency of behaviors. Patients are instructed to answer questions based on behaviors that occurred in the preceding 4 weeks or during any 4-week period in a designated time frame and are provided with a brief description of the behaviors that are being assessed and with a brief description of the Likert scale categories for frequency (eg, 0=never [not at all], 1=rarely [infrequently or 1 day/week]). Scores for each ICD and related disorder range from 0 to 16, with a higher score indicating greater severity (frequency) of symptoms. The total QUIP-RS score for all ICDs and related disorders combined ranges from 0 to 112.

8.3.3 Columbia-Suicide Severity Rating Scale

Suicidality will be monitored during the trial using the C-SSRS. This semi-structured interview was originally developed to evaluate the link between antidepressants and suicidal behavior and ideation in youth and AEs from pediatric clinical trials (Posner et al, 2011). It was designed to quantify the severity of suicidal ideation and behavior. Trial personnel who administer the C-SSRS must complete the appropriate training and have valid certification. Training on the scale will be provided via the sponsor.

This trial will use the “Baseline/Screening” and “Since Last Visit” versions of the scale. The “Baseline/Screening” version, which assesses the lifetime experience of the subject with suicide events and suicidal ideation and the occurrence of suicide events or ideation within a specified time period prior to entry into the trial, will be completed for all subjects at screening to determine eligibility and confirmed at baseline. Any subject with active suicidal ideation or suicidal behaviors within the last 6 months, suicidal behaviors within the last 2 years, or who in the clinical judgment of the investigator presents a serious risk of suicide should be excluded from the trial (Section 5.2, exclusion 8).

The “Since Last Visit” C-SSRS form will be completed at all visits after screening and baseline. The investigator will review the results of the “Since Last Visit” C-SSRS during the trial to determine whether it is safe for the subject to continue in the trial. If a subject demonstrates potential suicidal ideation associated with actual intent or method or plan as indicated by “YES” answers on item 4 or 5 of the C-SSRS, the investigator will evaluate whether a risk assessment by a qualified mental health professional (or the investigator alone if the investigator is a qualified mental health professional) is needed and whether the subject should continue in or be discontinued from the trial.

8.3.4 Physical and Neurological Examinations

A complete physical examination will consist of measurement of height (screening only) and weight and a review of the following body systems: head, ears, eyes, nose, mouth, skin, heart and lungs, lymph nodes, and gastrointestinal and musculoskeletal systems.

A full neurological examination will include an assessment of the subject's mental status (level of consciousness, orientation, speech, memory, etc), cranial nerves, motor (muscle appearance, tone, strength and reflexes), sensation (including Romberg sign), coordination, and gait.

Height will be measured with a stadiometer, measuring stick, or tape.

The following guidelines will aid in the standardization of body weight measurements:

- The same scale should be used to weigh a given subject each time, if possible.
- Scales should be calibrated and reliable; scales should be at zero just prior to each subject's weigh-in session.
- A subject should void prior to being weighed and be minimally clothed (ie, no shoes or heavy overgarments).
- Weight should be recorded before a subject's meal and at approximately the same time at each visit.

The investigator (or designee) is responsible for performing the physical and neurological examinations. If the appointed designee is to perform these examinations, he or she must be permitted by local regulations and his or her name must be included on the delegation of authority log. Whenever possible, the same individual should perform all physical and neurological examinations.

Any condition present at the posttreatment physical or neurological examination that was not present at the baseline examination should be documented as an AE and followed to a satisfactory conclusion.

8.3.5 Vital Signs

Vital signs include systolic and diastolic blood pressures, heart rate, and body temperature. Duplicate readings of blood pressure and heart rate will be obtained in supine (after 5 minutes of rest) and 1 measurement of blood pressure and heart rate will be obtained on standing (2 minutes after rising from supine to standing). The duplicate values will be individually recorded, and the values will be averaged by the sponsor for the time point assessment. Body temperature will be obtained once, at the time of the first blood pressure measurement.

Additional information related to measurement of blood pressure and heart rate is provided in the appropriate protocol-specific manuals.

8.3.6 Electrocardiograms

Single or triplicate 12-lead ECGs will be obtained during the trial. All ECG recordings be obtained after the subject has been supine and at rest for at least 5 minutes. A triplicate set of ECGs is 3 consecutive ECGs collected 1 to 2 minutes apart over a 5-minute period.

A single ECG will be obtained at the Screening Visit. One set of triplicate ECGs will be obtained before administration of the first dose of IMP on Day 1, and a single ECG will be obtained ~1 hour after administration of the first dose of IMP, just prior to the time of collection of the PK blood sample on Day 1. Single ECGs will be obtained at the Weeks 5, 11, 14, 22, and 27 clinic visits, just prior to the time of collection of the PK blood sample.

Additional 12-lead ECGs may be obtained at the investigator's discretion and should always be obtained in the event of an early termination.

The ECG results will be evaluated at the investigational site to determine the subject's eligibility and to monitor safety during the trial. The principal investigator (or qualified designee) will review, sign, and date each ECG reading, noting whether or not any abnormal results are of clinical significance. The ECG will be repeated if any results are considered to be clinically significant. A central ECG service will be used for reading all ECGs to standardize interpretations for the safety analysis.

If, during screening, any abnormal ECG finding is deemed medically significant (impacting the safety of the subject or the interpretation of the trial results) or meets an exclusion criterion (see Section 5.2), the subject should be excluded from the trial. Medically significant or exclusory abnormal results on an ECG at screening should be repeated with 2 additional ECG recordings to ensure reproducibility of the abnormality, and the 3 ECG recordings read by the central service to confirm the abnormality before excluding a subject. For subjects with a QTcF >450 msec at screening, a subject will be excluded if the QTcF intervals reported by the central service are >450 msec for 2 or more of the 3 ECG recordings, unless due to ventricular pacing. If, at the Baseline Visit, the QTcF interval is >450 msec on the machine readings, consult the medical monitor to determine whether the subject remains eligible to be randomized while awaiting the readings from the central service.

Exclusion criteria for screening do not apply as mandatory discontinuation criteria for subjects who are already randomized. A repeat ECG should be performed to confirm any clinically significant abnormality that is identified in a randomized subject during the treatment period (which will be confirmed by central service read) and, in these cases, the medical monitor should be consulted on the appropriateness of the subject continuing in the trial.

8.3.7 Clinical Safety Laboratory Assessments

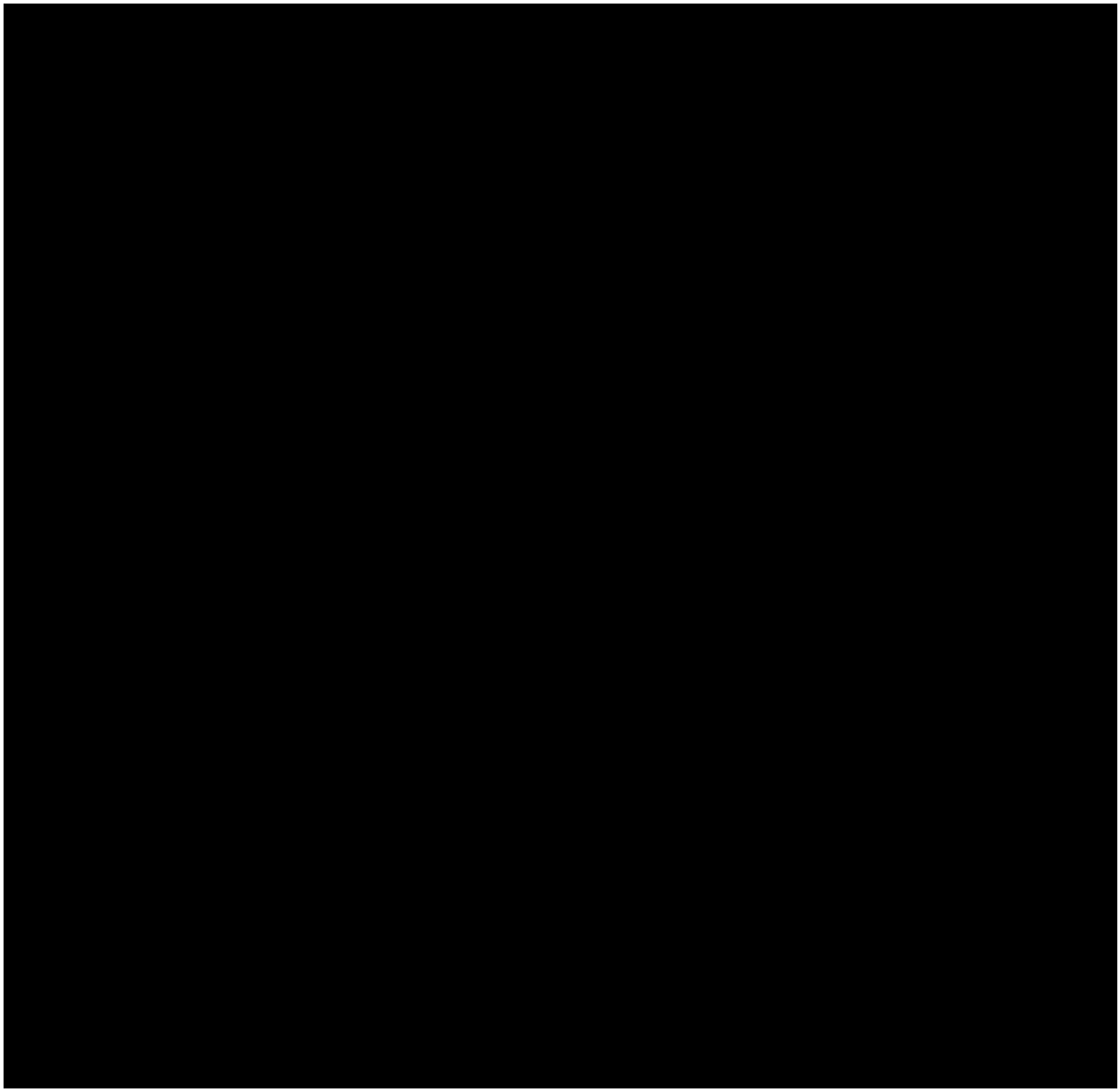
The list of clinical laboratory tests that are to be performed is provided in Section 10.2 (Appendix 2). All protocol-required laboratory assessments must be conducted in accordance with the laboratory manual and the Schedule of Assessments (Table 2).

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the trial in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying

disease, unless judged by the investigator to be more severe than expected for the subject's condition.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the trial should be repeated until the values return to normal, to baseline, or are no longer considered clinically significant by the investigator or medical monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory assessments, as defined in Section 10.2 (Appendix 2), must be conducted in accordance with the laboratory manual and the Schedule of Assessments (Table 2).



8.4 Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

The definitions of an AE and SAE are provided in Section 10.3 (Appendix 3). The AESI for this trial are defined in Section 8.4.6.

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative, as defined per local regulations).The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, SAE, or AESI and remain responsible for following up SAEs/AESI, considered related to the trial intervention or trial procedures, or cause the subject to discontinue IMP (see Section 7.3).

8.4.1 Time Period and Frequency for Collecting AE and SAE/AESI Information

All AEs and SAEs/AESIs will be recorded from the first dose of IMP until follow-up contact at the time points specified in the Schedule of Assessments (Table 2).

Medical occurrences that begin before the start of IMP dosing but after obtaining informed consent will be recorded as medical and/or psychiatric history.

All SAEs/AESI will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3 (Appendix 3). The investigator will submit any updated SAE/AESI data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs, SAEs, or AESI after conclusion of the trial participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the trial, or AESI and he/she considers the event to be reasonably related to the trial intervention or trial participation, the investigator must promptly notify the sponsor.

8.4.2 Method of Detecting AEs and SAEs/AESI

The method of recording, evaluating, and assessing causality of AEs and SAEs/AESI and the procedures for completing and transmitting SAE/AESI reports are provided in Section 10.3 (Appendix 3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs/AESI. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.4.3 Follow-up of AEs and SAEs/AESI

After the initial AE/SAE/AESI report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs/AESI will be followed until

resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is given in Section 10.3 (Appendix 3).

8.4.4 Regulatory Reporting Requirements for SAEs/AESI

Prompt notification by the investigator to the sponsor of an SAE/AESI is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a trial intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE/AESI or other specific safety information (eg, summary or listing of SAEs/AESI) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy

Details of all pregnancies in female subjects or in female partners of male subjects will be collected after the start of trial intervention and until 4 weeks after the last dose.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4 (Appendix 4).

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.6 Adverse Events of Special Interest

8.4.6.1 Adverse Events Potentially Related to Abuse

A key objective of the Abuse Potential Monitoring Plan (APMP) is to monitor for instances of abuse or diversion of the trial medication and other psychoactive substances.

In addition to monitoring for irregularities in medication handling, AEs that may be suggestive of a developing abuse issue will also receive special attention. As part of the APMP, medication handling irregularities (MHIs) must be reported, and AEs related to

abuse potential and AEs involving MHIs must be reported as events subject to additional monitoring (ESAMs), with detailed narratives.

Investigators and site staff at each trial site will be trained on reporting potentially abuse related AEs (eg, recording a description of the event in the subject's own words in the source documents as well as the eCRF, in addition to the clinical term, and to be aware that a subject's report may encompass more than one event and that these should be recorded separately). The investigators will be provided with examples of potentially abuse-related AEs and trained on how to handle such events (eg, additional monitoring).

While the investigators will be provided with examples of AE terms as a guide during trial conduct, the analysis of potentially abuse-related AEs will be based on a search by the sponsor of all relevant Medical Dictionary for Regulatory Activities (MedDRA) terms, all verbatim terms, and any open text fields within the AE data to identify text strings suggestive of abuse potential, consistent with US Food and Drug Administration (FDA) guidance (Guidance for Industry: Assessment of Abuse Potential of Drugs, January 2017).

Complete details, including documenting and reporting procedures, examples of potentially abuse-related terms and guidance for the training of investigators and trial site staff are provided in the APMP.

8.4.6.2 Abnormal Liver Function Tests

The finding of an elevated value for alanine aminotransferase (ALT) or aspartate aminotransferase (AST) of >3 × the upper limit of normal (ULN) in combination with either an elevated value for total bilirubin >2 × ULN or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report the occurrence of either of the following as AESI to the sponsor with 24 hours:

- Treatment-emergent value of >3 × ULN for ALT or AST and >2 × ULN for total bilirubin
- Treatment-emergent value of >3 × ULN for ALT or AST and clinical jaundice

Brief narratives will be written for any subjects who experience abnormalities in liver function tests that meet the criteria specified above.

8.4.6.3 Adverse Events Leading to Discontinuation

Any AE that leads to discontinuation of IMP or from the trial will be classified as an AESI. Brief narratives will be written for subjects who discontinue IMP or from the trial because of AEs.

8.5 Treatment of Overdose

Titrated doses of up to 25 mg QD of tavapadon have been evaluated subjects with PD (Trial B7601005). Across all doses (5, 15, and 25 mg QD), nausea, vomiting, headache, dizziness, and abnormal dreams were the most commonly reported TEAEs. A dose-related increase was observed between the 15 mg QD (n=11) and 25 mg QD (n=19) doses in the percentage of subjects who experienced gastrointestinal-related TEAEs (27% vs 58%), in particular, nausea (27% vs 42%) and vomiting (9.1% vs 21.1%), and in the percentage of subjects who discontinued from the trial due to gastrointestinal TEAEs (0% vs 16%). Other TEAEs were reported in comparable percentages of subjects. Based on these findings, as well as on PK findings, which showed a less-than-dose-proportional increase in exposure between the 15 and 25 mg doses (consistent with the moderate-to-low solubility of tavapadon at the pH of the gastrointestinal tract of 6.5), 15 mg QD was identified as the maximum dose in this trial (see also Section 4.3).

Any dose >15 mg of tavapadon (maximum dose in this trial) within the same calendar day will be considered an overdose. There is no specific antidote for overdose with tavapadon. In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately
2. Closely monitor the subject for any AE/SAE/AESI and laboratory abnormalities
3. Document the quantity of the excess dose, as well as the duration of the overdose, in the eCRF

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the subject.

8.6 Pharmacokinetics

Blood samples for measurement of plasma concentrations of tavapadon and its major metabolite (if required) will be collected ~1 hour after administration of the first dose of IMP on Day 1 and at the clinic visits at the end of Weeks 5, 11, 14, 22, and 27, just after ECG acquisition at each time point, as shown in the Schedule of Activities (Table 2). The date and time of the most recent dose, the dose amount, and the time of the blood draw will be recorded. Instructions for the collection and handling of biological samples will be provided by the sponsor.

Plasma samples will be processed, stored, and shipped to the bioanalytical facility according to the instructions that will be provided to the investigator in advance of the trial. A fully validated bioanalytical method will be used to quantitate plasma concentrations of tavapadon and its major metabolite (if required).

Drug concentration information will not be reported to investigative sites or blinded personnel until the trial has been unblinded.

8.7 Future Biospecimen Research

Studying the variation in genetic markers and other biomarkers may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomic/biomarker research. Comparing the DNA, RNA, protein, and metabolite variation patterns of subjects who respond well and those who respond poorly to treatment may help to better define the most appropriate group of subjects in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/biomarker analyses and retaining them at Cerevel makes it possible to better understand the drug's mechanism of action and to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of this trial.

Banked biospecimen samples will be collected from subjects who consent to this sample collection on a separate ICF. Research performed on these samples may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics and/or the measurement of other analytes. Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary efficacy endpoint is the change from baseline in "on" time without troublesome dyskinesias. The hypothesis of interest is a 2-sided test of superiority comparing tavapadon (CVL) to placebo:

$$H_0: \mu_{\text{placebo}} = \mu_{\text{CVL-751}} \text{ vs } H_1: \mu_{\text{placebo}} \neq \mu_{\text{CVL-751}}$$

9.2 Sample Size Determination

A sample size of 184 subjects per group (total, 368 subjects) will provide at least 90% power to detect a change in the primary outcome measure (change from baseline in "on" time without troublesome dyskinesia) of 1 hour with a standard deviation of 2.5, a 2-sided alpha level = 0.049, and assuming a 27% dropout rate.

In the event of higher than anticipated early terminations due to COVID-19 or other reasons, Cerevel may extend enrollment in order to maintain the planned statistical power.

9.3 Populations for Analyses

The analysis populations are defined (Table 8).

Table 8 Populations for Analysis

Population	Description	Analysis
ITT	All randomized subjects	Demographic and Baseline Characteristics
FAS	All randomized subjects who receive at least 1 dose of IMP. This will be the safety analysis set.	Safety analysis
mITT	All randomized subjects who receive at least 1 dose of IMP and have both a baseline and at least 1 postbaseline Hauser diary entry	Primary analysis set for efficacy
Endpoint completers	All subjects in the mITT population who complete the Hauser diary at endpoint	Sensitivity analysis for efficacy
PK Analysis Set	All randomized subjects who receive at least 1 dose of IMP and have at least 1 measurable tavapadon (CVL-751) concentration	PK analysis

Abbreviations: FAS = full analysis set, IMP = investigational medicinal product, ITT = intent-to-treat, mITT = modified intent-to-treat, PK = pharmacokinetic.

9.4 Statistical Analyses

Descriptive statistical methods will be used to summarize the data from this trial, with statistical testing performed for the efficacy endpoints. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects (n), mean, median, standard deviation, minimum, and maximum for continuous data, and frequencies and percentages for categorical data. All available data for enrolled subjects will be listed by subject. Unless otherwise noted, the data will be sorted first by treatment group and subject number and then by date within each subject number.

All statistical analyses will be conducted with the SAS® System, version 9.4 or higher.

The remainder of this section is a summary of the planned statistical analyses of the primary and secondary endpoints as well as a description of planned safety analyses. Full details of these analyses will be included in the statistical analysis plan. The statistical analysis plan will be developed and finalized before database lock and will provide descriptions of the subject populations that will be used in the analysis and procedures for addressing missing, unused, and spurious data.

9.4.1 Efficacy Analyses

The analysis of the primary and each secondary endpoint (Table 9) will include the comparison of tavapadon versus placebo. The hypothesis testing will be done in hierarchical order from the primary endpoint onward. To control for any potential inflation of Type I error that may be incurred from the interim analysis, the primary

hypothesis will be tested at an α level of 0.049 (2-sided) to ensure that the overall Type I error rate is below 0.05. Subsequent testing in the secondary endpoints will be conducted at an α level of 0.05 (2-sided).

Table 9 Efficacy Analysis

Endpoint	Statistical Analysis Methods
Primary and Key Secondary	The primary endpoint (change from baseline to endpoint in "on" time without troublesome dyskinesia) and the key secondary endpoint (change from baseline to endpoint in "off" time) will be analyzed using an MMRM on the mITT population. This estimand will be based on the 2-day average of the self-completed Hauser diary from each postbaseline visit. A hypothetical strategy will be used to address the intercurrent events of discontinuation or use of prohibited medications with the data post intercurrent events treated as censored. The baseline value will be included as a covariate, and the treatment group (tavapadon or placebo), visit, and interaction between treatment group and visit will be included as fixed factors in the MMRM. The difference between tavapadon versus placebo at endpoint will be estimated based on the LSMeans from the MMRM. The key secondary endpoint will be analyzed in a similar manner. Sensitivity analyses for the primary and secondary endpoints will be conducted with different assumptions on missing mechanism. Sensitivity analysis will also be conducted on the endpoint completer set with MMRM.
Secondary and Other	Continuous secondary and other endpoints (MDS-UPDRS, EQ-5D-5L index and VAS scores and PDQ-39 score) will be analyzed in a manner similar to that used for the primary and key secondary efficacy endpoints. Categorical endpoints will be analyzed on the mITT population using the SAS® GLIMMIX procedure for binomial data with logit link. This generalized linear mixed model analysis will include response data from each postbaseline visit that occurs before discontinuation of treatment or addition of rescue medication through endpoint. The model will include the treatment group, visit, and interaction between treatment group and visit. An unstructured covariance structure will be used for the repeated measures. If the model fails to converge with the unstructured covariance structure, the heterogeneous Toeplitz structure or further reduced covariance structure may be used instead. The odds ratio for the treatment difference, 95% CIs for the odds ratio, and p-value will be provided.

Abbreviations: CI = confidence interval, EQ-5D-5L = EuroQol 5 Dimension 5 Level, mITT = modified intent-to-treat, MDS-UPDRS = Movement Disorder Society – Unified Parkinson's Disease Rating Scale, LSMean = least squares mean, mITT = modified intent to treat, MMRM = Mixed Model for Repeated Measures, PDQ-39 = 39-Item Parkinson's Disease Questionnaire, VAS = visual analog scale.

9.4.2 Safety Analyses

All safety analyses (Table 10) will be performed on the full analysis set (FAS). Should any subjects receive a treatment other than their randomized treatment, the treatment as received will be used in the safety presentation.

Table 10 Safety Analysis

Endpoint	Statistical Analysis Methods
TEAEs, including abuse-related AEs and AEs related to MHIs	TEAEs will be coded according to MedDRA and summarized by treatment group, system organ class, and preferred term. Additional summaries by seriousness, severity, relationship to IMP, and dose at the time of onset will also be prepared.
Other safety	The C-SSRS, ESS, QUIP-RS, laboratory data, vital sign data, and ECG data will be summarized with descriptive statistics.

Abbreviations: AE = adverse events, C-SSRS = Columbia-Suicide Severity Rating Scale, ECG = electrocardiogram, ESS = Epworth Sleepiness Scale, IMP = investigational medicinal product, MedDRA = Medical Dictionary for Regulatory Activities, MHIs = medication handling irregularities, QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders – Rating Scale, TEAE = treatment-emergent adverse event.

9.4.3 Other Analyses

Plasma concentrations of tavapadon and its major metabolite (if required) will be summarized by dose, visit, and nominal time (if applicable). All PK exposure-response analyses will be described in a separate PK analysis plan that will be finalized before database lock.

Plasma concentrations will also be pooled with data from other trials in a population PK analysis to describe the time course of plasma concentrations of tavapadon and the influence of covariates (eg, body weight, age, sex, race, concomitant medications) on PK parameters. The results of population PK analysis and response-exposure analyses will be presented separately from the main clinical study report (CSR).

9.5 Interim Analysis

Given that the assumptions for the sample size were based on a preliminary study using a different dosing schedule, it is unknown if these assumptions are appropriate for this study as designed. To this end, an interim analysis of the primary efficacy endpoint will be included to assess the adequacy of the overall sample size relative to achieving the study objectives. This analysis will be conducted by an independent Interim Analysis Review Committee (IARC), which may make a recommendation to increase the overall sample size up to a maximum of 528 subjects. Full details and rules for the IARC and planned interim analysis will be provided in a separate IARC charter and in the statistical analysis plan.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This trial will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Conference on Harmonisation (ICH) GCP Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the trial is initiated. Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the trial to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs/AESI or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the trial at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical trials (if applicable), and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and for 1 year after completion of the trial.

10.1.3 Informed Consent Process

The investigator or his/her representative will explain the nature of the trial to the subject or his/her legally authorized representative (as defined per local regulations) and answer all questions regarding the trial.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative as applicable by local law will be required to sign a statement of informed consent (either electronic or written) that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or trial center.

The medical record must include a statement that informed consent was obtained before the subject was enrolled in the trial and the date the consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Subjects must be reconsented to the most current version of the ICF(s) during their participation in the trial. A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative (as defined per local regulations) .

A separate and similar consent process will be followed for the optional banked biospecimen research samples. The investigator or authorized designee will explain the objectives of the exploratory research to each subject. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document subject agreement to allow specimens to be used for exploratory research. Subjects who decline to participate in this optional research will not provide this separate signature.

10.1.4 Data Protection

Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal trial-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Dissemination of Clinical Trial Data

Cerevel fulfills its commitment to publicly disclose clinical trial results through posting trial results on ClinicalTrials.gov, the European Clinical Trials Database (EudraCT), and other public registries in accordance with applicable local laws/regulations.

In all cases, trial results are reported by Cerevel in an objective, accurate, balanced, and complete manner and are reported regardless of trial outcome or the country in which the trial was conducted.

US Basic Results are posted on Clinicaltrials.gov for all Cerevel-sponsored interventional trials that are conducted in subjects and that evaluate the safety and/or efficacy of a Cerevel product, regardless of the geographical location in which the trial is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date, as defined in Section 4.4, for trials in adult populations or within 6 months of the primary completion date for trials in pediatric populations.

Cerevel posts European Union (EU) Basic Results on EudraCT for all Cerevel-sponsored interventional trials that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date as defined in Section 4.4, for trials in adult populations or within 6 months of the primary completion date for trials in pediatric populations.

10.1.6 Data Quality Assurance

All subject data relating to the trial will be recorded on printed or eCRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Clinical Monitoring Plan.

The sponsor or designee is responsible for the data management of this trial including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

Trial monitors will perform ongoing source data verification to confirm that data entered onto the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the investigator for the longest of the following periods:

- At least 2 years after the date on which approval to market the drug is obtained (or if development of the IMP is discontinued, the date regulatory authorities were notified of discontinuation
- At least 3 years after the sponsor has notified the investigator that the final report has been filed with regulatory authorities
- A longer period if required by local regulations or institutional policies

No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7 Source Documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial. Also, current medical records must be available.

Definitions of what constitutes source data are included in the Clinical Monitoring Plan.

10.1.8 Trial and Site Closure

The sponsor designee reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of the sponsor. Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial-site closure visit has been performed.

The investigator may initiate trial-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a trial site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further trial intervention development

10.1.9 Publication Policy

The results of this trial may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of trial results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter trials only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 11 will be performed at the time points designated in the Schedule of Assessments (Table 2). Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations. .

Table 11 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**		
Hematology	Platelet count RBC count Hemoglobin Hematocrit MCV	WBC count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	BUN Creatinine Albumin Cholesterol Total HDL-C LDL-C Triglycerides	Potassium Sodium Calcium Bicarbonate Chloride Magnesium Glucose	ALT AST Alkaline phosphatase GGT CPK Total bilirubin Direct bilirubin Total protein TSH (with reflex-free T3/T4 if abnormal)
Urinalysis	Specific gravity Color	Dipstick[a] pH Glucose Protein Blood Ketones Bilirubin Urobilinogen Nitrite Leukocyte esterase	
Additional Tests	Prolactin (results will not be reported to investigative sites or other blinded personnel until the trial is unblinded). Serum pregnancy test (at screening and as needed for WOCBP). Urine dipstick pregnancy test (at all other time points as needed for WOCBP), followed by serum pregnancy test if urine dipstick test is positive. If serum CPK value is >3 × ULN, CPK reflex for isoenzymes. If serum CPK value is >5 × ULN, serum and urine myoglobin.		

Table 11 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Screening Tests	Urine drug screen for illicit drugs Serology (HIV, HbsAg, and HCV)

Abbreviations: AE = adverse event, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CPK = creatine phosphokinase, eCRF = electronic case report from, GGT = gamma-glutamyl transferase, HbsAg = hepatitis B surface antigen, HCV = hepatitis C virus, HDL-C = high-density lipoprotein cholesterol, HIV = human immunodeficiency virus, LDL-C = low-density lipoprotein cholesterol, MCV = mean corpuscular volume, RBC = red blood cell, T3 = triiodothyronine, T4 = thyroxine, TSH = thyroid-stimulating hormone, ULN = upper limit of normal, WBC = white blood cell, WOCBP = women of childbearing potential.

a. Results of the dipstick urine analysis will not be recorded on the eCRFs. Any clinically significant finding will be captured as an AE.

Investigators must document their review of each laboratory safety report and file the laboratory report as appropriate. Any clinically significant laboratory abnormality must be reported as an AE.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

Table 12 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical trial subject, temporally associated with the use of trial intervention, whether or not considered related to the trial intervention. • NOTE: Signs and symptoms and/or abnormal laboratory test result indicating a common underlying pathology/diagnosis should be reported as a single AE.

Abbreviation: AE = adverse event.

Table 13 Events Meeting the AE Definition

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after trial intervention administration even though it may have been present before the start of the trial. • Signs, symptoms, or the clinical manifestations of a suspected drug-drug interaction. • Signs, symptoms, or the clinical manifestations of a suspected overdose of either trial intervention or a concomitant medication. "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE/AESI. Such instances will be captured in the efficacy assessments.

Abbreviations: AE = adverse event, AESI = adverse event of special interest, ECG = electrocardiogram, SAE = serious adverse event.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under trial, death due to progression of disease).

Table 14 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose in the view of either the investigator or sponsor, results in any of the following outcome:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, or blood dyscrasias.

Abbreviations: AE = adverse event, SAE = serious adverse event.

10.3.3 Recording and Follow-Up of AEs and/or SAEs/AESI

Table 15 Recording of AEs and/or SAEs/AESI

AE and SAE/AESI Recording
• When an AE/SAE/AESI occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

• The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE/AESI.
• The investigator will then record all relevant AE/SAE/AESI information in the eCRF.
  ○ Nonserious AEs must be recorded on the AE eCRF with the current status noted. All nonserious events (that are not considered AESIs) that are ongoing at the last scheduled contact will be recorded as ongoing on the eCRF. For any AE, during analysis, additional relevant medical history information may be requested by the sponsor to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history and occupation).
  ○ If updated information (eg, resolved status) on SAE/AESI status becomes available after a subject's last scheduled contact (up to last in-clinic visit for the entire trial), this must be reported to the sponsor according to the appropriate reporting procedures. The investigator will follow SAEs/AESI until the events are resolved, stabilized, or the subject is lost to follow-up or has died. Resolution means that the subject has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the subject's condition. The investigator will continue to report any significant follow-up information to the sponsor up to the point the event has resolved or stabilized, or the subject is lost to follow-up, or has died.
  ○ Any new SAEs/AESI reported to the investigator that occur after the last scheduled contact and are determined by the investigator to be related to use of the IMP, should be reported to the sponsor. This may include SAEs/AESI that are captured on follow-up telephone contact or at any other time point after the defined trial period. The investigator should follow SAEs/AESI identified after the defined trial period and continue to report any significant follow-up information to the sponsor until the events are resolved or stabilized, or the subject is lost to follow-up or has died.
• It is **not** acceptable for the investigator to send photocopies of the subject's medical records to the sponsor or designee in lieu of completion of the AE/SAE/AESI eCRF page.
• There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the sponsor or designee.
• The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE/AESI.

Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE/AESI reported during the trial and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

Table 15 Recording of AEs and/or SAEs/AESI

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; AEs and SAEs/AESI can be assessed as severe

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between trial intervention and each occurrence of each AE/SAE/AESI.
- The investigator will assess the relationship as either of the following:
  - **Related**: . An AE will be considered "related" to the use of the IMP if there is evidence to suggest a reasonable possibility of a temporal and causal relationship between the IMP and the AE.
  - **Not Related**: An AE will be considered "not related" to the use of the IMP if there is no plausible causal relationship between the IMP and the AE.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IMP administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE/AESI, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/AESI and has provided an assessment of causality.
- There may be situations in which an SAE/AESI has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE/AESI data to the sponsor or designee.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE/AESI follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Abbreviations: AE = adverse event, AESI = adverse event of special interest, eCRF = electronic case report form, IMP = investigational medicinal product, SAE = serious adverse event.

Table 16 Follow-Up of AEs and SAEs/AESI

Follow-Up of AEs and SAEs/AESI
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE/AESI as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a subject dies during participation in the trial or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed eCRF. • The investigator will submit any updated SAE/AESI data to the sponsor or designee within 24 hours of receipt of the information.

Abbreviations: AE = adverse event, AESI = adverse event of special interest, SAE = serious adverse event.

10.3.4 Reporting of SAEs/AESI

Table 17 SAE/AESI Reporting to the Sponsor or Designee via an Electronic Data Collection Tool

SAE/AESI Reporting to Sponsor or Designee via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE/AESI to the sponsor or designee will be the electronic data collection tool. • The site will enter the SAE/AESI data as soon as it becomes available within 24 hours of awareness. • If the electronic data collection tool is unavailable, then the site will use the paper SAE/AESI form (see next section). • After the trial is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE/AESI from a trial subject or receives updated data on a previously reported SAE/AESI after the electronic data collection tool has been taken off-line, then the site can report this information on the paper SAE/AESI form (see next section) or to the sponsor or designee by telephone.

Abbreviations: AESI = adverse event of special interest, SAE = serious adverse event.

Table 18 SAE/AESI Reporting to Sponsor or Designee via Paper CRF (If Needed)

SAE/AESI Reporting to Sponsor or Designee via Paper CRF
• If the electronic data collection tool is unavailable, then the site will use the paper SAE/AESI form. The SAE/AESI paper form should be electronically transmitted (eg, email, facsimile) to the sponsor or designee. • Contacts for electronic transmission of the paper SAE/AESI form are provided in the Operations Manual. • In rare circumstances and in the absence of electronic transmission equipment, notification by telephone is acceptable with a copy of the SAE/AESI data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the appropriate SAE/AESI form within the designated reporting time frames.

Abbreviations: AESI = adverse event of special interest, CRF = case report form, SAE = serious adverse event.

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1 Definitions

10.4.1.1 Highly Effective Birth Control Methods (Failure Rate <1%)

A highly effective form of contraception (failure rate of <1%) is defined as follows:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

10.4.1.2 Acceptable Birth Control Methods (Failure Rate >1% per Year)

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide*
- Cap, diaphragm or sponge with spermicide.*

*A combination of male condom with a cap, diaphragm, or sponge with spermicide (double-barrier methods) is also considered acceptable but is not a highly effective birth control method.

10.4.1.3 Contraception and Pregnancy Avoidance Procedures

The following definitions apply for contraception and pregnancy avoidance procedures:

A woman is considered to be a woman of childbearing potential (WOCBP) following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Sterilized male subjects should be at least 1 year postbilateral vasectomy and must confirm that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

10.4.2 Collection of Pregnancy Information

10.4.2.1 Male Subjects With Partners Who Become Pregnant

- The investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this trial. This applies only to male subjects who receive trial intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.4.2.2 Female Subjects Who Become Pregnant

- The investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this trial. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a subject's pregnancy.
- The subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or

SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-trial pregnancy related SAE considered reasonably related to the trial intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former trial subjects, he or she may learn of an SAE through spontaneous reporting.

- Any female subject who becomes pregnant while participating in the trial will discontinue trial intervention and be withdrawn from the trial.

10.5 Appendix 5: Future Biospecimen Research

Use/Analysis of DNA

- Genetic variation may impact a subject's response to trial intervention, susceptibility to, and severity and progression of disease. Variable response to trial intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting subjects.
- DNA samples will be used for research related to tavapadon or PD and related diseases. They may also be used to develop tests/assays, including diagnostic tests related to tavapadon and PD. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- DNA samples will be analyzed as part of a multi-trial assessment of the genetic factors that are involved in response to tavapadon or IMPs of this class to understand the trial disease or related conditions
- The results of genetic analyses may be reported in the CSR or in a separate trial summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on tavapadon continues but for no longer than 15 years or other period as per local requirements.

10.6 Appendix 6: Examples of Moderate and Strong Inducers and Inhibitors of Cytochrome P450 3a (CYP3A)

Table 19 Examples of Moderate and Strong Inducers and Inhibitors of CYP3A

CYP3A Inhibitors	CYP3A Inducers
HIV antivirals	**HIV antivirals**
Indinavir	Efavirenz
Nelfinavir	Nevirapine
Ritonavir	Etravirine
Saquinavir	**Miscellaneous**
Boceprevir	Barbiturates
Lopinavir/ritonavir	Carbamazepine
Amprenavir	Glucocorticoids (systemic)
Atazanavir	Modafinil
Telaprevir	Oxcarbazepine
Darunavir/ritonavir	Phenobarbital
Fosamprenavir	Phenytoin
Antibiotics	Pioglitazone
Clarithromycin	Rifabutin
Erythromycin	Rifampin
Telithromycin	St. John's wort
Ciprofloxacin	Troglitazone
Anti-infectives	Bosentan
Itraconazole	Nafcillin
Ketoconazole	Avasimibe
Fluconazole	
Posaconazole	
Voriconazole	
Anti-anginal therapy	
Diltiazem	
Verapamil	
Anti-cancer therapy	
Crizotinib	
Imatinib	

Table 19 Examples of Moderate and Strong Inducers and Inhibitors of CYP3A

CYP3A Inhibitors	CYP3A Inducers
Miscellaneous	
Nefazodone	
Aprepitant	
Grapefruit juice[a,b]	
Conivaptan	
Mibefradil[c]	

Abbreviations: CYP = cytochrome P450, HIV = human immunodeficiency virus.

a. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Trials have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).
b. A 2-week washout before dosing is required if the subject was consuming grapefruit juice continually.
c. Withdrawn from US market.

10.7 Appendix 7: Abbreviations

Abbreviation	Definition
AE	Adverse event
Ae_{tau}	Amount of unchanged drug excreted into the urine over a dosing interval (tau) at steady state
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
APMP	Abuse Potential Monitoring Plan
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
C_{max}	Maximum observed plasma concentration
cAMP	Cyclic adenosine monophosphate
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COMT	Catechol-O-methyltransferase
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CRF	Case report form
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CVL-751	Tavapadon
D1Rs	Dopamine D1-like receptors
D2/D3R	Dopamine D2 and D3 receptor subtypes
DNA	Deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	Electrocardiogram
eCRF	Electronic case report form
EOT	End of treatment
EQ-5D-5L	EuroQol 5 Dimension 5 Level
ESAMs	Events subject to additional monitoring
ESS	Epworth Sleepiness Scale
ET	Early termination
EU	European Union

Abbreviation	Definition
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HbsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
ICD	Impulsive control disorder
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IOP	Intraocular pressure
IRAC	Interim Analysis Review Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System
LDL-C	Low-density lipoprotein cholesterol
L-Dopa	Levodopa
LSMean	Least square mean
MAO	Monoamine oxidase
MAO-B	Monoamine oxidase B
MCV	Mean corpuscular volume
MDS-UPDRS	Movement Disorder Society – Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MHIs	Medication handling irregularities
mITT	Modified intent-to-treat
MMRM	Mixed Model for Repeated Measures
MoCA	Montreal Cognitive Assessment
PD	Parkinson's disease
PDQ-39	39-Item Parkinson's Disease Questionnaire

Abbreviation	Definition
PF-0664975	Previous laboratory code for tavapadon
PK	Pharmacokinetic
QD	Once daily
QTcF	QT interval corrected for heart rate by Fridericia's formula
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SUSAR	Suspected unexpected serious adverse reaction
T3	Triiodothyronine
T4	Thyroxine
TEAE	Treatment-emergent adverse event
THC	Tetrahydrocannabinol
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
VAS	Visual analog scale
WBC	White blood cell
WOCBP	Women of childbearing potential

10.8 Appendix 8: Protocol Amendment History

Document History	
Document:	**Date (Day-Month-Year)**
Version 4.0	06 Jul 2023
Version 3.0	03 Sep 2021
Version 2.0	29 Jun 2020
Original Protocol Version 1.0	07 Oct 2019

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment: Protocol Version 3.0 (03 Sep 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment: The overall rationale for this amendment is to correct errors and to harmonize similar content across the Phase 3 tavapadon protocols via modification and clarification of eligibility criteria, procedural aspects, and statistical considerations.

Section # and Name	**Description of Change**	**Brief Rationale**
Title Page CLINICAL PROTOCOL PRINCIPAL INVESTIGATOR SIGNATURE PAGE	Revised sponsor legal address	Reflect change in location of company headquarters
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS	Objectives and Endpoints tables: Changed metabolites to singular (metabolite)	Correction of error in protocol
1.1 Synopsis 9 STATISTICAL CONSIDERATIONS	Statistical Methods: Added details regarding analysis of efficacy endpoints Clarified analyses associated with each analysis set Added details regarding analysis of efficacy endpoints	Alignment with corresponding content in current statistical analysis plan
1.2 Schema	Hauser Diary: Added text to specify completion “within 7 days” before each clinic visit	Consistency with diary completion instructions in Schedule of Assessments and Hauser Diary sections

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Assessments	Revised vital signs footnote language to specify that standing blood pressure and heart rate will consist of single measurement	Correction of error in protocol
1.3 Schedule of Assessments (continued)	Revised table to indicate that medical occurrences before the start of IMP dosing but after obtaining informed consent will be recorded as medical and/or psychiatric history and that AEs will be recorded from the first dose of IMP	Clarification of recording timeframes relative to informed consent and first dose of IMP
	Clarified ECG footnote language about timing of postbaseline PK samples relative to ECG assessments	Consistency with Section 8.6 Pharmacokinetics
4.1.2 Treatment Period	Added the following and deleted redundant text: Titration of tavapadon should be guided by absence of tolerability issues that are reported as AEs and that are of sufficient severity resulting in significant dysfunction or distress to the subject. Any questions regarding tolerability issues and titration of tavapadon should be directed to the medical monitor before adjustments are initiated.	To emphasize that titration of tavapadon should be related to tolerability issues and to further define tolerability issues
4.4 Definition of Completed Subject	Changed definition of completed subject from the contact at the end of the Safety Follow-up Period to the end of the Treatment Period (Week 27)	Consistency with other sponsor protocols that define completed subject according to last site visit rather than the final contact

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Inclusion Criterion #5: Deleted the following ...with bradykinesia and motor asymmetry Note: Motor asymmetry may or may not be present at the time of Screening, and is not an explicit requirement for inclusion, as long as the subject meets the UK Parkinson's Disease Society Brain Bank diagnostic criteria based on medical history or physical examination.	Clarification regarding presence of motor asymmetry with respect to inclusion criteria
	Added the following: Note: Subjects having more than one affected relative (Step 2 UK Parkinson's Disease Society Brain Bank exclusion criterion) but meeting all other criteria consistent with the UK criteria will be considered to have met eligibility criteria for a diagnosis of PD (Litvan et al, 2003; Massano and Bhatia, 2012).	Consistency with utilization of the historical UK criteria in current clinical practice, which no longer considers having more than one affected relative exclusory of a diagnosis of idiopathic PD based on the more recent understanding of the complex contributory genetic factors
	Inclusion Criterion #7: Added note that subjects receiving levodopa/carbidopa intestinal gel are not eligible	Clarification of eligibility criteria; inclusion criteria specify requirement of good response to levodopa, whereas levodopa/carbidopa intestinal gel is indicated for use when available combinations of Parkinson's treatments medicinal products have not yielded satisfactory results
	Inclusion Criterion #10: Added istradefylline as a permitted prior or concomitant medication	To reflect health authority approval and increase in common usage as adjunctive treatment in Parkinson's disease
5.1 Inclusion Criteria 6.5.2 Allowed Medications Before and During the Trial	Added language to allow use of levodopa/benserazide	Levodopa/benserazide is an acceptable alternative to levodopa/carbidopa that is commonly used in some countries where this trial is being conducted

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria 6.5.3 Prohibited Medications Before the Trial	Changed timing of treatment with COMT inhibitors, MAO-B inhibitors, amantadine, and anticholinergic drugs to be relative to Baseline Visit rather than signing of informed consent	Correction to be consistent with other sponsor protocols that define timing of washout periods for prohibited medications relative to the Baseline Visit
5.2 Exclusion Criteria	Exclusion Criterion #12: Added the following: Note: Subjects who were previously infected with hepatitis C but have been successfully treated (defined as a sustained virologic response or undetectable hepatitis C viral RNA levels at 12 or more weeks after the end of treatment) may be enrolled after discussion with the medical monitor.	Consistency with other sponsor protocols that allow enrollment of subjects with history of hepatitis C that has been successfully treated
5.4 Screen Failures	Deleted language about SAEs	Alignment with changes to language about AE recording starting from first dose of IMP
6.5.3 Prohibited Medications Before the Trial	Added istradefylline to item that includes COMT inhibitors, MAO-B inhibitors, amantadine, and anticholinergic drugs	Alignment with change to Inclusion Criterion #10 and to define washout, if required
6.5.3 Prohibited Medications Before the Trial 6.5.4 Prohibited Medications During the Trial	Added levodopa inhalation powder to prohibited medications Added apomorphine as a prohibited medication (ie, in the dopamine agonist rows of the corresponding tables)	Clarification regarding rescue therapies
	Added text to allow use of certain anticonvulsants (eg, pregabalin) if approved by the medical monitor	To provide options for use in treatment of events unrelated to seizures or psychiatric mood stabilization
6.5.4 Prohibited Medications During the Trial	Combined separate items for sedatives, hypnotics, antidepressants, anxiolytics into single item	Consistency with table of medications prohibited before the trial
	Added text to allow short-term use of lorazepam (or equivalent) if approved by the medical monitor	To provide options for treatment of anxiety or insomnia
	Added text to allow short-term use of scopolamine if approved by the medical monitor	To provide options for treatment of nausea during the trial

Section # and Name	Description of Change	Brief Rationale
6.5.4 Prohibited Medications During the Trial (continued)	Added the following: COMT inhibitors, MAO-B inhibitors, amantadine, istradefylline, or anticholinergic drugs (unless use was initiated >90 days before the Baseline Visit and dose will remain stable for the duration of the treatment phase)	Consistency with Table 6 (medications prohibited before the trial) and convention used for sedatives, hypnotics, antidepressants, and anxiolytics in the table of medications prohibited during the trial
7.3 Individual Subject Discontinuation	Revised list of potential reasons for subject discontinuation of IMP	To align more closely with eCRF
8.1 Screening and Baseline Assessments	Added the following: Data collected as part of the screening process may be submitted to sponsor/clinical research organization (CRO) in order to facilitate eligibility assessment.	To address recent regulatory updates observed during trial conduct
8.3.4 Physical and Neurological Examinations	Removal of genitourinary examination	Update in standard sponsor processes
8.3.5 Vital Signs	Added clarification that standing blood pressure and heart rate will consist of single measurement	Alignment across Phase 3 protocols and consistency with changes to Section 1.3
8.4.1 Time Period and Frequency for Collecting AE and SAE/AESI Information	Clarified that AEs will be recorded from the first dose of IMP and medical occurrences that begin before the start of IMP dosing but after obtaining informed consent will be recorded as medical and/or psychiatric history	Confirm timeframes for medical history and AE recording relative to informed consent and first dose of IMP
10.3.3 Recording and Follow-Up of AEs and/or SAEs/AESI	Deleted the following language: ...that are identified at any time during the trial... ...having been identified throughout the trial...	Alignment with changes to language about AE recording starting from first dose of IMP
11 REFERENCES	Added new references: Litvan et al, 2003 Massano and Bhatia, 2012	To reflect revision to Inclusion Criterion #5
Overall	Corrections/clarifications of grammar or typographical errors	To address minor errors in the previous version of the protocol

Abbreviations: AE = adverse event, AESI = adverse event of special interest, COMT = catechol-O-methyl transferase, eCRF = electronic case report form, ECG = electrocardiogram, IMP = investigational medicinal product, MAO-B = monoamine oxidase inhibitor B, PD = Parkinson's disease, PK = pharmacokinetic, RNA = ribonucleic acid, SAE = serious adverse event.

Amendment: Protocol Version 2.0 (29 Jun 2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The overall rationale for this amendment is to incorporate measures into the protocol to ensure the safety of the trial subjects and the validity of the trial data in the environment of the COVID-19 pandemic and to clarify other aspects of trial conduct unrelated to the COVID-19 pandemic.

Section # and Name	Description of Change	Brief Rationale
Sponsor Signatories	Changed name of biostatistician	Change in study personnel
1.1, Synopsis (Statistical Methods) 9.2, Sample Size Determination	Added provision to extend enrollment to maintain the planned statistical power in the event of higher than expected early terminations due to COVID-19 or other reasons	Unknown effect of COVID-19 pandemic on trial enrollment
1.3, Schedule of Assessments	Added a footnote to the Weeks 2, 5, 8, 11, 14, 18, and 22 visits in Table 2 to allow the visit to be completed remotely if the subject cannot attend the clinic visit in person due to restrictions related to COVID-19	Unknown effect of COVID-19 pandemic on trial conduct
	Added a footnote to the laboratory header in Table 2 to allow individual sites to conduct COVID-19 testing before randomization and after randomization at the discretion of the investigator	Provide flexibility for COVID-19 testing based on varying prevalence across regions
	Specified the urine pregnancy test as a urine dipstick test in Table 2	Clarify type of test
2.3, Benefit/Risk Assessment	Added a statement that, in response to the COVID-19 pandemic, Cerevel has performed a risk assessment of this trial and the investigator of each individual trial site and has implemented measures throughout the protocol, which prioritizes trial participant safety and data validity	Clarify that steps have been taken to mitigate potential effects of COVID-19 pandemic on subject safety and trial conduct

Section # and Name	Description of Change	Brief Rationale
5.1, Inclusion Criteria	Modified the wording related to use of contraceptives in inclusion criterion #2	Clarify contraceptive requirement
5.2, Exclusion Criteria	Modified the wording related to current and prior use of prohibited medications in exclusion criterion #19	Simplify language by referring to the tables that detail prohibited medications before (Table 6) and during (Table 7) the trial
	Modified the wording of exclusion criterion #21 to specify that the average of 2 supine blood pressure readings will be used to assess trial eligibility	Correct lack of clarity surrounding duplicate readings and the value that should be used to assess trial eligibility
	Expanded exclusion criteria related to prolonged QTcF interval in exclusion criterion #23	Align exclusion criterion with methods for obtaining ECGs in Section 8.3.6
	Clarified the process to be followed for subjects with medically significant or exclusionary abnormal ECG results in exclusion criterion #26	Align exclusion criterion with methods for obtaining ECGs in Section 8.3.6
6.5.3, Prohibited Medications Before the Trial	Added use of COMT inhibitors, MAO-B inhibitors, amantadine, or anticholinergic drugs <90 days before signing ICF and washout period to Table 6	Align information in table with inclusion criterion #10
6.5.4, Prohibited Medications During the Trial	Changed “stable for the duration of the trial” to “stable for the duration of the treatment phase” in entries 1, 2, 5, and 14 of Table 7	Clarify that subjects who do not proceed into the open-label extension trial may resume antiparkinsonian treatment during the Safety Follow-up Period
7.3, Individual Subject Discontinuation 8.4, Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest 10.1.3, Informed Consent Process	Added language to specify that individuals who are considered to be a “legal representative” for the subject will be defined per local regulations	Clarify term, which may differ among regions in which the trial is conducted
8.3.5, Vital Signs	Modified the section to specify that individual values from duplicate blood pressure and heart rate readings will be averaged by the sponsor	Clarify process for data collection

Section # and Name	Description of Change	Brief Rationale
8.3.6, Electrocardiograms	Modified the section to provide additional information related to ECG collection	Clarify the processes for acquiring ECGs at the Screening and Baseline Visits
10.2, Appendix 2: Clinical Laboratory Tests	Specified the urine pregnancy test as a urine dipstick test in Table 11	Clarify type of test
10.3, Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Revised section to remove redundant language and to clarify AE/SAE/AESI reporting procedures	Align wording with actual processes that will be followed in trial and for consistency across Cerevel clinical development programs
10.4, Contraceptive Guidance and Collection of Pregnancy Information	Revised title of Section 10.4.1.1	Consistency across Cerevel clinical development programs
10.8, Appendix 8: Protocol Amendment History	Added section	Consistency with corporate template
Overall	Minor grammatical corrections	Correct minor errors in the previous version of the protocol

Abbreviations: AE = adverse event, AESI = adverse event of special interest, COMT = catechol-O-methyl transferase, ICF = informed consent form, MAO-B = monoamine oxidase inhibitor B, SAE = serious adverse event.

11 REFERENCES

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.

Binde CD, Tvete IF, Gåsemyr J, Natvig B, Klemp M. A multiple treatment comparison meta-analysis of monoamine oxidase type B inhibitors for Parkinson's disease. Br J Clin Pharmacol. 2018;84(9):1917-27.

Connolly BS, Lang AE. Pharmacologic treatment of Parkinson's disease: a review. JAMA. 2014;11(16):1670-83.

de Rijk MC, Breteler MM, Graveland GA, et al. Prevalence of Parkinson's disease in the elderly: the Rotterdam Study. Neurology. 1995;45(12):2143-6.

Dietrichs E, Odin P. Algorithms for the treatment of motor problems in Parkinson's disease. Acta Neurol Scand. 2017;136(5):378-85.

Dorsey ER, Constantinescu R, Thompson JP, et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. Neurology. 2007;68(5):384-6.

Drutyte G, Forjaz MJ, Rodriguez-Blazquez C, Martinez-Martin P, Breen KC. What impacts on the stress symptoms of Parkinson's carers? Results from the Parkinson's UK Members' Survey. Disabil Rehabil. 2014;36(3):199-204.

Goetz CG, Poewe W, Rascol O, Sampaio C, Stebbins GT, Counsell C, et al. Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations. Mov Disord. 2004;19(9):1020-8.

Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord. 2008;15;23(15):2129-70.

Hauser RA, Auinger P; Parkinson Study Group. Determination of minimal clinically important change in early and advanced Parkinson's disease. Mov Disord. 2011;26(5):813-8.

Hauser RA, Friedlander J, Zesiewicz TA, Adler CH, Seeberger LC, O'Brien CF, et al. A home diary to assess functional status in patients with Parkinson's disease with motor fluctuations and dyskinesia. Clin Neuropharmacol. 2000;23(2):75-81.

Hauser RA, Gordon MF, Mizuno Y, Poewe W, Barone P, Schapira AH, et al. Minimal clinically important difference in Parkinson's disease as assessed in pivotal trials of pramipexole extended release. Parkinsons Dis. 2014;2014:467131.

Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011; 20(10):1727–36.

Hoehn M, Yahr M. Parkinsonism onset, progression and mortality. Neurology. 1967;17(5):427-42.

Horváth K, Aschermann Z, Ács P, Deli G, Janszky J, Komoly S, et al. Minimal clinically important difference on the Motor Examination part of MDS-UPDRS. Parkinsonism Relat Disord. 2015;21(12):1421-6.

Jasinska-Myga B, Heckman MG, Wider C, Putzke JD, Wszolek ZK, Uitti RJ. Loss of ability to work and ability to live independently in Parkinson's disease. Parkinsonism Relat Disord. 2012;18(2):130-5.

Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14(6):540-5.

Litvan I, Bhatia KP, Burn DJ, et al. Movement Disorders Society Scientific Issues Committee report: SIC Task Force appraisal of clinical diagnostic criteria for Parkinsonian disorders. Mov Disord. 2003;18(5):467-86.

Makkos A, Kovács M, Aschermann Z, Harmat M, Janszky J, Karádi K, et al. Are the MDS-UPDRS-Based Composite Scores Clinically Applicable? Mov Disord. 2018;33(5):835-9.

Marconi R, Lefebvre-Caparros D, Bonnet AM, Vidailhet M, Dubois B, Agid Y. Levodopa-induced dyskinesias in Parkinson's disease phenomenology and pathophysiology. Mov Disord. 1994;9(1):2-12.

Massano J, Bhatia KP. Clinical approach to Parkinson's disease: features, diagnosis, and principles of management. Cold Spring Harb Perspect Med. 2012;2(6):a008870.

Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53(4):695-9.

Peto V, Jenkinson C, Fitzpatrick R. PDQ-39: a review of the development, validation and application of a Parkinson's disease quality of life questionnaire and its associated measures. J Neurol. 1998;245(Suppl 1):S10-4.

Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia–Suicide Severity Rating Scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psych. 2011;168(12):1266-1277.

Rizek P, Kumar N, Jog MS. An update on the diagnosis and treatment of Parkinson disease. CMAJ. 2016;188(16):1157-65.

Stocchi F, Torti M, Fossati C. Advances in dopamine receptor agonists for the treatment of Parkinson's disease. Expert Opin Pharmacother. 2016;17(14):1889-902.

Stowe R, Ives N, Clarke CE, et al. Dopamine agonist therapy in early Parkinson's disease. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD006564.

Twelves D, Perkins KS, Counsell C. Systematic review of incidence studies of Parkinson's disease. Mov Disord. 2003;18(1):19-31.

US Food and Drug Administration (FDA). Guidance for Industry: E10 choice of control group and related issues in clinical trials; May 2001.

Vijayakumar D, Jankovic J. Drug-induced dyskinesia, part 1: treatment of levodopa-induced dyskinesia. Drugs. 2016;76(7):759-77.

Weintraub D, Mamikonyan E, Papay K, Shea JA, Xie SX, Siderowf A. Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale. MovDisord. 2012;27(2):242-7.

Zhuo C, Zhu X, Jiang R, et al. Comparison for efficacy and tolerability among ten drugs for treatment of Parkinson's disease: A network meta-analysis. Sci Rep. 2017;8:45865.

CLINICAL PROTOCOL PRINCIPAL INVESTIGATOR SIGNATURE PAGE

A PHASE 3, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL-GROUP, FLEXIBLE-DOSE, 27-WEEK TRIAL TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF TAVAPADON AS ADJUNCTIVE THERAPY FOR PARKINSON'S DISEASE IN LEVODOPA-TREATED ADULTS WITH MOTOR FLUCTUATIONS (TEMPO-3 TRIAL)

Protocol Number: CVL-751-PD-003

Compound: Tavapadon (CVL-751)

Trial Phase: 3

Sponsor Name: Cerevel Therapeutics, LLC

Legal Registered Address: 222 Jacobs Street, Suite 200, Cambridge, MA 02141 USA

Version 4.0: 06 Jul 2023

I, the undersigned principal investigator, have read and understand the protocol and agree that it contains the ethical, legal, and scientific information necessary to conduct this trial in accordance with the principles of Good Clinical Practices and as described herein and in the sponsor's (or designee's) Clinical Research Agreement.

Principal Investigator Printed Name

Principal Investigator Signature

Date (DD MMM YYYY)