STATISTICAL ANALYSIS PLAN

A PHASE 3, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL-GROUP, 27-WEEK TRIAL TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF TWO FIXED DOSES OF TAVAPADON IN EARLY PARKINSON'S DISEASE (TEMPO-1 TRIAL)

Protocol Number: CVL-751-PD-001

Compound: Tavapadon (CVL-751)

Trial Phase: 3

Short Title: Fixed-Dose Trial in Early Parkinson's Disease

Sponsor Name: Cerevel Therapeutics, LLC

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STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

This Statistical Analysis Plan has been prepared in accordance with team reviewers' specifications.

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1. INTRODUCTION

This document describes the statistical methods and data presentations planned for the analysis of the efficacy and safety data from Protocol CVL-751-PD-001. Background information is provided for the study designs and objectives. Further details of study conduct, and data collection are provided in the study protocol and electronic case report forms (eCRFs).

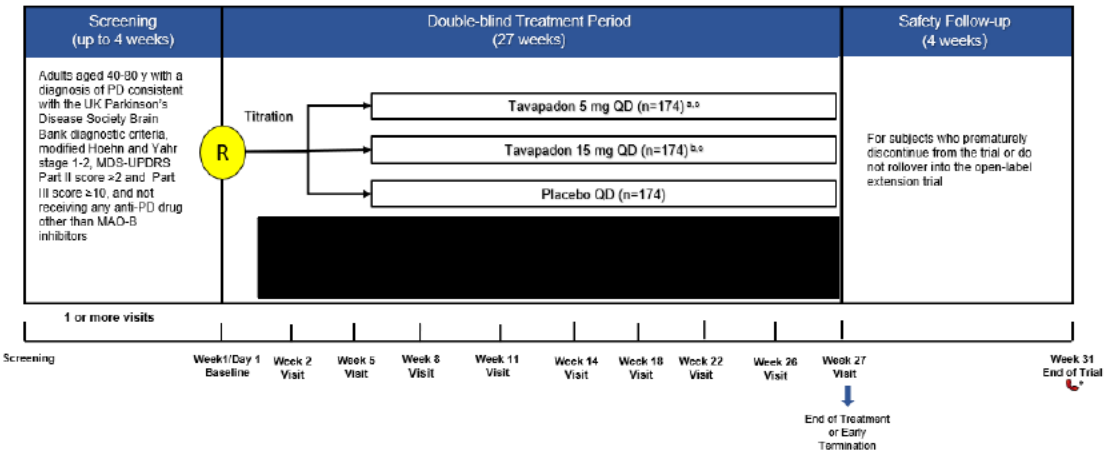
1.1. Study Overview

This is a prospective, Phase 3, multicenter, multinational, randomized, double blind, placebo controlled, parallel group, 27 week trial of the efficacy, safety, tolerability, and pharmacokinetics (PK) of 2 fixed doses of tavapadon (5 mg QD and 15 mg QD) in male and female subjects aged 40 to 80 years who have a diagnosis of Parkinson's disease (PD), consistent with the UK Parkinson's Disease Society Brain Bank diagnostic criteria; a modified Hoehn and Yahr stage of 1, 1.5, or 2; a Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS UPDRS) Part II score ≥2 and Part III score ≥10; and are not receiving antiparkinsonian medication other than monoamine oxidase B (MAO B) inhibitors.

A total of 522 subjects are planned to be randomized in a 1:1:1 ratio to receive tavapadon 5 mg QD, tavapadon 15 mg QD, or placebo QD. The dose of tavapadon will be titrated to a target dose using a fixed titration scheme. Randomization will be stratified by concurrent use of allowed Parkinson's disease (PD) medications (MAO-B inhibitors) during the Treatment Period. The planned duration of treatment is 27 weeks, including the Titration and Maintenance Phases. The trial will include a Screening Period (maximum of 4 weeks), a 27 week Treatment Period, and a 4 week Safety Follow-up Period. Details of schedule of assessments are provided in Section 9.1.

The trial design is depicted in Figure 1.

Figure 1: Trial Design Schematic



MAO-B = monoamine oxidase B, PD = Parkinson's disease, MDS-UPDRS = Movement Disorder Society – Unified Parkinson's Disease Rating Scale, QD = once daily, R = randomize.
Note: The change from baseline to endpoint in the MDS-UPDRS Parts II and III combined score is the primary endpoint.
[a]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.

1.2. Sample Size Considerations

A sample size of 174 subjects per group will provide 90% power to detect a change in the primary outcome measure (change from baseline to endpoint in the MDS-UPDRS Parts II and III combined score) of 4 points, with a standard deviation of 9, 2-sided alpha level = 0.025, 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.

1.3. Measures to Minimize Bias: Randomization and Blinding

1.3.1. Subject Assignment to Treatment

All subjects will be centrally randomized in a 1:1:1 ratio to 1 of 3 treatment arms (tavapadon 5 mg QD, tavapadon 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. Randomization will be stratified by concurrent use of allowed antiparkinsonian medication (MAO-B inhibitor).

1.3.2. 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 throughout 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 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.

Documentation of breaking the blind should be recorded in the subject's medical record and 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.

1.4. Treatment Period

The dose of tavapadon will be titrated to either 5 mg QD or 15 mg QD and then maintained for the duration of the 27-week Treatment Period. The titration schedule, as shown in Table 1, will be used for all subjects who are randomized to receive tavapadon. Subjects will take 3 tablets of investigational medicinal product (IMP), either all tavapadon tablets, all placebo tablets, or a combination of tavapadon and placebo tablets, throughout the trial to maintain the trial blind.

No deviations in the titration schedule up through [redacted] 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. Subjects who cannot achieve or tolerate the dose at [redacted] (5 mg QD) or [redacted] (10 mg QD) must be discontinued from the trial.

Starting on Day 74, subjects who achieve but do not tolerate the dose at [redacted] may go back to the dose at [redacted] Subjects may remain at the [redacted] dose or will be permitted a one-time rechallenge back to the [redacted] dose if needed for symptomatic control. Subjects must receive the [redacted] dose for at least 7 days before a rechallenge to the [redacted] dose is attempted. Subjects who are unable to tolerate the [redacted] dose upon rechallenge will be discontinued from the trial.

Table 1: Tavapadon and Placebo Dosing Schedule

2. OBJECTIVES AND ENDPOINTS

Table 2: Trial Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the efficacy of 2 fixed doses of tavapadon in subjects with early PD	Primary Efficacy Endpoint • Change from baseline to endpoint in the MDS-UPDRS Parts II and III combined score Key Secondary Efficacy Endpoints • Change from baseline to endpoint in the MDS-UPDRS Part II score • Percentage of responders at endpoint, defined as a score of "much improved" or "very much improved" on the PGIC Secondary Efficacy Endpoints (All Time Points) • Change from baseline in the MDS-UPDRS Parts II and III combined score • Change from baseline in the MDS-UPDRS Parts I, II, and III combined score • Change from baseline in the MDS-UPDRS Part I, Part II, and Part III individual scores • Change from baseline in the CGI-S score • CGI-I score • PGIC score Other Endpoints • Change from baseline in PDQ-39 score • Change from baseline in Schwab and England ADL score • Change from baseline in the EQ-5D-5L index and VAS scores
Secondary	
• To assess the safety and tolerability of 2 fixed doses of tavapadon in subjects with early PD	• ESS • QUIP-RS • C-SSRS • Nature, frequency, and temporality of TEAEs, including abuse-related AEs and AEs related to MHIs • Clinical laboratory evaluations • Vital signs • Physical and neurological examinations • ECGs
Pharmacokinetic	
• To evaluate the PK of tavapadon in this population	• Plasma concentrations of tavapadon and its major metabolite (if required) at baseline (Day 1) and Weeks 5, 11, 14, 22, and 27

Abbreviations: ADL = activities of daily living, AE = adverse event, CGI-I = Clinical Global Impression – Improvement, CGI-S = Clinical Global Impression – Severity of Illness, C-SSRS = Columbia-Suicide Severity Rating Scale, ECG = electrocardiogram, EQ-5D-5L = EuroQol 5 Dimension 5 Level, ESS = Epworth Sleepiness Scale, 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, PGIC = Patient Global Impression of Change, PK = pharmacokinetic, QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale, TEAE = treatment-emergent adverse event, VAS = visual analog scale.

3. KEY ASSESSMENTS AND DERIVATIONS

3.1. Efficacy Assessments

3.1.1. Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS)

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. Each evaluation item is rated on a scale from 0 to 4 on which 0 = normal, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe. This trial incorporates Part I, II, and III assessments for the specific trial population.

3.1.1.1. Part I Score

Part I of the MDS-UPDRS focuses on the non-motor aspects of experiences of daily living. The MDS-UPDRS Part I score value for a given visit is obtained as the sum of all 13 evaluation items in the MDS-UPDRS Part I subscale, including the 6 items which are rated by the Physician. Valid values for the sum are integers from 0-52, with 0 being the least severe and 52 being the most severe.

3.1.1.2. Part II Score

Part II of the MDS-UPDRS focuses on the motor aspects of experiences of daily living. The MDS-UPDRS Part II score value for a given visit is obtained as the sum of all 13 evaluation items in the MDS-UPDRS Part II subscale. Valid values for the sum are integers from 0-52, with 0 being the least severe and 52 being the most severe.

3.1.1.3. Part III Score

Part III of the MDS-UPDRS is the motor evaluation comprises 18 items that are assessed by the investigator (resulting in 33 scores by location and lateralization). Valid values for the sum are integers from 0-132, with 0 being the least severe and 132 being the most severe.

3.1.1.4. Handling of Missing Items from MDS-UPDRS

If individual items are missing from a given part of the MDS-UPDRS, the corresponding total score may be generated by prorating the response if the number of missing items is not excessive. For Part I and Part II assessments, only a single missing item score is allowable. For Part III, up to 7 missing item scores are allowable. To prorate the value, the following formula is utilized

$$P = \left(\frac{\sum_{i=1}^{n} j_i}{n} \right) U$$

Where n is the number of non-missing items, j_1-j_n represents the n non-missing values reported by the subject for the given subscale, and U is the number of total items in the subscale. If more than the allowable items are missing, the total score will be treated as missing.

3.1.1.5. Part II + III Combined Score

The MDS-UPDRS Part II + III Combined Score is defined as the sum of the total scores for Part II and Part III within a given assessment (i.e., to have a Part II + III Total score, the subject must have a non-missing Part II total score and a non-missing Part III total score on the same date). The Part II + III Combined Score will be derived after any imputation of missing values within each individual total score.

3.1.1.6. Part I, Part II, and Part III Combined Score

The MDS-UPDRS Part I, Part II, and Part III Combined Score is defined as the sum of the total scores for Parts I, II, and III within a given assessment (i.e., to have a Part I, Part II, and Part III Combined score, the subject must have a non-missing Part I total score, a non-missing Part II total score, and a non-missing Part III total score on the same date). The Part I, Part II, and Part III Combined Score will be derived after any imputation of missing values within each individual total score.

3.1.2. Patient Global Impression of Change (PGIC)

The PGIC is the patient-reported outcome in a 7 point scale to rate how much the patient's illness has improved or worsened relative to the baseline state at the beginning of the intervention. The qualitative assessment of meaningful change is determined by the patient in response to the question, “Compared to your condition at the beginning of treatment, how much has your condition changed?” Scores are: 1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; and 7=very much worse.

3.1.3. Clinical Global Impression – Severity of Illness (CGI-S)

The CGI-S scale is a 7 point scale that requires the clinician to rate the severity of the patient’s illness at the time of the assessment relative to the clinician’s experience with patients who have the same diagnosis. Raters select one response based on the following question: “Considering your total clinical experience with this particular population, how ill is the patient at this time?” Scores are: 1=normal, not at all ill; 2=borderline ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; and 7=among the most extremely ill patients.

3.1.4. Clinical Global Impression – Improvement (CGI-I)

The CGI-I is a 7 point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to the baseline state at the beginning of the intervention. Raters select one response based on the following question, “Compared to your patient’s condition at the beginning of treatment, how much has your patient changed?” Scores are: 1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; and 7=very much worse.

3.1.5. 39-Item Parkinson's Disease Questionnaire (PDQ-39) Score

The 39-item Parkinson's Disease Questionnaire (PDQ-39) 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).

A dimension score is calculated using the following formula:

$$d = \frac{1}{n * 4} \sum_{j=1}^{n} t_j * 100$$

where n is the number of items in the dimension, and t_j is the j^{th} item in the dimension. This transforms the scale linearly from 0 (perfect health as assessed by the measure) to 100 (worst health as assessed by the measure). If items are missing within a domain, the n in the above formula will be changed to the number of items in the dimension that the subject answered if at least half of the questions in the domain were answered. Otherwise, a domain and summary index will not be calculated.

A summary index called PDQ-39 SI, is calculated as the average of the 8-dimension scores.

3.1.6. 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 (Section 9.2). 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. For example, 11122 would represent the health state for someone who has no problems with mobility, self-care, or usual activities, but who has slight pain or discomfort and slight anxiety or depression. For each subject and visit, the 5-digit health state will be converted into a single summary index, the EQ-5D Index, using the EQ-5D-5L Index calculator with US value set (van Hout, Janssen et al. 2012; Section 9.9).

The EQ VAS records the patient's self-rated health on a 20-cm vertical visual analogue scale (VAS). The VAS is numbered from 0 to 100 with 0 meaning 'the worst health you can imagine' and 100 meaning 'the best health you can imagine'. This information can be used as a quantitative measure of health outcome that reflects the patient's own judgement.
The EQ-5D-5L asks respondents to simply 'mark an X on the scale to indicate how your health is TODAY' and then to 'write the number you marked on the scale in the box below'.

3.1.7. Schwab and England Activities of Daily Living (ADL) Scale

The Schwab and England ADL scale is a method of assessing a person's ability to perform daily activities in terms of speed and independence through a percentage figure. The clinician determines the rating according to the following criteria, with 100% indicating total independence and 0% indicating a state of complete dependence:

100%	Completely independent. Able to do all chores without slowness, difficulty, or impairment. Essentially normal. Unaware of any difficulty.
90%	Completely independent. Able to do all chores with some degree of slowness, difficulty, and impairment. May take twice as long. Beginning to be aware of difficulty
80%	Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.
70%	Not completely independent. More difficulty with some chores. Three to four times as long in some. May spend a large part of the day with chores.
60%	Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors; some impossible.
50%	More dependent. Help with half, slower, etc. Difficulty with everything.
40%	Very dependent. Can assist with all chores, but few alone
30%	With effort, now and then does a few chores alone or begins alone. Much help needed
20%	Nothing alone. Can be a slight help with some chores. Severe invalid
10%	Totally dependent, helpless. Complete invalid.
0%	Vegetative functions such as swallowing, bladder and bowel functions are not functioning. Bedridden.

3.2. Safety Assessments

3.2.1. Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale (QUIP-RS) Scores

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

Each question is scored using a 5 point Likert scale (score, 0=never [not at all], 1=rarely [infrequently or 1 day/week], 2=sometimes, 3=often, 4=very often). 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. In case of missing item scores, the missing value will be replaced by the average of non-missing scores at the same visit from the same subject. In case all item scores in any subcategory are missing, the total score will be set as missing.

3.2.2. Epworth Sleepiness Scale (ESS) Total Score

The ESS scale is used to determine the level of daytime sleepiness. There are 8 situations listed for which patients rate their likelihood of dozing or sleeping (0=no chance of dozing, 1=slight chance of dosing, 2=moderate chance of dosing, or 3=high chance of dozing). The total score is the sum of 8 item scores and can range between 0 and 24. The higher total score indicates the higher level of daytime sleepiness. A score of 10 or more is considered sleepy, and a score of 18 or more is very sleepy.

In case of missing item scores from the ESS, the missing value will be replaced by the average of non-missing scores at the same visit from the same subject. In case all item scores are missing, the total score will be set as missing.

3.2.3. Adverse Event (AE)

An AE is defined as any untoward medical occurrence in a patient or clinical trial subject, temporally associated with the use of trial intervention, whether 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.

All adverse events will be recorded on the ADVERSE EVENTS eCRF. Adverse events with missing severity will have the severity imputed as ‘Severe’ for the AE tabulations. Adverse events with missing relationship to IMP will have the relationship imputed as ‘Related’ for the AE tabulations if the AE started on or after the first dose of IMP. However, in the data listings these missing severity and/or relationship will be presented as missing.

3.2.3.1. Adverse Event of Special Interest (AESI)

For this study, any AEs related to abuse potential, AEs involving MHIs, abnormal liver function tests with a value >3 × ULN for ALT or AST and >2 × ULN for total bilirubin within the same visit, a value of >3 × ULN for ALT or AST and clinical jaundice, an AE leading to the discontinuation of IMP or from the study will be considered AESIs. These events will be noted by the investigator in the ADVERSE EVENTS eCRF.

3.2.3.2. Treatment-emergent Adverse Event (TEAE)

Any event reported on the eCRF that occurs on or after the initiation of IMP until the end of AE reporting period per protocol is considered treatment emergent.

Additionally, it is assumed that an Adverse Event which was reported to have started on Day 1 without an associated onset time is assumed to be treatment emergent.

3.2.4. Clinical Safety Laboratory Assessments

The clinical laboratory tests as listed in the protocol will be performed in accordance with the laboratory manual and the Schedule of Assessments. All results, including repeats, will be included in the laboratory reports. 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.

3.2.4.1. Treatment-emergent Laboratory Abnormality and Toxicity

A treatment-emergent laboratory abnormality is defined as value outside the normal range which occurs on or after the start of IMP and up to the last contact following discontinuation of IMP.

A treatment-emergent laboratory toxicity is defined as an increase of at least one abnormality severity grade (specifications in Section 9.8) from the baseline assessment at any post baseline visit which occurs after the first administration of IMP and through last test results of the study. If a laboratory assessment obtained on Day 1 with unknown collection times will be assumed to be an assessment prior to the initiation of IMP. If the relevant baseline assessments are missing for a given subject, any post-baseline severity grade at 1 or more is considered a treatment-emergent laboratory toxicity.

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

Suicidality will be monitored during the trial using the C-SSRS. It was designed to quantify the severity of suicidal ideation and behavior.

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.

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.

Details of C-SSR categories as well as definition of treatment emerging events are provided in Section 9.3.

3.2.6. Vital Signs

Vital signs include systolic and diastolic blood pressures, heart rate, and body temperature. 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). 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.

3.2.7. 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. For US sites, three sets of triplicate ECGs will be obtained during the 45 minutes before administration of the first dose of IMP on Day 1 (at -45, -30, and -15 minutes), and a single set of triplicate ECGs will be obtained ~1 hour after administration of the first dose of IMP on Day 1, just prior to the time of collection of the PK blood sample. One set of triplicate 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. The triplicate ECG information from US sites will be used in a C-QT analysis with results reported separately. For non-US sites, 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 on Day 1, just prior to the time of collection of the PK blood sample. 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. A central ECG service will be used for reading all ECGs to standardize interpretations for the safety analysis.

3.2.8. Prior Medications, Concomitant Medications and Medications Taken Post Last Dose of IMP

Prior medications are those medications taken prior and ended prior to the initiation of IMP. These medications will be captured in the CONCOMITANT MEDICATIONS eCRF.

Concomitant medications are those medications taken on or after the initiation of IMP. These medications include those medications started before the initiation of IMP and continuing post Day 1. Medications that start after the last dose of IMP until the end of protocol-specified reporting period will be classified as taken post last dose and will not be considered concomitant. These medications will be recorded in the eCRF. 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 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.

3.2.9. Physical and Neurological Examinations

A complete physical and neurological examinations will be conducted at screening and at the end of treatment visit (Visit 11 or early termination visit). Any condition present post-baseline physical or neurological examination that was not present at the baseline examination should be documented as an AE and followed to a satisfactory conclusion.

[redacted]

3.3. Pharmacokinetics

Blood samples for measurement of plasma concentrations of tavapadon and CVL-0000053, its major metabolite, 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.

Drug concentration information will not be reported to investigative sites, clinical database or any blinded study personnel until the trial has been completed and unblinded.

4. DATA CONVENTIONS AND VISIT WINDOWS

4.1. Data Conventions

4.1.1. Age

Age is the age at the time of informed consent and is as captured on the eCRF (note: date of birth is not captured on the eCRF).

4.1.2. Day 1

Day 1 is the day IMP is first initiated.

4.1.3. Endpoint

Endpoint as defined as the primary time point for the efficacy assessments is Week 26.

4.1.4. Study Day of an Event

Study day of an event is defined relative to Day 1 as:

Study Day = event date – date of Day 1 (+ 1, if event date ≥ date of Day 1).

This calculation will result in negative study days for an event occurring prior to the start of IMP and positive study days for an event on or after the start of IMP. There will be no Day 0 value to match the schedule of events.

4.1.5. Days on Study

Days on Study is the number of days from Day 1 to the date of study completion or early termination as recorded on the END OF STUDY eCRF.

4.1.6. Days on IMP

Days on IMP is the number of days from Day 1 to the date of last dose of IMP as recorded on the EXPOSURE eCRF.

4.1.7. Baseline Value

For purposes of analysis, the baseline value of a given assessment is defined as the last value obtained prior to initiation of IMP. Should the Day 1 visit value be obtained after the first dose of IMP or if this value is not available at Day 1, the most recent value obtained prior to the first dose of IMP will be used for the baseline value.

For US subjects with triplicate ECGs taken at 3 pre-dose timepoints, the baseline value will be defined as the average of the available pre-dose ECG values (i.e. triplicate ECGs at -45 minutes pre-dose, -30 minutes pre-dose, and -15 minutes pre-dose). For non-US subjects, the baseline value will be defined as the average of the available pre-dose ECG values. Scheduled records will be selected over unscheduled records if a tie breaker is needed.

For blood pressure and heart rate measurements, baseline is defined as the average of the duplicates at the last visit prior to the IMP administration. If no duplicate is available, the last non-missing value prior to the initiation of IMP will be used.

4.1.8. Change from Baseline

Change from baseline for a given variable is defined as the value on a given Study Day (Time Point) minus the Baseline Value.

4.1.9. Orthostatic Change

Orthostatic change is calculated as the difference in the standing value from the supine value (i.e., supine value – standing value). If an average value is available at a given visit and date, it will be used for the calculation of orthostatic change. If an average value is not available, the individual record obtained on a given visit and date will be used.

4.1.10. Duration of Titration Phase

The duration of the titration phase will be calculated as the days in [redacted] of the dosing schedule.

4.1.11. Duration of Maintenance Phase

The duration of the maintenance phase will be calculated as the days in [redacted] of the dosing schedule.

4.1.12. Average Dose of Titration Phase

The average dose of the titration phase will be calculated as the sum of the milligrams of study drug taken in [redacted] of the dosing schedule divided by the duration of days in the titration phase.

4.1.13. Average Dose of Maintenance Phase

The average dose of the maintenance phase will be calculated as the sum of the milligrams of study drug taken in [redacted] of the dosing schedule divided by the duration of days in the maintenance phase.

4.1.14. Compliance with Study Drug

Accountability and compliance will be assessed through self-reporting by the subject and by tablet count at each clinic visit. For analysis purposes, evaluation of compliance will be based on the site assessment of compliance as recorded on the DRUG ACCOUNTABILITY eCRF. Compliance will be calculated as a percentage based on the total number of tablets taken relative to the total expected number of tablets based on days on study. If a kit was lost and return information was available, the return information will be used for the compliance calculation. If a kit was lost and no return information was available, it is assumed that the tablets were not taken for the compliance calculation. If return information is not available and the kit was not lost, it is assumed that the tablets were taken for the compliance calculation.

If a kit was redispensed and the number of tablets redispensed is not available, it is assumed that the number of tablets that were partially returned were redispensed for the compliance calculation.

4.1.15. Handling of Incomplete or Missing Dates Associated with an Event

An incomplete date occurs when the exact date an event (e.g. an adverse event) occurred or ended cannot be obtained from a subject. The database contains data fields for month, day, and year. A date is incomplete if at least one of these three fields is not known.

For many of the planned analyses, a complete date is necessary to determine if the event should be included in the analysis (e.g. if the event is treatment-emergent) or to establish the duration of an event. In such cases, incomplete dates will be imputed as described below.

For the purposes of handling partially reported start and stop dates for an event the following algorithm will be applied:

- Missing start day, but month and year present:

  If the event occurs same month and year as the occurrence of IMP, then the start day of the event will be assigned to the day of first dose of IMP (i.e., Day 1).

  Otherwise the start day will be set to the first day of the month.
- Missing start day and month, but year present:

  If event occurs in the same year as IMP, then the start date of the event will be assigned to Day 1.

  Otherwise the start day and month will be set to 01 January.
- In the unlikely event of a completely missing start date (year not present), the start date will be imputed as Day 1.
- Missing end day, but month and year present:

  The day will be set to the last day of the month.
- Missing end day and month, but year present:

  The end day and month will be set to the date of study completion. However, if study completion year is greater than the year of the event, then the day and month will be set to 31 December.
- Missing all components of an end date and the event is not marked as ongoing:

  The event will be considered as ‘ongoing’ and will be considered treatment-emergent if the start date is on or after Day 1.

If any imputed start date causes the start date to occur after the end date, the end date will be used for the imputation of the start date. If any imputed end date causes the end date to occur prior to the start date of the event, the start date of the event will be used for the imputation of the end date. If the imputed date is later than the date of study withdrawal, then the date of study withdrawal will be used to impute the date in question. In subject data listings, start and stop date of events will be displayed as reported on the eCRF without imputed dates.

For the purposes of handling partially reported diagnosis date of Parkinson's disease, the following algorithm will be applied to randomized subjects:

- Missing day, but month and year present:

  If the diagnosis date occurs same month and year as the occurrence of the subject's screening date, then the day of the diagnosis date will be assigned to the day of the subject's screening date.

  Otherwise the diagnosis day will be set to the first day of the month.

- Missing day and month, but year present:

  If the diagnosis date occurs in the same year as the occurrence of the subject's screening date, then the diagnosis date will be assigned to the subject's screening date.

  Otherwise the diagnosis day and month will be set to 01 January.

- In the event of missing year or a completely missing diagnosis date, the diagnosis date will be assigned to the subject's screening date.

In subject data listings, diagnosis dates will be displayed as reported on the eCRF without imputed dates. For screen failures, no imputation will be made to the date of diagnosis of Parkinson's disease.

4.1.16. Handling of Alphanumeric Data

Should there be instances where a clinical laboratory parameter is reported with imbedded non-numeric characters, as for example, "<0.1" or ">10", the data will be imputed as described below for quantitative summaries. The actual alphanumeric values as reported in the database will be presented in data listings.

- The values < LLN will be replaced with ½ the value of the lower limit. For example, "< 0.1" will be replaced with 0.05 if the LLN is 0.1.
- The values > ULN will be replaced by values of increased precision by one level. For example, ">0.1" will be imputed to "0.11" if the ULN is 0.1, and ">10" will be imputed to "10.1" if the ULN is 10.

Additionally, in the event of the upper limit of normal (ULN)/lower limit of normal (LLN) reported as alphanumeric (e.g., '<5', '≤5', '>5', '≥5'), the determination of the laboratory abnormality severity grade will be based on the convention on the ULN and LLN below:

- If the ULN is in the form of ≤5, only the numeric part will be used for determining the abnormality severity grade of the test results (i.e., the ULN is set to 5). If the ULN is in the form of <5, the numeric value of the ULN will be decreased by two levels of precision in the direction of the symbol (i.e., the ULN is set to 4.99).

- If the LLN is in the form of ≥5, only the numeric part will be used for determining the abnormality severity grade of the test results (i.e., the LLN is set to 5). If the LLN is in the form of >5, the numeric value of LLN will be increased by two levels of precision in the direction of the symbol (i.e., the LLN is set to 5.01).

4.2. Visit Windows

Data collected longitudinally across visits will be summarized and analyzed by visit.

Laboratory data will be presented according to the nominal visit as collected from the eCRF or laboratory data unless the visit is an early termination or unscheduled visit. Early termination and unscheduled visits will be assigned visit windows based on the study day completed according to Table 3. Baseline will be determined per the baseline definition in Section 4.1.7. Other assessment data, including efficacy assessments data, will be mapped to the appropriate time point based on the window as defined in Table 3 from Baseline to Week 22 to appropriately captured time of assessment in cases of visit schedule variations. Due to the short interval between Visit 10 (Week 26) and Visit 11 (Week 27), data obtained at the nominal visit at this two time points will be used with the exception of early termination/unscheduled visits.

Table 3: Visit Windows

Analysis Visit	Analysis Visit Target Day	Analysis Visit Window
Baseline	1	≤ 1
Day 1*	1	1
Week 2	14	2 - 24
Week 5	35	25 - 45
Week 8	56	46 – 66
Week 11	77	67 – 86
Week 14	98	87 – 111
Week 18	126	112 – 140
Week 22	154	141 – 168
Week 26	182	169 – 185
Week 27	189	186 and higher

* Day 1 assessments are pre-IMP except ECG with a 60 minute post-dose assessment

If assessments are collected multiple times within a given visit window the result closest to the analysis visit target day will be used for summary presentations. If two measurements have the same distance to the target day, the later value will be used. If a subject has multiple non-missing values on the same date, the average record will be used (if applicable). If there are multiple average records on the same date, the average based on the scheduled measurements will be used. If no averages exist, the last record as determined by the time collected will be used.

5. STATISTICAL ANALYSIS METHODS

5.1. General Considerations

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), number of observations (n), arithmetic mean, median, standard deviation (SD), geometric mean and coefficient of variation (CV%) (for concentration data only), first quartile (Q1), third quartile (Q3), minimum, and maximum for continuous data, and frequencies and percentages for categorical data. Certain figure presentations will include the standard error of the mean (SE). The term "treatment group" refers to treatment assignment: placebo, tavapadon 5 mg, and tavapadon 15 mg. All data collected from subjects who sign the informed consent form, including screen failures, will be included in data listings. Unless otherwise noted, the data listings will be sorted first by treatment group and subject number and then by date within each subject number.

The number and proportion of missing visits and key assessments due to COVID-19 control measures and the frequency of remote assessments performed due to COVID-19 restrictions will be tabulated by treatment, visit, and assessment as well as the overall number and proportion of subjects with any such missing visits, assessments, or remote visits in each treatment group.

The statistical analyses will be conducted with the SAS® software package version 9.4 or higher.

5.2. Populations for Analyses

The analysis populations are defined Table 4.

Table 4: 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 a baseline and at least one postbaseline MDS-UPDRS assessment.	Primary analysis set for efficacy
Endpoint completers	All subjects in the mITT population who have an MDS-UPDRS assessment at baseline and endpoint	Sensitivity analysis set for efficacy
PK	All randomized subjects who receive at least 1 dose of tavapadon and have at least one measurable scheduled tavapadon (CVL751) concentration	PK analysis set

Abbreviations: FAS = full analysis set, IMP = investigational medicinal product, ITT = intent-to-treat, mITT = modified intent-to-treat, PK = pharmacokinetic, MDS-UPDRS = Movement Disorder Society – Unified Parkinson's Disease Rating Scale.

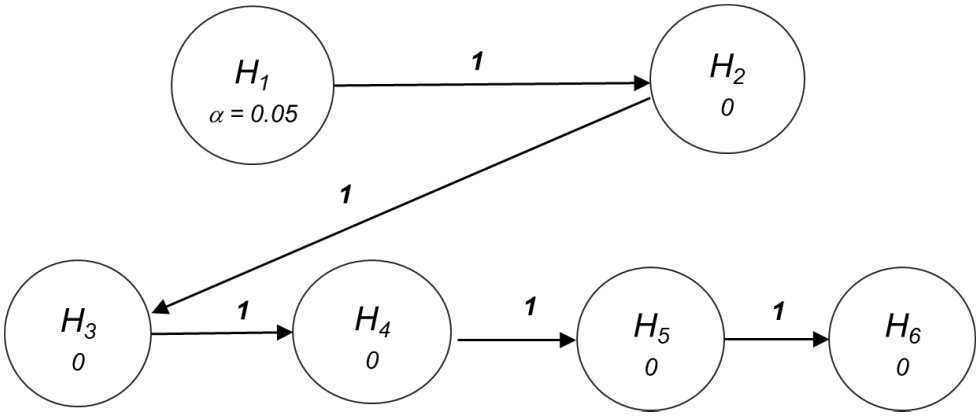
5.3. Statistical Hypotheses

The primary and key secondary hypotheses are summarized below. All will be tested based on 2-sided α.

Primary Endpoint	**Tavapadon 15 mg QD vs Placebo**	**Tavapadon 5 mg QD vs Placebo**
Change from baseline to endpoint in MDS-UPDRS Part II and III combined score	$H_1: \mu_{active} = \mu_{placebo}$ vs $\mu_{active} \neq \mu_{placebo}$	$H_2: \mu_{active} = \mu_{placebo}$ vs $\mu_{active} \neq \mu_{placebo}$
Key Secondary Endpoints		
Change from baseline to endpoint in the MDS-UPDRS Part II score	$H_3: \mu_{active} = \mu_{placebo}$ vs $\mu_{active} \neq \mu_{placebo}$	$H_5: \mu_{active} = \mu_{placebo}$ vs $\mu_{active} \neq \mu_{placebo}$
Proportion of responders on the PGIC at endpoint	$H_4: \pi_{active} = \pi_{placebo}$ vs $\pi_{active} \neq \pi_{placebo}$	$H_6: \pi_{active} = \pi_{placebo}$ vs $\pi_{active} \neq \pi_{placebo}$

5.4. Multiplicity Adjustment

A graphical approach depicted below is utilized to illustrate the hierarchal multiple testing strategy planned for the hypotheses described above to control the overall Type I error rate. The primary endpoint of the tavapadon 15 mg QD will be compared with that of placebo (H_1) with full α of 0.05 and, if successful, the available α will be passed along fully (r=1) to the comparison of the primary endpoint of tavapadon 5 mg QD with placebo (H_2). If H_2 is successful, the full α will be available to the secondary hypothesis H_3. The sequence will continue until H_6 or until the sequence breaks with no α remaining available.



5.5. Strata and Covariates

The randomization is stratified by concurrent use of MAO-B inhibitor. This factor is planned to be included as a covariate in the efficacy analyses. However, due to isolated administrative errors at a few sites during randomization through IRT system, 15 subjects were randomized to the incorrect strata (3 non-MAO-B inhibitor users were randomized to the MAO-B inhibitor use stratum and 12 MAO-B inhibitor users were randomized to the non-user stratum; details in Section 9.7). The actual MAO-B inhibitor use status, as recorded in eCRF, will be used as a covariate instead of the randomization strata in these cases.

The baseline value of each efficacy variable (if applicable) will also be included as a covariate in the efficacy analyses.

5.6. Subject Disposition, Demographic and Baseline Characteristics

Subject disposition will be based on the ITT population with tabulation of the number of subjects who complete the study and the number of discontinued and from the study and the reasons by treatment group. Additionally, the number of days on study will be summarized.

Tabulation of subject randomization by country and site will be presented for the ITT population and for completed subjects. A listing of randomization number, subject, treatment randomized, country, and site will be provided. Further tabulation by region (United States, Non-US) and country will also be presented. Subject disposition data will also be tabulated for all subjects screened to include the number of subjects screened, the number of screen failures, and the reason for screen failure.

Kaplan-Meier plots will be used to assess time to discontinuation of study treatment, time to discontinuation of treatment due to adverse events, and time to discontinuation of treatment due to subject withdrawal. The complete subjects or subjects discontinued treatment for reasons other than adverse events and withdrawal of consent will be censored at the time of end of treatment for the respective KM analyses. If a subject died without treatment discontinuation date information, date of death will be used as the time of discontinuation.

Number of subjects in each analysis population set will be summarized.

Demographic data and baseline characteristics including age, age categorical distribution, sex, childbearing potential, race, ethnicity, height at screening, weight at screening and at baseline, BMI at screening and at baseline, MAO-B inhibitor use at baseline, history of Parkinson's disease (including years from initial diagnosis), Montreal Cognitive Assessment (MoCA) total score, Modified Hoehn & Yahr assessment at screening, MDS-UPDRS (all parts, Part I + Part II + Part III combined, and Part II + III combined) score at baseline, and CGI-S at baseline will be summarized using descriptive statistics for the ITT population. Further tabulation by region and country will also be presented.

5.7. Medical and Psychiatric History

Medical and psychiatric history events will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) version 27.0 or higher preferred term and system organ class.

Medical and psychiatric history will be summarized by treatment group using preferred terms and system organ classes. All events will be listed.

5.8. Exposure to Treatment

The number of days on study drug, reasons for premature discontinuation of IMP, treatment compliance, days in each phase (Titration and Maintenance), and average dose in each phase, will be summarized by treatment group for the FAS Population. Exposure data, including dose level as received, will be listed.

5.9. Primary Efficacy Analysis

5.9.1. Primary Estimand

The key research question for the primary endpoint will be addressed with an estimand based on the following attributes:

1) Treatments: treatments as randomized regardless of the actual treatment received or the final dose level achieved following the titration steps.
2) Target study population of interest: subjects in the modified intent-to-treat (mITT) population regardless the completion status of dose titration steps.
3) Endpoint (variable) of interest: change from baseline to Week 26 in the MDS-UPDRS Part II + III Combined Score.
4) Population level summary of interest: estimated mean difference between each tavapadon dose group and placebo group in the endpoint of interest.
5) Strategy for Intercurrent events (ICEs): a hypothetical strategy will be used to address intercurrent events (ICEs) of potential death, treatment discontinuations, missed visits/assessments, and start of prohibited concomitant Parkinson's disease medications. The data after treatment discontinuations or after the start of prohibited Parkinson's disease concomitant medications will be censored under the hypothetical strategy. Prohibited Parkinson's disease concomitant medications are defined as medications in ATC classifications of ADAMANTANE DERIVATIVES, DOPAMINE AGONISTS, MONOAMINE OXIDASE B INHIBITORS, OTHER ANTIPARKINSON DRUGS, OTHER DOPAMINERGIC AGENTS, or DOPA AND DOPA DERIVATIVES that are started after the first dose of IMP and prior to the last dose of IMP with duration of use 7 days or more. The hypothetical strategy allows the study to assess the effect of tavapadon treatment without the confounding effect of prohibited concomitant Parkinson's disease treatments.

5.9.2. Main Analytical Approach

The change from baseline to each study visit in MDS-UPDRS Part II and III combined score will be summarized by visit and treatment group. A mixed model repeated measures (MMRM) analysis will be used to analyze the data from all post-randomization timepoints up to Week 27 with fixed effect of treatment group, visits, interaction between treatment group and visit, and baseline MAO-B inhibitor use. The baseline value of MDS-UPDRS Part II and III combined score will also be included as a covariate. Subject will be included as a random effect. An unstructured covariance structure will be used for the repeated measures. If the unstructured covariance matrix results in convergence issue, the heterogeneous Toeplitz covariance structure followed by the heterogeneous first-order autoregressive (AR(1)) structure will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The difference between each active dose and placebo at the endpoint visit (Week 26) will be estimated based on the Least Squares Mean (LSMean) difference derived from the MMRM with the associated 95% confidence intervals (CI) and P-values. A Cohen's D value will also be derived as the ratio of the estimated difference to the population standard deviation at each visit estimated from the model (the square root of the diagonal elements of the estimated covariance matrix). The missing values, including missing due to missed visits or early termination due to COVID-19 control measures, are assumed to be missing at random (MAR) in the main MMRM analysis. Sensitivity analyses will be performed to assess the impact of deviation from MAR assumptions on the analysis results. Time curve plots will be presented for both raw Mean (SEM) and LSMean (SE).

5.9.3. Sensitivity Analyses

5.9.3.1. Treatment Effect at Final Dose Levels

To assess the treatment effect at the final dose level, a sensitivity analysis will be conducted on the mITT set using the MMRM analysis method described in Section 5.9.2 with treatment defined as the actual final dose level achieved. The final dose level is defined as the dose received at the Week 26 timepoint or at the time of early termination if the subject achieved a minimum of 5 mg prior to discontinuation.

5.9.3.2. Treatment Effect based on Actual Treatment Received

Should a discrepancy between the study treatment received and the randomized treatment assignment occurred in 6 or more subjects, a sensitivity analysis may be conducted based on the study treatments that subjects actually received using the MMRM analysis method described in Section 5.9.2.

5.9.3.3. Remote Assessments Excluded (treated as missing)

In addition, a sensitivity analysis excluding the MDS-UPDRS Part II + Part III combined score obtained remotely may be performed if such remote assessments are conducted due to COVID-19 restrictions. It should be noted that the study only has provision of remote assessments for Parts I & II of the MDS-UPDRS assessments, as the clinician administered motor examination required for Part III cannot be reliably completed remotely.

5.9.3.4. Impact of Missing Values Handling

Whilst every effort will be made to prevent avoidable missing values during the study conduct (National Research Council, 2010), it is unrealistic to expect no missing values in clinical trials. The impact of missing values on the analysis results will be assessed by the sensitivity analyses described below.

Under Missing at Random (MAR) Assumption

Multiple imputation (MI) will be performed to replace each missing value with a set of plausible values that represent the uncertainty about the correct value to impute. The Markov chain (MCMC) method will be utilized for the mITT set. SAS PROC MI will be used to generate 27 possible imputed datasets: Each of these datasets will be analyzed using PROC MIXED in SAS using the MMRM model as described in Section 5.9.2. The results of the analyses of the datasets will be combined using PROC MIANALYZE to produce an inferential result.

Considerations of Data Potentially Missing Not at Random (MNAR)

A pattern mixture model (PMM) approach will be used to address potentially MNAR patterns. The following three patterns of subjects in the mITT set will be considered:

1) Subjects with no missing values from discontinuation or from initiation of prohibited Parkinson's disease concomitant mediation during treatment period.
2) Subjects with missing values from the types of ICEs below will be considered having MNAR
    a. Subjects who discontinue due to reasons, as recorded on the eCRF, of lack of efficacy, adverse events associated with motor symptoms of Parkinson's disease, physician decision, and withdrawal by subject.
    b. Subjects who initiated concomitant Parkinson's disease medications (ATC classifications of ADAMANTANE DERIVATIVES, DOPAMINE AGONISTS, MONOAMINE OXIDASE B INHIBITORS, OTHER ANTIPARKINSON DRUGS, OTHER DOPAMINERGIC AGENTS, or DOPA AND DOPA DERIVATIVES) after the first dose of IMP and prior to the last dose of IMP with a use duration of 7 days or more will be considered having a potential confounding ICE. The efficacy data post ICE will be treated as missing with the missing pattern of MNAR.

The MNAR cases will be identified and documented prior to database lock and unblinding (Section 9.5).

3) Subjects with missing values from the type of ICEs below will be considered as having MAR
    a. Missing values after discontinuation due to reasons, as recorded on the eCRF, of death, pregnancy, loss to follow-up, adverse event unrelated to motor symptoms of Parkinson's disease, non-compliance, site termination, protocol deviation, failure to meet continuation criteria and other will be considered as MAR.

The MNAR pattern 2) above in the active treatment group will be imputed using the jump to reference (J2R) method (Cro et. al. 2020) by assuming that patients jump to behave like those in the placebo group following their last observed time point. However, such MNAR in the placebo group will still be imputed as MAR using the standard multiple imputation method.

The MAR patterns 3) will be imputed using the standard multiple imputation method described above.

Other missing values due to missed visits/assessments before endpoint or discontinuation will also be assumed as MAR and imputed using the standard multiple imputation method for all three patterns.

Core codes for MAR and MNAR imputations are provided in Section 9.6.

Under Missing Completely at Random (MCAR) Assumption

An additional sensitivity analysis will be conducted on the Endpoint (Week 26) Completer set using the MMRM analysis method described in Section 5.9.2.

5.9.4. Subgroup Analyses

Subgroup analyses of the primary endpoint will be made based on the mITT set to assess consistency of the intervention effect across the following subgroups:

- Age group: < 65 vs ≥ 65 years
- Sex: female vs male
- Hoehn and Yahr Status at screening: 1 vs 1.5 vs 2
- Baseline MDS-UPDRS Part II score: ≤ baseline median vs > baseline median (median of the mITT set regardless of treatment group)
- Baseline MDS-UPDRS Part III score: ≤ baseline median vs > baseline median (median of the mITT set regardless of treatment group)
- Use of concomitant MAO-B inhibitor: yes vs no
- Years since initial diagnosis:(<1 year vs 1 to < 2 years vs 2 to < 3 years
- Race: white vs other
- Region: United States vs Non-US

If the number of subjects within a subgroup is too small (less than 10% of the mITT set), the subgroup categories may be redefined prior to unblinding the study or the specific subgroup analysis may not be performed. Provided that the sample sizes in the subgroups allow, the MMRM analysis method described in Section 5.9.2 will be applied to the subgroup analysis (excluding the covariate of MAO-B inhibitor use in the MAO-B subgroup models). The treatment effect across subgroups will be summarized by forest plots.

5.10. Key Secondary Efficacy Analyses

5.10.1. Secondary Estimand 1

The key research question for the first secondary efficacy variable will be addressed with an estimand based on the following attributes:

1) Treatments: treatments as randomized regardless of the actual treatment received or the final dose level achieved following the titration steps.
2) Target study population of interest: subjects in the modified intent-to-treat (mITT) population regardless the completion status of dose titration steps.
3) Endpoint (variable) of interest: change from baseline to Week 26 in the MDS-UPDRS Part II Score.
4) Population level summary of interest: estimated mean difference between each tavapadon (CVL-751) dose group and placebo group in the endpoint of interest.
5) Strategy for Intercurrent events (ICEs): a hypothetical strategy will be used to address intercurrent events (ICEs) of potential death, treatment discontinuations, missed visits/assessments, and start of prohibited concomitant Parkinson's disease medications (see definitions in Section 5.9.1). The data after treatment discontinuations or after the start of prohibited concomitant Parkinson's disease treatments will be censored under the hypothetical strategy.

5.10.1.1. Main Analytical Approach

Similar to the analysis of the primary efficacy variable, the change from baseline to each study visit in MDS-UPDRS Part II score will be summarized by visit and treatment group. A mixed model repeated measures (MMRM) analysis will be used with fixed effect of treatment group, visits, and interaction between treatment group and visit, and MAO-B inhibitor use. The baseline value of MDS-UPDRS Part II score will be included as a covariate. Subject will be included as a random effect. An unstructured covariance structure will be used for the repeated measures. If the unstructured covariance matrix results in convergence issue, the heterogeneous Toeplitz covariance structure followed by the heterogeneous first-order autoregressive (AR(1)) structure will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The difference between each active dose and placebo at the endpoint visit (Week 26) will be estimated based on the Least Squares Mean (LSMean) difference derived from the MMRM with the associated 95% confidence intervals (CI) and P-values. A Cohen's D value will also be derived as the ratio of the estimated difference to the population standard deviation at each visit estimated from the model (the square root of the diagonal elements of the estimated covariance matrix). The missing values, including missing due to missed visits or early termination due to COVID-19 control measures, are assumed to be missing at random (MAR) in the main MMRM analysis. Sensitivity analyses will be performed to assess the impact of deviation from MAR assumptions on the analysis results. Time curve plots will be presented for both raw Mean (SEM) and LSMean (SE).

5.10.1.2. Sensitivity Analyses

The sensitivity analyses described in Section 5.9.3 for the primary estimand will also be performed for the secondary efficacy estimand 1.

5.10.1.3. Subgroup Analyses

The subgroup analyses described in Section 5.9.4 for the primary estimand will also be performed for the secondary efficacy estimand 1.

5.10.2. Secondary Estimand 2

The key research question for the second secondary efficacy variable will be addressed with an estimand based on the following attributes:

1) Treatments: treatments as randomized regardless of the actual treatment received or the final dose level achieved following the titration steps.
2) Target study population of interest: subjects in the modified intent-to-treat (mITT) population regardless the completion status of dose titration steps.
3) Endpoint (variable) of interest: proportion of responders, defined as subjects with a score of “much improved” or “very much improved” on the PGIC, at Week 26.
4) Population level summary of interest: : estimated difference expressed as odds ratio between each tavapadon (CVL-751) dose group and placebo group in achieving response.
5) Strategy for Intercurrent events (ICEs): a hypothetical strategy will be used to address intercurrent events (ICEs) of potential death, treatment discontinuations, missed visits/assessments, and start of prohibited concomitant Parkinson’s disease medications (see definitions in Section 5.9.1). The data after treatment discontinuations or after the start of prohibited concomitant Parkinson’s disease treatments will be censored under the hypothetical strategy.

5.10.2.1. Main Analytical Approach

The number and percentage of responders will be summarized by visit and treatment group. The binomial repeated measures up to Week 27 will be analyzed using a generalized linear mixed model with logit link (SAS® GLIMMIX procedure). The treatment group, MAO-B inhibitor use, visits, and interaction between treatment group and visit will be included as fixed effect. An unstructured covariance structure will be used for the repeated measures. If the model does not converge with the unstructured covariance structure, the heterogeneous Toeplitz structure will be used. The odds ratio of each active dose to placebo at the endpoint visit will be estimated based on the Least Squares Mean difference in logit between the treatment groups from the GLIMMIX model with the associated 95% confidence intervals (CI) and P-values. The missing values are assumed to be missing at random, including missing due to missed visits or early termination due to COVID-19 control measures. Sensitivity analyses will be performed to assess the impact of deviation from MAR assumptions on the analysis results.

5.10.2.2. Sensitivity Analyses

The sensitivity analyses described in Section 5.9.3 for the primary estimand will also be performed for the secondary efficacy estimand 2 except for the sensitivity analyses to assess the impact of missing value handling. For the secondary efficacy estimand 2, the case of potential MNAR will be imputed as "non-responder" for the sensitivity analysis. No additional sensitivity analysis under the MAR assumption using multiple imputations will be performed. In addition, a sensitivity analysis excluding the PGIC score obtained remotely may be performed if such remote assessments are conducted due to COVID-19 restrictions.

5.10.2.3. Subgroup Analyses

The subgroup analyses described in Section 5.9.4 for the primary estimand will also be performed for the secondary efficacy estimand 2: proportion of responders at Week 26.

5.11. Summary of Primary and Key Secondary Efficacy Analyses

ICE Strategy	Primary Analysis	Sensitivity Analysis	Subgroup Analysis
Primary Endpoint: Change from baseline in the MDS UPDRS Part II + III combined score at Week 26			
Hypothetical strategy with data after treatment discontinuations or after the start of prohibited concomitant medications censored	• mITT population • Treatment as randomized • MMRM described in Section 5.9.2	• Treatment effect at final dose levels • Treatment effect based on actual treatment received, if applicable • Missing values imputation using multiple imputations (MI) • Missing values imputation using pattern mixture model (PMM) • Endpoint completer analysis • Analysis with remote assessments excluded (treated as missing)	• Age • Sex • Hoehn&Yahr Status • MAO-B inhibitor use • Baseline MDS-UPDRS Part II and Part III baseline • Years since diagnosis • Race • Region
Key Secondary Endpoint 1: Change from baseline in the MDS UPDRS Part II score at Week 26			
Hypothetical strategy with data after treatment discontinuations or after the start of prohibited concomitant medications censored	• mITT population • Treatment as randomized • MMRM described in Section 5.9.2	• Treatment effect at final dose levels • Treatment effect based on actual treatment received, if applicable • Missing values imputation using multiple imputations (MI) • Missing values imputation using pattern mixture model (PMM) • Endpoint completer analysis • Analysis with remote assessments excluded (treated as missing)	• Age • Sex • Hoehn&Yahr Status • MAO-B inhibitor use • Baseline MDS-UPDRS Part II and Part III baseline • Years since diagnosis • Race • Region
Key Secondary Endpoint 2: Proportion of PGIC responders at Week 26			
Hypothetical strategy with data after treatment discontinuations or after the start of prohibited concomitant medications censored	• mITT population • Treatment as randomized • GLIMMIX model described in Section 5.10.2.1	• Treatment effect at final dose levels • Treatment effect based on actual treatment received, if applicable • Potential MNAR missing values treated as non-responders • Endpoint completer analysis • Analysis with remote assessments excluded (treated as missing)	• Age • Sex • Hoehn&Yahr Status • MAO-B inhibitor use • Baseline MDS-UPDRS Part II and Part III baseline • Years since diagnosis • Race • Region

5.12. Other Efficacy Analyses

Endpoint	Analysis Population	ICE Strategy	Analysis Method	Subgroup Analysis
Secondary Endpoints				
Change from baseline in the MDS UPDRS Part II + III combined score (all time points)	mITT	Hypothetical	MMRM described in Section 5.9.2	• Age • Sex • Hoehn&Yahr Status • MAO-B inhibitor use • Baseline MDS-UPDRS Part II and Part III baseline • Years since diagnosis • Race • Region
Change from baseline in the MDS UPDRS Part I, Part II, and Part III combined score (all time points)	mITT	Hypothetical	MMRM described in Section 5.9.2	• Age • Sex • Hoehn&Yahr Status • MAO-B inhibitor use • Baseline MDS-UPDRS Part II and Part III baseline • Years since diagnosis • Race • Region
Change from baseline in the MDS UPDRS Part I score (all time points)	mITT	Hypothetical	MMRM described in Section 5.9.2	• Age • Sex • Hoehn&Yahr Status • MAO-B inhibitor use • Baseline MDS-UPDRS Part II and Part III baseline • Years since diagnosis • Race • Region
Change from baseline in the MDS UPDRS Part II score (all time points)	mITT	Hypothetical	MMRM described in Section 5.9.2	• Age • Sex • Hoehn&Yahr Status • MAO-B inhibitor use • Baseline MDS-UPDRS Part II and Part III baseline • Years since diagnosis • Race • Region

Endpoint	Analysis Population	ICE Strategy	Analysis Method	Subgroup Analysis
Change from baseline in the MDS UPDRS Part III score (all time points)	mITT	Hypothetical	MMRM described in Section 5.9.2	• Age • Sex • Hoehn&Yahr Status • MAO-B inhibitor use • Baseline MDS-UPDRS Part II and Part III baseline • Years since diagnosis • Race • Region
Change from baseline in the CGI-S score (all time points)	mITT	Hypothetical	MMRM described in Section 5.9.2	• Age • Sex • Hoehn&Yahr Status • MAO-B inhibitor use • Baseline MDS-UPDRS Part II and Part III baseline • Years since diagnosis • Race • Region
CGI-I score (all time points)	mITT	Hypothetical	MMRM described in Section 5.9.2	• Age • Sex • Hoehn&Yahr Status • MAO-B inhibitor use • Baseline MDS-UPDRS Part II and Part III baseline • Years since diagnosis • Race • Region
PGIC score (all time points)	mITT	Hypothetical	MMRM described in Section 5.9.2	• Age • Sex • Hoehn&Yahr Status • MAO-B inhibitor use • Baseline MDS-UPDRS Part II and Part III baseline • Years since diagnosis • Race • Region

Endpoint	Analysis Population	ICE Strategy	Analysis Method	Subgroup Analysis
Other Endpoints				
Change from baseline in the PDQ 39 score	mITT	Hypothetical	MMRM described in Section 5.9.2	None
Change from baseline in the Schwab and England ADL score	mITT	Hypothetical	MMRM described in Section 5.9.2	None
Change from baseline in the EQ-5D-5L index score	mITT	Hypothetical	MMRM described in Section 5.9.2	None
Change from baseline in EQ-5D-5L VAS score	mITT	Hypothetical	MMRM described in Section 5.9.2	None

Cohen's D effect size by time point will be derived for MDS-UPDRS Part II+III and MDS-UPDRS Part II only. Time curve plots will be presented for LSMean (SE) of change from baseline for MDS-UPDRS Part II+III, Part I+II+III, individual Part I, II and III, CGI-S, and Schwab and England ADL scores as well as for LSMean (SE) of CGI-I and PGIC over time.

5.13. Interim and Final Analysis

A final analysis will be conducted once the last subject completes or discontinues the study, and the resulting clinical database has been cleaned, quality checked, and the database has been locked.

No interim analysis is planned.

5.14. Safety Analyses

All safety analyses 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.

5.14.1. Adverse Events

Adverse events will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) version 27.0 or higher preferred term and system organ class. If a subject experiences multiple events that map to a single preferred term, the greatest severity and strongest investigator assessment of relation to IMP will be assigned to the preferred term for the appropriate summaries. Events with missing severity or relationship will be classified as outlined in Section 3.2. Missing onset dates will be imputed as previously outlined in Section 4.1 as required to determine treatment-emergent events.

Summaries of treatment-emergent AEs will include any AEs reported beginning with the initiation of study drug on Day 1 through end of reporting period specified in the protocol post the last dose of IMP. The occurrence of TEAEs will be summarized by treatment group using preferred terms, system organ classes, and severity. The TEAEs by subgroup of MAO-B inhibitor use will be summarized by treatment, organ class, and preferred term. Separate summaries of treatment-emergent serious adverse events (TESAEs), TEAEs related to IMP, AESIs (including AEs related to abuse potential and AEs involving medication handling irregularities), events leading to the discontinuation of IMP, and AESIs that did not result in discontinuation of IMP or study will be generated respectively. A summary of AEs by treatment phase and by dose at event onset will also be presented. Adverse events leading to the discontinuation of IMP by preferred term and phase at onset will be prepared. All adverse events reported will be listed for individual subjects showing both verbatim and preferred terms. All adverse events that occurred prior to the initiation of study treatment or after the protocol-specified reporting period post the last dose of IMP will be excluded from the summary tables but will be included in the listings.

In addition, TEAEs rate per 100 person-years of exposure (PYE) will be summarized by treatment group using system organ class and preferred term. TEAEs with ≥2% incidence in either tavapadon dose group and a greater incidence than the placebo group will be summarized by treatment group using preferred term in descending order of the incidence in the tavapadon15 mg group followed by that in the tavapadon 5 mg group. The most common TEAEs, defined as an incidence ≥5% in either tavapadon dose group and greater than 2 times of the incidence in the placebo group, will also be summarized by treatment group using preferred term in descending order of the incidence in the tavapadon15 mg group followed by that in the tavapadon 5 mg group.

5.14.2. Epworth Sleepiness Scale (ESS)

The ESS individual questions and total score and corresponding changes from baseline will be summarized by treatment group and study visit. The percentage of subjects with sleepy (10 or more) and very sleepy (18 or more) scores will also be summarized. ESS individual question score as well as the total score will be presented in a listing. The ESS total score will also be analyzed using the same method (MMRM analysis) describer in Section 5.9.2 to explore any treatment difference in sleepiness. Time curve plot will be presented for LSMean (SE) of change from baseline.

5.14.3. Questionnaire for Impulsive-Compulsive Disorders in Parkinson Disease Rating Scale (QUIP-RS)

The QUIP-RS component scores (Gambling, Sex, Buying, Eating, Hobbyism-Punding, PD Medication Use), total ICD score, and total score and corresponding changes from baseline will be summarized by treatment group and study visit. QUIP-RS individual data will be presented in a listing. The total ICD score will also be analyzed using the same method (MMRM analysis) describer in Section 5.9.2 to explore any treatment difference in impulsive-compulsive behaviors. Time curve plots will be presented for LSMean (SE) of change from baseline.

5.14.4. Non-IMP Medications and Non-Drug Therapy/Procedures

The use of non-IMP medications will be coded using the World Health Organization (WHO) drug dictionary (WHODrug) (Version: Global B3 September 2019 or later). Concomitant medications, with start date on or after the date of the first IMP through the last IMP dose date, will be summarized by treatment group, frequency of drug classification, and generic drug name. Medications with start date after the last dose of IMP through the end of protocol-defined reporting period, will also be summarized. Prior medications use will be similarly summarized. All prior, concomitant, and post IMP medications will be presented in a data listing.

The use of non-drug therapy/procedures will be coded using MedDRA Version 27.0 or higher. Concomitant and post-IMP non-drug therapy/procedures will be summarized by treatment group, frequency of system organ class and preferred term. All non-drug therapy/procedures will be presented in a data listing.

5.14.5. Clinical Laboratory Assessments

Descriptive summaries of selected (quantitative) clinical laboratory results will be presented by treatment group and study visit. Laboratory values outside the normal range for each systematically collected hematology, blood chemistry, and urinalysis parameter will be identified. Each subject's hematology, blood chemistry, and quantitative urinalysis values will be flagged as "low" (below the lower limit of normal/LLN), "normal" (within the normal range), or "high" (above the upper limit of normal/ULN) relative to the normal ranges of the central laboratory. Each subject's qualitative urinalysis results will be flagged as "normal" or "abnormal". In addition, the severity of laboratory abnormality will be graded based on toxicity criteria specified in Section 9.8 in reference to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. The result of each laboratory test for individual subjects will be presented in a listing with the normal range defined by the central laboratory, the status relative to the normal range, and the toxicity grade.

Shift table will be used to summarize shifts from baseline toxicity grades to greatest (worst) treatment-emergent laboratory toxicity grade. For hematology and, blood chemistry, and quantitative urinalysis parameters that toxicity grade was not defined, a shift table for each laboratory test will be based on the shift from baseline high/normal/low status to the status of the maximum post-baseline value and the minimum post-baseline value (including test results from unscheduled visits, if any). Similarly, for qualitative urinalysis parameters, shifts from baseline normal/abnormal status to the worst post-baseline status will be summarized.

The number and percentage of subjects who have post-baseline elevations in liver transaminase (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) or bilirubin abnormalities in relation to fold above the upper limit of normal will be summarized according to the Food and Drug Administration's Premarketing Clinical Evaluation on Drug-Induced Liver Injury Guidance for Industry (FDA 2009). Abnormal hepatic laboratory values will be categorized and evaluated for any occurrence among all post-baseline assessments (where "and" in the bulleted list below indicates elevations occurring at the same visit). Within each laboratory parameter grouping, a subject may be counted once per elevation criteria using the worst-case result.

That is, a subject with a worst case ALT elevation > 5 × the ULN would be counted once in the ALT > 3 × ULN category and once in the ALT > 5 × ULN category, regardless of how many ALT elevations the subject had that met the > 3 × ULN and > 5 × ULN elevation criteria.

- ALT and/or AST > 3 × ULN and total bilirubin > 1.5 or 2 × ULN
- AST > 3, 5, 10, 20 × ULN
- ALT > 3, 5, 10, 20 × ULN
- Total bilirubin > 1.5, 2 × ULN
- Alkaline phosphatase (ALP) > 1.5 × ULN

In addition, an eDISH plot, a shift plot showing liver safety panel tests over time (baseline vs. post-baseline), and distribution plots of ALT, AST, ALP, and bilirubin over time will be produced to aid identification of any potential cases (Merz M. et. al. 2014). The plots to be included are the scatter plot of maximum transaminase versus maximum bilirubin, the liver test safety panel over time, and the distribution of ALT by time. The distribution plots for AST, ALP, and bilirubin will use the same format as used for ALT.

5.14.6. Vital Signs

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

5.14.6.1. Blood Pressure and Heart Rate

Blood pressure and heart rate measurements and corresponding changes from baseline will be summarized by treatment group, position (if applicable), and visit using descriptive statistics. The distribution of diastolic and systolic blood pressure over time will be evaluated using box plots. Average records will be used for the analysis where available.

Number and percent of subjects with at least one of the out-of-range value in blood pressure and heart rate will be summarized by treatment group based on the following criteria:

Supine Systolic Blood Pressure (mmHg)

- < 80 mmHg
- < 90 mmHg
- > 140 mmHg
- > 160 mmHg
- > 200 mmHg

Change from Baseline in Supine Systolic Blood Pressure (mmHg)

- < -20 mmHg
- < -10 mmHg
- > 10 mmHg
- > 20 mmHg

Orthostatic Systolic Blood Pressure (mmHg)

- ≥ 20 mmHg decrease upon standing compared with supine position
- ≥ 20 mmHg increase upon standing compared with supine position

Supine Diastolic Blood Pressure (mmHg)

- < 50 mmHg
- > 90 mmHg
- > 100 mmHg
- > 120 mmHg

Change from Baseline in Supine Diastolic Blood Pressure (mmHg)

- < -15 mmHg
- < -10 mmHg
- > 10 mmHg
- > 25 mmHg

Orthostatic Diastolic Blood Pressure (mmHg)

- ≥ 10 mmHg decrease upon standing compared with supine position
- ≥ 10 mmHg increase upon standing compared with supine position

Supine Heart Rate (beats/min)

- < 50 bpm
- < 60 bpm
- > 100 bpm and ≤ 120 bpm
- > 120 bpm

The number and percentage of the out-of-range values will also be summarized by treatment phase (titration and maintenance phase). For supine measurements, the average of the duplicate will be used to determined out-of-range status, unless in isolated cases where only a single measurement was taken.

5.14.6.2. Body Weight

Body weight measurements at baseline and at the end of treatment with corresponding changes from baseline will be summarized by treatment group using descriptive statistics.

Number and percent of subjects with out-of-range body weight changes will be summarized based on the following criteria:

- Decrease from Baseline 7% or more (i.e. change from baseline ≤ -7%)
- Increase from baseline 7% or more (i.e. change from baseline ≥7%)

5.14.6.3. Temperature

Temperature and corresponding changes from baseline will be summarized by treatment group, and visit using descriptive statistics. Number and percent of subjects with out-of-range temperature will be summarized based on the following criteria:

- >38.0 °C
- <36.0 °C

5.14.7. Electrocardiograms (ECGs)

Single or triplicate 12 lead ECGs will be obtained during the trial. All ECG recordings will 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. Any values taken in triplicate will be averaged for analysis. ECGs and corresponding changes from baseline will be summarized by treatment group and visit using descriptive statistics. Average records will be used for the analysis where available.

The number and percentage of subjects who experience any post-baseline occurrence of potentially clinically significant corrected QT values using Fridericia's method (QTcF) will be summarized by treatment group. These presentations will include QTcF values > 450 to ≤ 480, > 480 to ≤ 500, and > 500 msec; or changes of > 30 to ≤ 60 or > 60 msec (FDA, 2005). For this categorization, the average of triplicate values will be utilized rather than the individual values comprising the triplicate measurement. An out-of-range categorical tabulation will also be presented for the subgroup of U.S subjects.

Additionally, a distribution plot of QTcF over time will be presented as an aid in identification of any possible time trend and outliers.

A substudy to evaluate the effect of tavapadon on the QT interval using C-QT modelling is also included in this trial. Matched triplicate ECGs and plasma tavapadon concentrations that are collected at preselected sites will be used to characterize the effects of tavapadon on the QT interval. The analysis plan is summarized separately.

5.14.8. Physical and Neurological Examinations

Physical and Neurological examination data will be listed.

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

The maximum post-baseline results from the C-SSRS will be summarized. The maximum of each subscale (suicidal ideation [Categories 1-5], suicidal behavior [Categories 6-10], suicidal ideation or behavior [Categories 1-10], and self-injurious behavior without suicidal intent) will be presented. The number of patients with suicide-related treatment-emergent events, treatment-emergent suicidal ideation, and suicidal behavior, based on a comparison of the C-SSRS at baseline and/or previous lifetime experience to maximum C-SSRS scores across all post-baseline assessments will be provided. All C-SSRS elements will be reflected in a listing.

[redacted]

5.15. Pharmacokinetics

Plasma concentrations of tavapadon and CV-0000053 (metabolite) will be determined using a validated LC-MS/MS method. PK data listings will be presented for the PK population. PK summary tables and mean figures will be presented using the PK analysis set.

5.15.1. Pharmacokinetic Data Analysis

Plasma concentrations of tavapadon and CV-0000053 (metabolite) will be summarized separately using descriptive statistics by visit. Plasma concentrations of tavapadon and CV-0000053 that are <LLOQ will be reported as 'BLQ' in the data listings. Plasma concentrations that are BLQ will be treated as 0 for calculation of descriptive statistics. The geometric mean, however, will be calculated by imputing BLQ values as ½ LLOQ. If the calculated mean concentration is below the limit of quantitation, the mean will be reported as BLQ and the SD and CV% shall be reported as not determined (ND). Mean plasma concentrations (SD) of tavapadon and CV-0000053 will also be plotted versus time (in both linear and semi-logarithmic scale) based on nominal visit.

5.16. Protocol Deviations

All protocol deviations will be reviewed by the project team prior to database lock and unblinding to identify subjects with important protocol deviations. The number and percentage of subjects with important deviations will be tabulated by treatment and further tabulated by category and treatment. All deviations from the protocol will be listed by category along with a description and any additional comments.

6. CHANGES IN THE PLANNED ANALYSES

Should any deviations from the analyses specified in the final approved (prior to database lock and unblinding) statistical analysis plan arise, such deviations will be documented in the final clinical study report.

7. REVISION HISTORY

Date	Revision	Rationale

8. REFERENCES

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9. APPENDICES

9.1. Schedule of Assessments

Table 5: 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												
MDS-UPDRS[f]	X	X		X	X	X	X	X	X	X	X	
CGI-S		X		X	X	X	X	X	X	X	X	
CGI-I[g]				X	X	X	X	X	X	X	X	
PGIC[g]				X	X	X	X	X	X	X	X	
PDQ-39		X								X	X	
Schwab and England ADL		X		X	X	X	X	X	X	X	X	
EQ-5D-5L		X					X			X	X	
Safety Assessments												
ESS		X	X	X	X	X	X	X	X	X	X	

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]**
QUIP-RS		X	X	X	X	X	X	X	X	X	X	
C-SSRS[h]	X	X	X	X	X	X	X	X	X	X	X	
Physical/neurological examination[i]	X										X	
Weight	X	X									X	
Vital signs[j]	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECGs												
US sites												
Single ECG	X											
Three sets of triplicate ECGs[k] (-45, -30, and -15 min prior to first dose of IMP)		X										
One set of triplicate ECGs[k,l]		X		X		X	X		X		X	
Non-US sites												
Single ECG[l]	X	X		X		X	X		X		X	
One set of triplicate ECGs[k,l] prior to first dose of IMP		X										
Eye examination						X[v]					X[w]	
Prior/concomitant medications	←----------→											
Adverse events[m]		←----------→										
Laboratory[n]												
Safety laboratory blood sample	X	X				X			X		X	
Prolactin level		X[u]									X[u]	
Serology (HIV, HbsAg, and HCV)	X											
Dipstick urinalysis[o]	X	X				X			X		X	

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]**
Serum pregnancy test[p]	X											
Urine dipstick pregnancy test[p]		←----------→										
Urine drug screen[q]	X	←----------→									X	
Plasma PK sample[r]		X		X		X	X		X		X	
Future biospecimen research blood sample[s]		X										
IMP Administration and Compliance[t]												
Dispense IMP		X	X	X	X	X	X	X	X	X		
Assess IMP compliance			X	X	X	X	X	X	X	X	X	

Abbreviations: ADL = activities of daily living, CGI-I = Clinical Global Impression – Improvement, CGI-S = Clinical Global Impression – Severity of Illness, 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], MDS-UPDRS = Movement Disorder Society – Unified Parkinson's Disease Rating Scale, MoCA = Montreal Cognitive Assessment, PDQ-39 = 39-Item Parkinson's Disease Questionnaire, PGIC = Patient Global Impression of Change, 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. MDS-UPDRS Parts I, II, and III will be conducted before the first dose of IMP at the Baseline Visit and at ~2 to ~6 hours after dosing (at home) at clinic visits during the Treatment Period.

g. All responses will be relative to the subject's condition at the Baseline Visit (Day 1) before the first dose of IMP.

h. 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.

i. 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.

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]

j. Duplicate measurements 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).

k. A triplicate set of ECGs is 3 consecutive ECGs collected 1 to 2 minutes apart over a 5-minute period.

l. The postdose ECGs (triplicate set for US sites at all visits and single for non-US sites at all visits) 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. 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.

n. 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.

o. Dipstick urinalysis results are not to be recorded on the eCRFs; any clinically significant abnormality should be captured as an adverse event.

p. 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.

q. 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.

r. 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.

s. Future biospecimen research sample is optional and is to only be collected if signed consent is obtained from the subject.

t. 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.

u. Prolactin results will be blinded.

[redacted]

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]

[redacted]

9.2. EQ-5D-5L Dimensions

EQ-5D-5L Dimensions (UK English Sample Version)

Dimensions	Item	Coded Value
Mobility	I have no problems in walking about	1
	I have slight problems in walking about	2
	I have moderate problems in walking about	3
	I have severe problems in walking about	4
	I am unable to walk about	5
Self-care	I have no problems washing or dressing myself	1
	I have slight problems washing or dressing myself	2
	I have moderate problems washing or dressing myself	3
	I have severe problems washing or dressing myself	4
	I am unable to wash or dress myself	5
Usual activities (e.g., work, study, housework, family or leisure activities)	I have no problems doing my usual activities	1
	I have slight problems doing my usual activities	2
	I have moderate problems doing my usual activities	3
	I have severe problems doing my usual activities	4
	I am unable to do my usual activities	5
Pain/discomfort	I have no pain or discomfort	1
	I have slight pain or discomfort	2
	I have moderate pain or discomfort	3
	I have severe pain or discomfort	4
	I have extreme pain or discomfort	5
Anxiety/depression	I am not anxious or depressed	1
	I am slightly anxious or depressed	2
	I am moderately anxious or depressed	3
	I am severely anxious or depressed	4
	I am extremely anxious or depressed	5

9.3. Columbia-Suicide Severity Rating Scale (C-SSRS) Suicidal Ideation and Suicidal Behavior Scores

The C-SSRS is comprised of 10 categories with binary responses. The 10 categories include:

Category 1 – Wish to be Dead

Category 2 – Non-specific Active Suicidal Thoughts

Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act

Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan

Category 5 – Active Suicidal Ideation with Specific Plan and Intent

Category 6 – Preparatory Acts or Behavior

Category 7 – Aborted Attempt

Category 8 – Interrupted Attempt

Category 9 – Actual Attempt (non-fatal)

Category 10 – Completed Suicide

Categories 1-5 represent Suicidal Ideation and categories 6-10 represent Suicidal Behavior. Each category is scored as 1 if there is a positive response in the category and a 0 if there are no positive responses in the category.

- Self-Injurious Behavior Without Suicidal Intent During Treatment

A subject will be categorized as having self-injurious behavior without suicidal intent if there is an occurrence of non-suicidal self-injurious behavior on the C-SSRS – Since Last Visit eCRF at any post-baseline visit.

- Baseline C-SSRS Score

Baseline represents the pre-treatment assessment of recent history, with elements of suicidal ideation assessed over the prior 6 months and elements of suicidal behavior assessed over the prior 2 years. It is scaled from 0 (no suicidal ideation or behavior) to 10 (completed suicide)

- Treatment-Emergent Suicide-Related Event

A subject will be categorized as having a treatment-emergent suicide-related event if at least one post-baseline suicidal ideation or suicidal behavior score is greater than 0.

- Treatment-Emergent Suicidal Ideation Compared to Recent History

A subject will be categorized as having treatment-emergent suicidal ideation compared to recent history when there is at least one post-baseline suicidal ideation score > 0 and is an increase from baseline. Lifetime scores are not considered for baseline suicidal ideation responses.

- Treatment-Emergent Serious Suicidal Ideation Compared to Recent History

A subject will be categorized as having treatment-emergent serious suicidal ideation compared to recent history if the baseline score was < 4 and the post-baseline suicidal ideation score increases to 4 or 5. Lifetime scores are not considered for baseline suicidal ideation responses.

- Emergence of Serious Suicidal Ideation Compared to Recent History

A subject will be categorized as having emergence of serious suicidal ideation compared to recent history if baseline score was 0 (no suicidal ideation) and post-baseline C-SSRS suicidal ideation score is either 4 or 5. Lifetime scores are not considered for baseline suicidal ideation responses.

- Emergence of Suicidal Behavior Compared to all Prior History

A subject will be categorized as having emergence of suicidal behavior compared to all prior history if there had been no suicidal behavior in Categories 6-10 reported at any pre-treatment assessment, including responses to lifetime history questions, and there is at least one positive post-baseline C-SSRS assessment in Categories 6-10. 'All Prior History' represents lifetime history.

9.4. Programming Conventions

- Page orientation, margins, and fonts: Summary tables, listings, and figures will appear in landscape orientation. There should be a 1.0" boundary on the left and right edges. The top and bottom margins are 1.0" for tables and listings, but may vary for figures. Output should be printed in Courier New with a point size of 8.
- Identification of analysis population: Every summary table, listing, and figure will clearly specify the analysis population being summarized/listed. Listings will be prepared for all subjects randomized.
- Group headers: In the summary tables, the group headers will identify the within-group sample size for the indicated analysis population. Of note, the header's sample size does not necessarily equal the number of subjects actually summarized within any given summary module; some subjects in the analysis population may have missing values and thus may not be summarized.
- Suppression of percentages corresponding to null categories: When count data are presented as category frequencies and corresponding percentages, the percent should be suppressed when the count is zero in order to draw attention to the non-zero counts.
- Presentation of sample sizes: Summary modules should indicate, in one way or another, the number of subjects actually contributing to the summary statistics presented in any given summary module. As mentioned above, this may be less than the number of subjects in the analysis population.
    - In the quantitative modules describing continuous variables (and thus presenting sample size, means, and standard deviations), the sample size should be the number of non-missing observations
    - For categorical variables that are presented in frequency tables, the module should present the total count in addition to the count in each category. Percentages should be calculated using this total as the denominator, and the percentage corresponding to the sum itself (that is, 100%) should be presented so as to indicate clearly to a reviewer the method of calculation.
- Sorting: Listings will be sorted by treatment, subject number and date, if applicable. If a listing is sorted in a different manner, it will be indicated on the listing shells.
- General formatting rules: Rounding for all variables will occur only as the last step, immediately prior to presentation in listings, tables, and figures. No intermediate rounding will be performed on derived variables. The standard rounding practice of rounding numbers ending in 0-4 down and numbers ending in 5-9 up will be employed.
- The presentation of numerical values will adhere to the following guidelines (exceptions may be necessary in some circumstances for derived analysis variables to allow readability):
    - Raw measurements will be reported to the number of significant digits as captured electronically or on the eCRFs.

  - Standard deviations will be reported to two decimal places beyond the number of decimal places the original parameter is presented. EQ-5D-5L Index Score summaries will use 4 decimal places for standard deviation.
  - Means medians, and quartiles will be reported to one decimal place beyond the number of decimal places the original parameter is presented.
  - will be reported to the one decimal place beyond the number of decimal places the original parameter is presented.
  - Calculated percentages will be reported with one decimal place.
  - Coefficient of variation will be reported to the same number of decimal places as the standard deviation.
  - P-values will be reported to 4 decimal places

- Dates will be formatted as DDMMMYYYY. Partial dates will be presented on data listings as recorded on eCRFs.
- Time will be presented according to the 24-hour clock (HH:MM).
- Verification of Results: All analyses will be subject to formal verification procedures. Specifically, results will be verified utilizing independent programming prior to issuance of the draft statistical report. All documents will be verified by the lead statistician to ensure accuracy and consistency of analyses.

9.5. MNAR Cases Identified Prior to Database Lock

Site	Subject ID	IMP Start Date	IMP End Date	Intercurrent Event	Prohibited PD Medication Start Date
[redacted]				PHYSICIAN DECISION	
				WITHDRAWAL BY SUBJECT	
				WITHDRAWAL BY SUBJECT	
				ADVERSE EVENT	
				ADVERSE EVENT	
				WITHDRAWAL BY SUBJECT	
				WITHDRAWAL BY SUBJECT	
				WITHDRAWAL BY SUBJECT	
				WITHDRAWAL BY SUBJECT	
				ADVERSE EVENT	
				WITHDRAWAL BY SUBJECT	
				WITHDRAWAL BY SUBJECT	
				WITHDRAWAL BY SUBJECT	
				WITHDRAWAL BY SUBJECT	
				WITHDRAWAL BY SUBJECT	
				WITHDRAWAL BY SUBJECT	
				WITHDRAWAL BY SUBJECT	
				ADVERSE EVENT	
				WITHDRAWAL BY SUBJECT	
				WITHDRAWAL BY SUBJECT	
				WITHDRAWAL BY SUBJECT	
				WITHDRAWAL BY SUBJECT	
				WITHDRAWAL BY SUBJECT	
				WITHDRAWAL BY SUBJECT	
				PROHIBITED MEDICATION	[redacted]
				WITHDRAWAL BY SUBJECT	
				WITHDRAWAL BY SUBJECT	
				LACK OF EFFICACY	
				WITHDRAWAL BY SUBJECT	
				LACK OF EFFICACY	
				LACK OF EFFICACY	

Site	Subject ID	IMP Start Date	IMP End Date	Intercurrent Event	Prohibited PD Medication Start Date
[redacted]				WITHDRAWAL BY SUBJECT	.
				WITHDRAWAL BY SUBJECT	.
				ADVERSE EVENT	.
				WITHDRAWAL BY SUBJECT	.
				WITHDRAWAL BY SUBJECT	.
				WITHDRAWAL BY SUBJECT	.
				WITHDRAWAL BY SUBJECT	.
				LACK OF EFFICACY	.
				ADVERSE EVENT	.
				WITHDRAWAL BY SUBJECT	.
				WITHDRAWAL BY SUBJECT	.
				WITHDRAWAL BY SUBJECT	.
				WITHDRAWAL BY SUBJECT	.
				WITHDRAWAL BY SUBJECT	.
				ADVERSE EVENT	.
				LACK OF EFFICACY	.

9.6. Core Codes for imputation of MAR and MNAR

9.6.1. Imputation of Missing at Random (MAR) Cases

SAS PROC MI will be used to generate 27 possible imputed datasets using the following SAS code:

proc mi data=mcmc1 seed=SEED1 nimpute=27 out=Out1X;
mcmc chain=multiple displayinit initial=em(itprint);
var TRT y0 y1 y2 … yn;
run;

Here, TRT is an indicator variable representing treatment with values of 'CVL-751 5 mg', CVL-751 15 mg', or 'Placebo', Y_1 - Y_N represent the response variable (e.g., MDS-UPDRS Part II+III score) for each visit, Y_0 is the baseline score, and SEED1 is a random number.

Each of these datasets will be analyzed using PROC MIXED in SAS using the MMRM model. The results of the analyses of the datasets will be combined using PROC MIANALYZE to produce an inferential result.

9.6.2. Imputation of Missing Not at Random (MNAR) Cases

The MNAR cases are imputed using reference based imputation (J2R) method. The five macros; SAS code for reference based multiple imputation [https://www.lshtm.ac.uk/research/centres-projects-groups/missing-data#dia-working-group] will be used to generate 27 possible imputed datasets using the following sample SAS code:

```
%include "&Path\part1A_33.sas";
%include "&Path\part1B_47.sas";
%include "&Path\part2A_40.sas";
%include "&Path\part2B_31.sas";
%include "&Path\part3_55.sas";
%include "&Path\plotter_7.sas";

%part1A(Jobname=X,Data=XX,Subject=usubjid,Response=aval,Time=avisitn,Treat=Trt01pn, cov=BASE, Catcov=MAOBINHI, covgroup=trt01pn,Debug=1);
%part1b(Jobname=X, Ndraws=27, thin=350, seed=s, Debug=1);

%part2a(Jobname=X_J2R, inname=XX, method=J2R,ref=0, Debug=1);
%part2b(Jobname=X_J2R, seed=s, Debug=1);
```

Each of these datasets will be analyzed using PROC MIXED in SAS using the MMRM model. The results of the analyses of the datasets will be combined using PROC MIANALYZE to produce an inferential result.

9.7. Randomization Stratum Errors

Site	Subject	Confirmed Status of MAO-B Inhibitor Use	IRT Randomization Stratum of MAO-B Inhibitor Use
[redacted]	[redacted]	No	Yes
		No	Yes
		No	Yes
		Yes	No
		Yes	No
		Yes	No
		Yes	No
		Yes	No
		Yes	No
		Yes	No
		Yes	No
		Yes	No
		Yes	No
		Yes	No
		Yes	No

9.8. CTCAE Based Laboratory Test Results Grading Specifications

Lab Test = Albumin

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death

Albumin will have grades 1-3,

- Grade 1 being any values from the LLN to 3 g/dL,
- Grade 2 from 2 to < 3 g/dL and
- Grade 3 < 2 g/dL

Lab Test = Amylase

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic	>5.0 x ULN and with signs or symptoms	-

Amylase will have Grades 1, 2 and 3:

- Grade 1 being any values from the ULN to 1.5 x ULN
- Grade 2 from >1.5 to 5.0 x ULN
- Grade 3 from>5 x ULN

Lab Test = Alkaline Phosphatase

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-

Alkaline Phosphatase will have grades 1-4 and grading is based ULN only.

- Grade 1 being any values from the ULN to 2.5 x ULN
- Grade 2 from >2.5 to 5.0 x ULN
- Grade 3 from >5.0 to 20.0 x ULN
- Grade 4 from>20.0 x ULN

Lab Test = Alanine Aminotransferase

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-

ALT will have grades 1-4 and grading is based ULN only.

- Grade 1 being any values from the ULN to 3.0 x ULN
- Grade 2 from >3.0 to 5.0 x ULN
- Grade 3 from >5.0 to 20.0 x ULN
- Grade 4 from>20.0 x ULN

Lab Test = Aspartate Aminotransferase

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-

AST will have grades 1-4 and grading is based ULN only.

- Grade 1 being any values from the ULN to 3.0 x ULN
- Grade 2 from >3.0 to 5.0 x ULN
- Grade 3 from >5.0 to 20.0 x ULN
- Grade 4 from>20.0 x ULN

Lab Test = Bilirubin

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal	-

Bilirubin will have grades 1-4 and grading is based ULN only

- Grade 1 being any values from the ULN to 1.5 x ULN
- Grade 2 from >1.5 to 3.0 x ULN
- Grade 3 from >3.0 to 10.0 x ULN
- Grade 4 from>10.0 x ULN

Lab Test = Corrected Serum Calcium

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences	Death
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences	Death

Calcium will have to be corrected for albumin using Payne's formula:

Corrected calcium = measured Ca (mg/dL) + 0.8 × (4.0 g/dL – patient albumin (g/dL)).

(NOTE: It should be confirmed with the lab whether or not the correction has already been applied).

The grading is in both directions High and Low. Both directions are graded in 4 categories as

Hypercalcemia

- Grade 1 being any values from the ULN to 11.5 mg/dL,
- Grade 2 from >11.5 to 12.5 mg/dL,
- Grade 3 from >12.5 to 13.5 mg/dL,
- Grade 4 >13.5 mg/dL

Hypocalcemia

- Grade 1 being any values from the LLN to 8.0 mg/dL,
- Grade 2 from 7.0 to <8.0 mg/dL,
- Grade 3 from 6.0 to <7.0 mg/dL,
- Grade 4 <6.0 mg/dL

Lab Test = Cholesterol

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	-

Cholesterol will have grades 1-4,

- Grade 1 being any values from the ULN to 300 mg/dL,
- Grade 2 from >300 to 400 mg/dL,
- Grade 3 from >400 to 500 mg/dL,
- Grade 4 >500 mg/dL

Lab Test = Creatine Kinase

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	-

Creatine Kinase will have grades 1-4,

- Grade 1 being any values from the ULN to 2.5 x ULN ,
- Grade 2 from >2.5 to 5 x ULN ,
- Grade 3 from >5 to 10 x ULN ,
- Grade 4 >10 ULN

Lab Test = Creatinine

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-

Creatinine will have grades 1-4

- Grade 1 being any values from the ULN to 1.5 x ULN ,
- Grade 2 from >1.5 to 3.0 x ULN or >1.5 - 3.0 x baseline ,
- Grade 3 from >3.0 to 6.0 x ULN or >3.0 x baseline ,
- Grade 4 >6.0 x ULN

Lab Test = Fibrinogen

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fibrinogen decreased	<1.0 - 0.75 x LLN; if abnormal, <25% decrease from baseline	<0.75 - 0.5 x LLN; if abnormal, 25 - <50% decrease from baseline	<0.5 - 0.25 x LLN; if abnormal, 50 - <75% decrease from baseline	<0.25 x LLN; if abnormal, 75% decrease from baseline; absolute value <50 mg/dL	-

Fibrinogen will have Grades 1- 4:

- Grade 1 <1.0 - 0.75 x LLN
- Grade 2 <0.75 - 0.5 x LLN
- Grade 3 <0.5 - 0.25 x LLN
- Grade 4 <0.25 x LLN

Lab Test = Gamma-Glutamyl Transpeptidase

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
GGT increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-

Gamma-Glutamyl Transpeptidase will have grades 1-4 and based on ULN only

- Grade 1 being any values from the ULN to 2.5 x ULN,
- Grade 2 from >2.5 to 5.0 x ULN
- Grade 3 from >5.0 to 20.0 x ULN
- Grade 4 from>20.0 x ULN

Lab Test = Glucose

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hyperglycemia	Abnormal glucose above baseline with no medical intervention	Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Insulin therapy initiated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures	Death

Hypoglycemia will have grades 1-4,

- Grade 1 being any values from the LLN to 55 mg/dL,
- Grade 2 from 40 to <55 mg/dL,
- Grade 3 from 30 to <40 mg/dL,
- Grade 4 <30 mg/dL

Hyperglycemia will have one grade using the WHO criterion below

- Grade 1 >200 mg/dL;

Lab Test = Lipase

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Serum lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic	>5.0 x ULN and with signs or symptoms	-

Lipase will have Grades 1, 2 and 3:

- Grade 1 being any values from the ULN to 1.5 x ULN
- Grade 2 from >1.5 to 5.0 x ULN
- Grade 3 from>5 x ULN

Lab Test = Magnesium

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences	Death
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences	Death

Hypermagnesemia will have grades 1, 3, and 4,

- Grade 1 being any values from the ULN to 3.0 mg/dL,
- Grade 3 from >3.0 to 8.0 mg/dL,
- Grade 4 from>8.0 mg/dL

Hypomagnesemia will have grades 1 - 4,

- Grade 1 being any values from the LLN to 1.2 mg/dL,
- Grade 2 from 0.9 to <1.2 mg/dL,
- Grade 3 from 0.7 to <0.9 mg/dL,
- Grade 4 <0.7 mg/dL

Lab Test = Potassium

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; intervention initiated	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death
Hypokalemia	<LLN - 3.0 mmol/L	Symptomatic with <LLN - 3.0 mmol/L; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death

Hyperkalemia will have grades 1-4,

- Grade 1 being any values from the ULN to 5.5 mmol/L,
- Grade 2 from >5.5 to 6.0 mmol/L,
- Grade 3 from >6.0 to 7.0 mmol/L,
- Grade 4 from>7.0 mmol/L

Hypokalemia will have grades 1, 3, and 4,

- Grade 1 being any values from the LLN to 3.0 mmol/L,
- Grade 3 from >2.5 to 3.0 mmol/L,
- Grade 4 <2.5 mmol/L

Lab Test = Sodium

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Hyponatremia	<LLN - 130 mmol/L	125-129 mmol/L and asymptomatic	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms	<120 mmol/L; life-threatening consequences	Death

Hypernatremia will have grades 1-4,

- Grade 1 being any values from the ULN to 150 mmol/L,
- Grade 2 from >150 to 155 mmol/L,
- Grade 3 from >155 to 160 mmol/L,
- Grade 4 from>160 mmol/L

Hyponatremia will have grades 1-4,

- Grade 1 being any values from the LLN to 130 mmol/L,
- Grade 2 from 125 to <130 mmol/L,
- Grade 3 from 120 to <125 mmol/L,
- Grade 4 <120 mmol/L

Lab Test = Triglycerides

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences	Death

Triglycerides will have grades 1-4,

- Grade 1 being any values from the 150 to 300 mg/dL,
- Grade 2 from >300 to 500 mg/dL,
- Grade 3 from >500 to 1000 mg/dL,
- Grade 4 from>1000 mmol/L

Lab Test = Uric Acid

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hyperuricemia	>ULN without physiologic consequences	-	>ULN with physiologic consequences	Life-threatening consequences	Death

Uric Acid will not be CTCAE graded.

Lab Test = Bicarbonate or CO2

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Blood bicarbonate decreased	<LLN and no intervention initiated	-	-	-	-

Bicarbonate or CO2 will not be CTCAE graded.

Lab Test = Phosphorus or Phosphate

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypophosphatemia	Laboratory finding only and intervention not indicated	Oral replacement therapy indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	Life-threatening consequences	Death
Hyperphosphatemia	Laboratory finding only and intervention not indicated	Noninvasive intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	Life-threatening consequences; urgent intervention indicated (e.g., dialysis)	Death

Phosphorus or Phosphate will not be CTCAE graded.

Lab Test = Serum pH [This is not urine pH]

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Acidosis	pH <normal, but >=7.3	-	pH <7.3	Life-threatening consequences	-
Alkalosis	pH >normal, but <=7.5	-	pH >7.5	Life-threatening consequences	-

Serum pH will be graded in both directions with Grades 1 and 3 only.
Acidosis Grade 1 .<LLN, but >=7.3 Grade 3, pH < 7.3
Alkaosis Grade 1 .>ULN, but <=7.5 Grade 3, pH < 7.5

Lab Test = Activated Partial Thromboplastin Time

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; bleeding	-	-

APTT will be graded in Grade 1-3

- Grade 1 being any values from the >ULN to 1.5 x ULN,
- Grade 2 from >1.5 to 2.5 x ULN,
- Grade 3 from >2.5 x ULN,

Lab Test = International Normalized Ratio

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
INR increased	>1.2 - 1.5; >1 - 1.5 x baseline if on anticoagulation; monitoring only indicated	>1.5 - 2.5; >1.5 - 2.5 x baseline if on anticoagulation; dose adjustment indicated	>2.5; >2.5 x baseline if on anticoagulation; bleeding	-	-

INR will be graded in Grade 1-3 without baseline factor

- Grade 1 being any values from the >1.2 to 1.5,
- Grade 2 from >1.5 to 2.5,
- Grade 3 from >2.5,

Lab Test = Eosinophils

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Eosinophilia	>ULN and >Baseline	-	Steroids initiated	-	-

Eosinophils will not be CTCAE graded

Lab Test = Hemoglobin

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Hemoglobin Increased	Increase in > 0-2	Increase in >2-4g/dL	Increase > 4 g/DL	-	Death

Decreased Hemoglobin will have grades 1-3, with

- Grade 1 being any values from the LLN to 10 g/DL,
- Grade 2 from 8 to < 10 g/DL and
- Grade 3 < 8 g/DL

Increased Hemoglobin will not be graded.

Lab Test = CD4 Lymphocytes

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
CD4 lymphocytes decreased	<LLN - 500/mm3; <LLN - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200 - 50/mm3; <0.2 x 0.05 - 10e9 /L	<50/mm3; <0.05 x 10e9 /L	-

Decreased CD4 count will have grades 1-4, with

- Grade 1 being any values from the LLN to 500/mm3,
- Grade 2 from <500 to 200/mm3 and
- Grade 3 from <200 to 50/mm3 and
- Grade 4 <50/mm3

Lab Test = Lymphocytes

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	Lymphocyte count decreased
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	Lymphocyte count increased

Decreased Lymphocytes will have grades 1-4, with

- Grade 1 being any values from the LLN to 800/mm3,
- Grade 2 from <800 to 500/mm3 and
- Grade 3 from <500 to 200/mm3 and
- Grade 4 <200/mm3

Increase Lymphocytes will have grades 2 and 3 only, with

- Grade 2 from >4000 to 20,000/mm3 and
- Grade 3 >20,000/mm3

Lab Test = Neutrophils

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-

Neutrophils will have grades 1-4, with

- Grade 1 being any values from the LLN to 1500/mm3,
- Grade 2 from 1000 to <1500/mm3 and
- Grade 3 from 500 to <1000/mm3 and
- Grade 4 <500/mm3

Lab Test = Platelets

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-

Platelet count will not be CTCAE graded

Lab Test = WBC

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-
Leukocytosis	-	-	>100,000/mm3	Clinical manifestations of leucostasis; urgent intervention indicated	Death

Decreased WBC will have grades 1-4, with

- Grade 1 being any values from the LLN to 3000/mm3,
- Grade 2 from 2000 to <3,000/mm3 and
- Grade 3 from 1000 to <2,000/mm3 and
- Grade 4 <1000/mm3

High WBC will have grade 1, with

- Grade 1 >11,000/mm3 (https://www.aafp.org/afp/2000/1101/p2053 html),

Lab Test = Urine Glucose

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Glucosuria	Present	-	-	-	-

Urine Glucose will have grades 1,

- Grade 1 if not negative or trace

Lab Test = Urine Protein

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Proteinuria	1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs	**Adult:** 2+ and 3+ proteinuria; urinary protein 1.0 - <3.5 g/24 hrs; **Pediatric:** Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	**Adult:** Urinary protein >=3.5 g/24 hrs; 4+ proteinuria; **Pediatric:** Urine P/C (Protein/Creatinine) ratio >1.9	-	-

Urine Protein will have grades 1-3, with

- Grade 1 =1+,
- Grade 2 = 2+ to 3+
- Grade 3 = 4+

Lab Test: Urine RBCs/Blood

CTCAE Term	Grade 1	Grade 2		Grade 3	Grade 4	Grade 5
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL		Gross hematuria; transfusion, IV medications, or hospitalization indicated; elective invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent invasive intervention indicated	Death

Urine blood will not be CTCAE graded

Lab Test: eGFR or CrCl

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
eGFR decreased/CrCL decreased	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN - 60 ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5	eGFR or CrCl 59 - 30 ml/min/1.73 m2	eGFR or CrCl 29 - 15 ml/min/1.73 m2	eGFR or CrCl <15 ml/min/1.73 m2; dialysis or renal transplant indicated	Death

Values will be graded using the CTCAE values noted above with Grade 1 – Grade 4 values.
eGFR/CrCL:
Grade 1: < LLN – 60 ml/min/1.73 m2
Grade 2: 30 - < 60 ml/min/1.73 m2
Grade 3: 15 - < 30 ml/min/1.73 m2
Grade 4: < 15 ml/min/1.73

9.9. EQ-5D-5L Index Cross-walk Mapping

US Value Set

Health State (5L profile)	US
11111	1.000
11112	0.876
11113	0.844
11114	0.700
11115	0.550
11121	0.861
11122	0.820
11123	0.809
11124	0.669
11125	0.524
11131	0.827
11132	0.806
11133	0.800
11134	0.661
11135	0.517
11141	0.682
11142	0.663
11143	0.659
11144	0.544
11145	0.426
11151	0.463
11152	0.450
11153	0.446
11154	0.369
11155	0.289
11211	0.888
11212	0.846
11213	0.835
11214	0.695
11215	0.550
11221	0.832
11222	0.796
11223	0.786
11224	0.654
11225	0.517
11231	0.818
11232	0.783
11233	0.774
11234	0.644
11235	0.508
11241	0.676
11242	0.647
11243	0.640
11244	0.532
11245	0.421
11251	0.463

Health State (5L profile)	US
11252	0.443
11253	0.437
11254	0.365
11255	0.289
11311	0.860
11312	0.839
11313	0.833
11314	0.694
11315	0.550
11321	0.825
11322	0.790
11323	0.781
11324	0.650
11325	0.515
11331	0.816
11332	0.778
11333	0.768
11334	0.639
11335	0.506
11341	0.675
11342	0.643
11343	0.635
11344	0.529
11345	0.419
11351	0.463
11352	0.441
11353	0.435
11354	0.363
11355	0.289
11411	0.783
11412	0.764
11413	0.759
11414	0.641
11415	0.518
11421	0.751
11422	0.721
11423	0.713
11424	0.601
11425	0.485
11431	0.742
11432	0.710
11433	0.701
11434	0.591
11435	0.477
11441	0.618
11442	0.591
11443	0.584
11444	0.490
11445	0.393
11451	0.431
11452	0.412

Health State (5L profile)	US
11453	0.406
11454	0.338
11455	0.266
11511	0.626
11512	0.613
11513	0.609
11514	0.532
11515	0.452
11521	0.599
11522	0.579
11523	0.574
11524	0.501
11525	0.425
11531	0.592
11532	0.571
11533	0.565
11534	0.493
11535	0.418
11541	0.501
11542	0.483
11543	0.478
11544	0.410
11545	0.339
11551	0.365
11552	0.352
11553	0.348
11554	0.285
11555	0.220
12111	0.854
12112	0.815
12113	0.805
12114	0.665
12115	0.520
12121	0.802
12122	0.765
12123	0.756
12124	0.623
12125	0.486
12131	0.789
12132	0.753
12133	0.743
12134	0.613
12135	0.478
12141	0.647
12142	0.617
12143	0.609
12144	0.502
12145	0.390
12151	0.433
12152	0.413
12153	0.408

Health State (5L profile)	US
12154	0.335
12155	0.259
12211	0.828
12212	0.792
12213	0.782
12214	0.650
12215	0.513
12221	0.778
12222	0.731
12223	0.719
12224	0.595
12225	0.467
12231	0.765
12232	0.716
12233	0.703
12234	0.581
12235	0.455
12241	0.630
12242	0.587
12243	0.576
12244	0.477
12245	0.374
12251	0.426
12252	0.393
12253	0.385
12254	0.320
12255	0.252
12311	0.822
12312	0.786
12313	0.776
12314	0.646
12315	0.511
12321	0.772
12322	0.723
12323	0.710
12324	0.588
12325	0.462
12331	0.759
12332	0.707
12333	0.693
12334	0.574
12335	0.449
12341	0.625
12342	0.580
12343	0.568
12344	0.471
12345	0.370
12351	0.424
12352	0.388
12353	0.379
12354	0.316

Health State (5L profile)	US
12355	0.250
12411	0.748
12412	0.717
12413	0.709
12414	0.597
12415	0.482
12421	0.703
12422	0.659
12423	0.648
12424	0.545
12425	0.438
12431	0.692
12432	0.645
12433	0.632
12434	0.531
12435	0.427
12441	0.573
12442	0.533
12443	0.522
12444	0.437
12445	0.348
12451	0.395
12452	0.364
12453	0.356
12454	0.295
12455	0.230
12511	0.596
12512	0.576
12513	0.571
12514	0.498
12515	0.422
12521	0.562
12522	0.529
12523	0.521
12524	0.456
12525	0.388
12531	0.554
12532	0.518
12533	0.508
12534	0.445
12535	0.380
12541	0.466
12542	0.437
12543	0.429
12544	0.368
12545	0.304
12551	0.335
12552	0.315
12553	0.310
12554	0.251
12555	0.190

Health State (5L profile)	US
13111	0.825
13112	0.803
13113	0.797
13114	0.658
13115	0.514
13121	0.790
13122	0.754
13123	0.745
13124	0.614
13125	0.479
13131	0.781
13132	0.742
13133	0.732
13134	0.603
13135	0.470
13141	0.640
13142	0.608
13143	0.599
13144	0.493
13145	0.383
13151	0.427
13152	0.406
13153	0.400
13154	0.328
13155	0.253
13211	0.816
13212	0.781
13213	0.771
13214	0.641
13215	0.505
13221	0.767
13222	0.718
13223	0.705
13224	0.583
13225	0.456
13231	0.755
13232	0.702
13233	0.689
13234	0.569
13235	0.444
13241	0.620
13242	0.575
13243	0.563
13244	0.466
13245	0.364
13251	0.418
13252	0.383
13253	0.374
13254	0.311
13255	0.244
13311	0.814

Health State (5L profile)	US
13312	0.775
13313	0.765
13314	0.636
13315	0.503
13321	0.761
13322	0.709
13323	0.695
13324	0.575
13325	0.451
13331	0.748
13332	0.693
13333	0.678
13334	0.560
13335	0.438
13341	0.615
13342	0.567
13343	0.554
13344	0.459
13345	0.360
13351	0.416
13352	0.378
13353	0.368
13354	0.306
13355	0.242
13411	0.740
13412	0.707
13413	0.699
13414	0.589
13415	0.474
13421	0.693
13422	0.647
13423	0.635
13424	0.533
13425	0.428
13431	0.682
13432	0.632
13433	0.619
13434	0.519
13435	0.416
13441	0.564
13442	0.521
13443	0.510
13444	0.426
13445	0.339
13451	0.387
13452	0.355
13453	0.346
13454	0.286
13455	0.223
13511	0.590
13512	0.569

Health State (5L profile)	US
13513	0.563
13514	0.491
13515	0.416
13521	0.555
13522	0.519
13523	0.510
13524	0.447
13525	0.381
13531	0.546
13532	0.507
13533	0.497
13534	0.436
13535	0.372
13541	0.459
13542	0.427
13543	0.419
13544	0.359
13545	0.297
13551	0.329
13552	0.308
13553	0.302
13554	0.244
13555	0.184
14111	0.753
14112	0.733
14113	0.728
14114	0.604
14115	0.475
14121	0.720
14122	0.688
14123	0.680
14124	0.563
14125	0.442
14131	0.712
14132	0.677
14133	0.668
14134	0.553
14135	0.434
14141	0.583
14142	0.554
14143	0.546
14144	0.450
14145	0.349
14151	0.388
14152	0.369
14153	0.364
14154	0.294
14155	0.221
14211	0.746
14212	0.715
14213	0.706

Health State (5L profile)	US
14214	0.590
14215	0.469
14221	0.701
14222	0.656
14223	0.644
14224	0.536
14225	0.423
14231	0.690
14232	0.641
14233	0.629
14234	0.523
14235	0.412
14241	0.567
14242	0.525
14243	0.514
14244	0.426
14245	0.333
14251	0.382
14252	0.350
14253	0.342
14254	0.280
14255	0.215
14311	0.745
14312	0.710
14313	0.701
14314	0.586
14315	0.467
14321	0.696
14322	0.648
14323	0.635
14324	0.529
14325	0.419
14331	0.684
14332	0.633
14333	0.619
14334	0.515
14335	0.407
14341	0.563
14342	0.518
14343	0.506
14344	0.420
14345	0.330
14351	0.380
14352	0.346
14353	0.337
14354	0.276
14355	0.213
14411	0.681
14412	0.651
14413	0.644
14414	0.544

Health State (5L profile)	US
14415	0.440
14421	0.638
14422	0.595
14423	0.584
14424	0.492
14425	0.397
14431	0.627
14432	0.581
14433	0.569
14434	0.479
14435	0.386
14441	0.517
14442	0.478
14443	0.468
14444	0.390
14445	0.310
14451	0.353
14452	0.324
14453	0.316
14454	0.257
14455	0.196
14511	0.551
14512	0.532
14513	0.527
14514	0.457
14515	0.384
14521	0.518
14522	0.486
14523	0.478
14524	0.416
14525	0.351
14531	0.510
14532	0.475
14533	0.466
14534	0.406
14535	0.343
14541	0.425
14542	0.396
14543	0.389
14544	0.331
14545	0.270
14551	0.297
14552	0.278
14553	0.273
14554	0.217
14555	0.160
15111	0.529
15112	0.516
15113	0.512
15114	0.435
15115	0.355

Health State (5L profile)	US
15121	0.503
15122	0.482
15123	0.477
15124	0.404
15125	0.328
15131	0.496
15132	0.474
15133	0.468
15134	0.396
15135	0.321
15141	0.405
15142	0.386
15143	0.381
15144	0.313
15145	0.242
15151	0.268
15152	0.255
15153	0.251
15154	0.188
15155	0.123
15211	0.529
15212	0.509
15213	0.503
15214	0.430
15215	0.354
15221	0.496
15222	0.463
15223	0.454
15224	0.389
15225	0.321
15231	0.487
15232	0.452
15233	0.442
15234	0.379
15235	0.312
15241	0.400
15242	0.370
15243	0.362
15244	0.301
15245	0.237
15251	0.268
15252	0.248
15253	0.242
15254	0.184
15255	0.123
15311	0.529
15312	0.507
15313	0.501
15314	0.429
15315	0.354
15321	0.494

Health State (5L profile)	US
15322	0.458
15323	0.449
15324	0.385
15325	0.319
15331	0.485
15332	0.446
15333	0.436
15334	0.374
15335	0.310
15341	0.398
15342	0.366
15343	0.358
15344	0.298
15345	0.235
15351	0.268
15352	0.246
15353	0.240
15354	0.183
15355	0.123
15411	0.497
15412	0.478
15413	0.472
15414	0.403
15415	0.332
15421	0.464
15422	0.434
15423	0.426
15424	0.364
15425	0.299
15431	0.456
15432	0.423
15433	0.414
15434	0.354
15435	0.291
15441	0.372
15442	0.344
15443	0.337
15444	0.279
15445	0.219
15451	0.245
15452	0.226
15453	0.221
15454	0.167
15455	0.110
15511	0.431
15512	0.418
15513	0.414
15514	0.351
15515	0.286
15521	0.404
15522	0.384

Health State (5L profile)	US
15523	0.379
15524	0.320
15525	0.260
15531	0.397
15532	0.376
15533	0.370
15534	0.313
15535	0.253
15541	0.318
15542	0.300
15543	0.295
15544	0.241
15545	0.186
15551	0.199
15552	0.186
15553	0.182
15554	0.134
15555	0.084
21111	0.880
21112	0.840
21113	0.830
21114	0.690
21115	0.544
21121	0.826
21122	0.790
21123	0.780
21124	0.648
21125	0.511
21131	0.813
21132	0.777
21133	0.768
21134	0.638
21135	0.502
21141	0.671
21142	0.641
21143	0.634
21144	0.526
21145	0.415
21151	0.457
21152	0.437
21153	0.432
21154	0.359
21155	0.283
21211	0.853
21212	0.816
21213	0.807
21214	0.675
21215	0.538
21221	0.803
21222	0.756
21223	0.744

Health State (5L profile)	US
21224	0.620
21225	0.491
21231	0.790
21232	0.741
21233	0.728
21234	0.606
21235	0.480
21241	0.655
21242	0.612
21243	0.601
21244	0.502
21245	0.398
21251	0.451
21252	0.418
21253	0.409
21254	0.344
21255	0.276
21311	0.846
21312	0.810
21313	0.801
21314	0.671
21315	0.536
21321	0.797
21322	0.748
21323	0.735
21324	0.613
21325	0.486
21331	0.785
21332	0.732
21333	0.719
21334	0.599
21335	0.474
21341	0.651
21342	0.605
21343	0.593
21344	0.495
21345	0.394
21351	0.449
21352	0.413
21353	0.404
21354	0.340
21355	0.274
21411	0.772
21412	0.741
21413	0.733
21414	0.622
21415	0.507
21421	0.728
21422	0.684
21423	0.673
21424	0.569

Health State (5L profile)	US
21425	0.462
21431	0.717
21432	0.670
21433	0.658
21434	0.556
21435	0.451
21441	0.598
21442	0.558
21443	0.547
21444	0.462
21445	0.373
21451	0.420
21452	0.389
21453	0.381
21454	0.319
21455	0.255
21511	0.620
21512	0.600
21513	0.595
21514	0.522
21515	0.446
21521	0.586
21522	0.554
21523	0.546
21524	0.480
21525	0.412
21531	0.578
21532	0.543
21533	0.534
21534	0.470
21535	0.404
21541	0.491
21542	0.462
21543	0.454
21544	0.392
21545	0.329
21551	0.359
21552	0.339
21553	0.334
21554	0.276
21555	0.215
22111	0.823
22112	0.786
22113	0.777
22114	0.645
22115	0.507
22121	0.772
22122	0.725
22123	0.713
22124	0.589
22125	0.461

Health State (5L profile)	US
22131	0.760
22132	0.710
22133	0.697
22134	0.575
22135	0.449
22141	0.624
22142	0.581
22143	0.570
22144	0.471
22145	0.368
22151	0.420
22152	0.387
22153	0.379
22154	0.314
22155	0.246
22211	0.799
22212	0.751
22213	0.739
22214	0.616
22215	0.487
22221	0.738
22222	0.678
22223	0.662
22224	0.547
22225	0.427
22231	0.723
22232	0.659
22233	0.643
22234	0.530
22235	0.412
22241	0.594
22242	0.537
22243	0.523
22244	0.432
22245	0.338
22251	0.400
22252	0.354
22253	0.342
22254	0.285
22255	0.226
22311	0.793
22312	0.743
22313	0.730
22314	0.609
22315	0.483
22321	0.729
22322	0.666
22323	0.649
22324	0.536
22325	0.419
22331	0.714

Health State (5L profile)	US
22332	0.647
22333	0.629
22334	0.518
22335	0.403
22341	0.587
22342	0.527
22343	0.511
22344	0.422
22345	0.330
22351	0.396
22352	0.346
22353	0.333
22354	0.278
22355	0.221
22411	0.724
22412	0.680
22413	0.668
22414	0.565
22415	0.459
22421	0.666
22422	0.608
22423	0.593
22424	0.498
22425	0.400
22431	0.652
22432	0.590
22433	0.574
22434	0.482
22435	0.386
22441	0.540
22442	0.485
22443	0.471
22444	0.394
22445	0.314
22451	0.372
22452	0.327
22453	0.316
22454	0.262
22455	0.207
22511	0.583
22512	0.550
22513	0.542
22514	0.477
22515	0.409
22521	0.537
22522	0.490
22523	0.478
22524	0.421
22525	0.362
22531	0.525
22532	0.475

Health State (5L profile)	US
22533	0.462
22534	0.407
22535	0.351
22541	0.444
22542	0.401
22543	0.390
22544	0.337
22545	0.282
22551	0.322
22552	0.289
22553	0.281
22554	0.230
22555	0.178
23111	0.811
23112	0.775
23113	0.766
23114	0.635
23115	0.500
23121	0.761
23122	0.712
23123	0.699
23124	0.577
23125	0.451
23131	0.749
23132	0.696
23133	0.683
23134	0.563
23135	0.439
23141	0.615
23142	0.569
23143	0.557
23144	0.460
23145	0.359
23151	0.413
23152	0.377
23153	0.368
23154	0.305
23155	0.239
23211	0.788
23212	0.738
23213	0.726
23214	0.604
23215	0.477
23221	0.725
23222	0.662
23223	0.645
23224	0.532
23225	0.414
23231	0.709
23232	0.643
23233	0.626

Health State (5L profile)	US
23234	0.514
23235	0.399
23241	0.582
23242	0.522
23243	0.507
23244	0.418
23245	0.326
23251	0.390
23252	0.341
23253	0.328
23254	0.273
23255	0.216
23311	0.782
23312	0.729
23313	0.716
23314	0.596
23315	0.472
23321	0.716
23322	0.649
23323	0.632
23324	0.521
23325	0.405
23331	0.700
23332	0.630
23333	0.611
23334	0.502
23335	0.389
23341	0.574
23342	0.511
23343	0.494
23344	0.408
23345	0.318
23351	0.385
23352	0.332
23353	0.319
23354	0.266
23355	0.211
23411	0.714
23412	0.667
23413	0.655
23414	0.554
23415	0.449
23421	0.654
23422	0.593
23423	0.577
23424	0.484
23425	0.388
23431	0.639
23432	0.574
23433	0.558
23434	0.467

Health State (5L profile)	US
23435	0.373
23441	0.528
23442	0.471
23443	0.456
23444	0.381
23445	0.303
23451	0.362
23452	0.315
23453	0.303
23454	0.251
23455	0.197
23511	0.576
23512	0.540
23513	0.531
23514	0.468
23515	0.402
23521	0.527
23522	0.477
23523	0.464
23524	0.409
23525	0.352
23531	0.515
23532	0.462
23533	0.448
23534	0.395
23535	0.340
23541	0.435
23542	0.389
23543	0.377
23544	0.325
23545	0.272
23551	0.315
23552	0.279
23553	0.270
23554	0.221
23555	0.170
24111	0.741
24112	0.709
24113	0.701
24114	0.584
24115	0.463
24121	0.695
24122	0.650
24123	0.638
24124	0.530
24125	0.418
24131	0.684
24132	0.636
24133	0.623
24134	0.517
24135	0.407

Health State (5L profile)	US
24141	0.561
24142	0.519
24143	0.508
24144	0.420
24145	0.328
24151	0.376
24152	0.344
24153	0.336
24154	0.274
24155	0.210
24211	0.722
24212	0.677
24213	0.665
24214	0.557
24215	0.444
24221	0.663
24222	0.604
24223	0.589
24224	0.489
24225	0.385
24231	0.648
24232	0.586
24233	0.570
24234	0.472
24235	0.371
24241	0.532
24242	0.477
24243	0.462
24244	0.382
24245	0.299
24251	0.357
24252	0.312
24253	0.301
24254	0.247
24255	0.191
24311	0.717
24312	0.669
24313	0.656
24314	0.550
24315	0.440
24321	0.655
24322	0.593
24323	0.577
24324	0.479
24325	0.377
24331	0.640
24332	0.574
24333	0.557
24334	0.461
24335	0.362
24341	0.525

Health State (5L profile)	US
24342	0.466
24343	0.451
24344	0.373
24345	0.292
24351	0.353
24352	0.305
24353	0.292
24354	0.240
24355	0.186
24411	0.659
24412	0.616
24413	0.604
24414	0.513
24415	0.418
24421	0.602
24422	0.545
24423	0.531
24424	0.447
24425	0.361
24431	0.588
24432	0.528
24433	0.512
24434	0.431
24435	0.347
24441	0.485
24442	0.432
24443	0.418
24444	0.349
24445	0.277
24451	0.331
24452	0.288
24453	0.277
24454	0.226
24455	0.173
24511	0.539
24512	0.507
24513	0.499
24514	0.437
24515	0.372
24521	0.494
24522	0.448
24523	0.437
24524	0.383
24525	0.327
24531	0.483
24532	0.434
24533	0.421
24534	0.369
24535	0.315
24541	0.404
24542	0.362

Health State (5L profile)	US
24543	0.351
24544	0.301
24545	0.248
24551	0.286
24552	0.254
24553	0.245
24554	0.197
24555	0.148
25111	0.523
25112	0.503
25113	0.498
25114	0.425
25115	0.349
25121	0.490
25122	0.457
25123	0.449
25124	0.383
25125	0.315
25131	0.481
25132	0.446
25133	0.437
25134	0.373
25135	0.307
25141	0.394
25142	0.365
25143	0.357
25144	0.295
25145	0.232
25151	0.262
25152	0.242
25153	0.237
25154	0.179
25155	0.118
25211	0.517
25212	0.484
25213	0.475
25214	0.410
25215	0.342
25221	0.470
25222	0.424
25223	0.412
25224	0.355
25225	0.296
25231	0.459
25232	0.409
25233	0.397
25234	0.342
25235	0.284
25241	0.377
25242	0.335
25243	0.324

Health State (5L profile)	US
25244	0.270
25245	0.215
25251	0.255
25252	0.223
25253	0.214
25254	0.164
25255	0.111
25311	0.515
25312	0.479
25313	0.470
25314	0.406
25315	0.340
25321	0.465
25322	0.416
25323	0.403
25324	0.348
25325	0.291
25331	0.453
25332	0.400
25333	0.387
25334	0.334
25335	0.279
25341	0.373
25342	0.328
25343	0.316
25344	0.264
25345	0.211
25351	0.253
25352	0.218
25353	0.209
25354	0.160
25355	0.109
25411	0.486
25412	0.455
25413	0.447
25414	0.385
25415	0.320
25421	0.441
25422	0.397
25423	0.386
25424	0.332
25425	0.276
25431	0.430
25432	0.383
25433	0.371
25434	0.319
25435	0.265
25441	0.352
25442	0.311
25443	0.301
25444	0.251

Health State (5L profile)	US
25445	0.199
25451	0.234
25452	0.203
25453	0.195
25454	0.148
25455	0.099
25511	0.425
25512	0.405
25513	0.400
25514	0.341
25515	0.280
25521	0.391
25522	0.359
25523	0.350
25524	0.299
25525	0.247
25531	0.383
25532	0.347
25533	0.338
25534	0.289
25535	0.238
25541	0.308
25542	0.278
25543	0.270
25544	0.223
25545	0.174
25551	0.194
25552	0.173
25553	0.168
25554	0.124
25555	0.078
31111	0.854
31112	0.833
31113	0.827
31114	0.688
31115	0.543
31121	0.819
31122	0.783
31123	0.774
31124	0.643
31125	0.508
31131	0.810
31132	0.771
31133	0.761
31134	0.632
31135	0.499
31141	0.669
31142	0.637
31143	0.628
31144	0.522
31145	0.412

Health State (5L profile)	US
31151	0.456
31152	0.435
31153	0.429
31154	0.357
31155	0.282
31211	0.845
31212	0.810
31213	0.801
31214	0.670
31215	0.535
31221	0.796
31222	0.748
31223	0.735
31224	0.613
31225	0.486
31231	0.784
31232	0.732
31233	0.719
31234	0.598
31235	0.473
31241	0.650
31242	0.604
31243	0.593
31244	0.495
31245	0.393
31251	0.448
31252	0.413
31253	0.403
31254	0.340
31255	0.273
31311	0.843
31312	0.804
31313	0.794
31314	0.666
31315	0.533
31321	0.791
31322	0.739
31323	0.725
31324	0.605
31325	0.480
31331	0.778
31332	0.723
31333	0.708
31334	0.590
31335	0.467
31341	0.645
31342	0.597
31343	0.584
31344	0.488
31345	0.389
31351	0.446

Health State (5L profile)	US
31352	0.407
31353	0.397
31354	0.335
31355	0.271
31411	0.769
31412	0.736
31413	0.728
31414	0.618
31415	0.504
31421	0.723
31422	0.676
31423	0.664
31424	0.563
31425	0.457
31431	0.711
31432	0.662
31433	0.649
31434	0.549
31435	0.445
31441	0.594
31442	0.551
31443	0.539
31444	0.455
31445	0.368
31451	0.417
31452	0.384
31453	0.375
31454	0.315
31455	0.252
31511	0.619
31512	0.598
31513	0.592
31514	0.520
31515	0.445
31521	0.584
31522	0.549
31523	0.540
31524	0.476
31525	0.410
31531	0.575
31532	0.537
31533	0.527
31534	0.465
31535	0.401
31541	0.488
31542	0.457
31543	0.449
31544	0.389
31545	0.326
31551	0.358
31552	0.337

Health State (5L profile)	US
31553	0.331
31554	0.274
31555	0.214
32111	0.816
32112	0.780
32113	0.770
32114	0.640
32115	0.505
32121	0.766
32122	0.716
32123	0.704
32124	0.582
32125	0.455
32131	0.753
32132	0.701
32133	0.687
32134	0.567
32135	0.443
32141	0.619
32142	0.573
32143	0.561
32144	0.464
32145	0.364
32151	0.418
32152	0.382
32153	0.372
32154	0.309
32155	0.244
32211	0.792
32212	0.743
32213	0.730
32214	0.608
32215	0.482
32221	0.729
32222	0.666
32223	0.650
32224	0.536
32225	0.419
32231	0.714
32232	0.647
32233	0.630
32234	0.518
32235	0.403
32241	0.586
32242	0.527
32243	0.511
32244	0.422
32245	0.330
32251	0.395
32252	0.346
32253	0.333

Health State (5L profile)	US
32254	0.278
32255	0.221
32311	0.786
32312	0.734
32313	0.720
32314	0.600
32315	0.476
32321	0.720
32322	0.654
32323	0.636
32324	0.525
32325	0.410
32331	0.704
32332	0.634
32333	0.616
32334	0.506
32335	0.393
32341	0.578
32342	0.515
32343	0.499
32344	0.412
32345	0.322
32351	0.389
32352	0.337
32353	0.323
32354	0.270
32355	0.215
32411	0.719
32412	0.672
32413	0.659
32414	0.558
32415	0.454
32421	0.658
32422	0.597
32423	0.581
32424	0.489
32425	0.392
32431	0.643
32432	0.579
32433	0.562
32434	0.471
32435	0.377
32441	0.533
32442	0.475
32443	0.460
32444	0.385
32445	0.307
32451	0.367
32452	0.319
32453	0.307
32454	0.255

Health State (5L profile)	US
32455	0.202
32511	0.581
32512	0.545
32513	0.535
32514	0.472
32515	0.407
32521	0.531
32522	0.482
32523	0.469
32524	0.414
32525	0.357
32531	0.519
32532	0.466
32533	0.452
32534	0.399
32535	0.344
32541	0.440
32542	0.393
32543	0.381
32544	0.330
32545	0.277
32551	0.320
32552	0.284
32553	0.274
32554	0.226
32555	0.175
33111	0.808
33112	0.769
33113	0.759
33114	0.630
33115	0.497
33121	0.755
33122	0.703
33123	0.689
33124	0.569
33125	0.445
33131	0.742
33132	0.687
33133	0.672
33134	0.554
33135	0.432
33141	0.609
33142	0.561
33143	0.548
33144	0.453
33145	0.354
33151	0.410
33152	0.371
33153	0.361
33154	0.300
33155	0.236

Health State (5L profile)	US
33211	0.782
33212	0.729
33213	0.716
33214	0.596
33215	0.471
33221	0.716
33222	0.650
33223	0.633
33224	0.521
33225	0.405
33231	0.700
33232	0.630
33233	0.612
33234	0.502
33235	0.389
33241	0.574
33242	0.511
33243	0.495
33244	0.408
33245	0.317
33251	0.384
33252	0.332
33253	0.319
33254	0.265
33255	0.210
33311	0.775
33312	0.720
33313	0.705
33314	0.587
33315	0.465
33321	0.706
33322	0.637
33323	0.619
33324	0.509
33325	0.395
33331	0.689
33332	0.616
33333	0.597
33334	0.490
33335	0.378
33341	0.565
33342	0.499
33343	0.482
33344	0.397
33345	0.309
33351	0.378
33352	0.323
33353	0.308
33354	0.257
33355	0.204
33411	0.709

Health State (5L profile)	US
33412	0.659
33413	0.646
33414	0.546
33415	0.443
33421	0.645
33422	0.581
33423	0.565
33424	0.474
33425	0.379
33431	0.630
33432	0.562
33433	0.545
33434	0.456
33435	0.363
33441	0.520
33442	0.460
33443	0.444
33444	0.371
33445	0.295
33451	0.356
33452	0.306
33453	0.293
33454	0.244
33455	0.192
33511	0.573
33512	0.534
33513	0.524
33514	0.463
33515	0.399
33521	0.521
33522	0.468
33523	0.454
33524	0.401
33525	0.346
33531	0.508
33532	0.452
33533	0.437
33534	0.386
33535	0.333
33541	0.430
33542	0.380
33543	0.368
33544	0.318
33545	0.267
33551	0.312
33552	0.273
33553	0.263
33554	0.216
33555	0.167
34111	0.739
34112	0.704

Health State (5L profile)	US
34113	0.695
34114	0.580
34115	0.461
34121	0.690
34122	0.642
34123	0.629
34124	0.523
34125	0.413
34131	0.678
34132	0.627
34133	0.613
34134	0.509
34135	0.401
34141	0.556
34142	0.512
34143	0.500
34144	0.413
34145	0.324
34151	0.374
34152	0.339
34153	0.330
34154	0.270
34155	0.207
34211	0.717
34212	0.668
34213	0.656
34214	0.550
34215	0.439
34221	0.655
34222	0.593
34223	0.577
34224	0.479
34225	0.377
34231	0.639
34232	0.574
34233	0.557
34234	0.461
34235	0.362
34241	0.525
34242	0.466
34243	0.451
34244	0.373
34245	0.291
34251	0.352
34252	0.304
34253	0.292
34254	0.240
34255	0.186
34311	0.711
34312	0.660
34313	0.646

Health State (5L profile)	US
34314	0.542
34315	0.434
34321	0.646
34322	0.581
34323	0.564
34324	0.468
34325	0.369
34331	0.630
34332	0.561
34333	0.543
34334	0.450
34335	0.352
34341	0.517
34342	0.455
34343	0.439
34344	0.363
34345	0.284
34351	0.347
34352	0.296
34353	0.282
34354	0.232
34355	0.180
34411	0.654
34412	0.608
34413	0.596
34414	0.506
34415	0.413
34421	0.594
34422	0.535
34423	0.519
34424	0.438
34425	0.353
34431	0.580
34432	0.516
34433	0.500
34434	0.421
34435	0.338
34441	0.478
34442	0.422
34443	0.407
34444	0.340
34445	0.270
34451	0.326
34452	0.280
34453	0.268
34454	0.219
34455	0.169
34511	0.537
34512	0.502
34513	0.493
34514	0.433

Health State (5L profile)	US
34515	0.370
34521	0.489
34522	0.440
34523	0.428
34524	0.375
34525	0.321
34531	0.477
34532	0.425
34533	0.411
34534	0.361
34535	0.309
34541	0.400
34542	0.354
34543	0.343
34544	0.294
34545	0.244
34551	0.283
34552	0.248
34553	0.239
34554	0.193
34555	0.145
35111	0.522
35112	0.501
35113	0.495
35114	0.423
35115	0.348
35121	0.487
35122	0.452
35123	0.443
35124	0.379
35125	0.313
35131	0.478
35132	0.440
35133	0.430
35134	0.368
35135	0.304
35141	0.391
35142	0.360
35143	0.352
35144	0.292
35145	0.229
35151	0.261
35152	0.240
35153	0.234
35154	0.177
35155	0.117
35211	0.514
35212	0.479
35213	0.469
35214	0.406
35215	0.339

Health State (5L profile)	US
35221	0.465
35222	0.416
35223	0.403
35224	0.348
35225	0.290
35231	0.452
35232	0.400
35233	0.387
35234	0.334
35235	0.278
35241	0.372
35242	0.327
35243	0.315
35244	0.264
35245	0.210
35251	0.252
35252	0.217
35253	0.208
35254	0.159
35255	0.108
35311	0.512
35312	0.473
35313	0.463
35314	0.401
35315	0.337
35321	0.459
35322	0.407
35323	0.393
35324	0.340
35325	0.285
35331	0.446
35332	0.391
35333	0.376
35334	0.325
35335	0.272
35341	0.368
35342	0.319
35343	0.307
35344	0.257
35345	0.206
35351	0.250
35352	0.212
35353	0.202
35354	0.155
35355	0.106
35411	0.483
35412	0.450
35413	0.441
35414	0.381
35415	0.318
35421	0.436

Health State (5L profile)	US
35422	0.389
35423	0.377
35424	0.325
35425	0.271
35431	0.424
35432	0.374
35433	0.361
35434	0.312
35435	0.260
35441	0.347
35442	0.304
35443	0.293
35444	0.245
35445	0.195
35451	0.231
35452	0.198
35453	0.190
35454	0.144
35455	0.097
35511	0.424
35512	0.403
35513	0.397
35514	0.339
35515	0.279
35521	0.389
35522	0.353
35523	0.344
35524	0.295
35525	0.244
35531	0.380
35532	0.341
35533	0.331
35534	0.284
35535	0.235
35541	0.305
35542	0.273
35543	0.265
35544	0.219
35545	0.172
35551	0.193
35552	0.171
35553	0.165
35554	0.122
35555	0.077
41111	0.824
41112	0.804
41113	0.798
41114	0.663
41115	0.523
41121	0.790
41122	0.755

Health State (5L profile)	US
41123	0.747
41124	0.620
41125	0.489
41131	0.781
41132	0.744
41133	0.734
41134	0.609
41135	0.480
41141	0.643
41142	0.612
41143	0.604
41144	0.501
41145	0.394
41151	0.436
41152	0.415
41153	0.410
41154	0.339
41155	0.264
41211	0.816
41212	0.782
41213	0.773
41214	0.647
41215	0.516
41221	0.769
41222	0.721
41223	0.708
41224	0.590
41225	0.468
41231	0.757
41232	0.706
41233	0.692
41234	0.576
41235	0.456
41241	0.626
41242	0.581
41243	0.570
41244	0.475
41245	0.376
41251	0.429
41252	0.394
41253	0.386
41254	0.322
41255	0.256
41311	0.814
41312	0.777
41313	0.767
41314	0.643
41315	0.514
41321	0.763
41322	0.712
41323	0.699

Health State (5L profile)	US
41324	0.583
41325	0.462
41331	0.751
41332	0.696
41333	0.682
41334	0.568
41335	0.450
41341	0.621
41342	0.574
41343	0.561
41344	0.468
41345	0.371
41351	0.427
41352	0.389
41353	0.380
41354	0.318
41355	0.254
41411	0.744
41412	0.711
41413	0.703
41414	0.596
41415	0.485
41421	0.698
41422	0.653
41423	0.641
41424	0.542
41425	0.439
41431	0.687
41432	0.638
41433	0.625
41434	0.529
41435	0.428
41441	0.572
41442	0.530
41443	0.519
41444	0.437
41445	0.351
41451	0.398
41452	0.366
41453	0.358
41454	0.298
41455	0.236
41511	0.599
41512	0.578
41513	0.573
41514	0.501
41515	0.427
41521	0.565
41522	0.531
41523	0.522
41524	0.459

Health State (5L profile)	US
41525	0.393
41531	0.556
41532	0.519
41533	0.509
41534	0.448
41535	0.384
41541	0.470
41542	0.439
41543	0.431
41544	0.372
41545	0.310
41551	0.340
41552	0.320
41553	0.314
41554	0.257
41555	0.198
42111	0.787
42112	0.752
42113	0.743
42114	0.617
42115	0.486
42121	0.738
42122	0.690
42123	0.677
42124	0.560
42125	0.437
42131	0.726
42132	0.674
42133	0.661
42134	0.545
42135	0.425
42141	0.595
42142	0.550
42143	0.539
42144	0.444
42145	0.346
42151	0.399
42152	0.364
42153	0.355
42154	0.292
42155	0.227
42211	0.764
42212	0.716
42213	0.704
42214	0.586
42215	0.464
42221	0.703
42222	0.641
42223	0.624
42224	0.515
42225	0.402

Health State (5L profile)	US
42231	0.687
42232	0.622
42233	0.605
42234	0.498
42235	0.386
42241	0.563
42242	0.505
42243	0.490
42244	0.403
42245	0.314
42251	0.377
42252	0.329
42253	0.316
42254	0.262
42255	0.205
42311	0.759
42312	0.707
42313	0.694
42314	0.578
42315	0.459
42321	0.694
42322	0.629
42323	0.612
42324	0.504
42325	0.393
42331	0.678
42332	0.609
42333	0.591
42334	0.486
42335	0.377
42341	0.555
42342	0.494
42343	0.477
42344	0.393
42345	0.306
42351	0.372
42352	0.320
42353	0.307
42354	0.254
42355	0.200
42411	0.694
42412	0.648
42413	0.636
42414	0.538
42415	0.436
42421	0.635
42422	0.575
42423	0.559
42424	0.469
42425	0.376
42431	0.620

Health State (5L profile)	US
42432	0.557
42433	0.540
42434	0.452
42435	0.361
42441	0.512
42442	0.455
42443	0.441
42444	0.367
42445	0.291
42451	0.349
42452	0.303
42453	0.291
42454	0.240
42455	0.187
42511	0.562
42512	0.527
42513	0.518
42514	0.455
42515	0.390
42521	0.513
42522	0.465
42523	0.452
42524	0.398
42525	0.341
42531	0.501
42532	0.449
42533	0.436
42534	0.383
42535	0.329
42541	0.422
42542	0.377
42543	0.365
42544	0.314
42545	0.261
42551	0.303
42552	0.268
42553	0.259
42554	0.210
42555	0.160
43111	0.779
43112	0.741
43113	0.732
43114	0.607
43115	0.478
43121	0.728
43122	0.677
43123	0.663
43124	0.547
43125	0.427
43131	0.715
43132	0.660

Health State (5L profile)	US
43133	0.646
43134	0.533
43135	0.414
43141	0.585
43142	0.538
43143	0.525
43144	0.433
43145	0.336
43151	0.391
43152	0.353
43153	0.344
43154	0.282
43155	0.219
43211	0.754
43212	0.703
43213	0.690
43214	0.574
43215	0.454
43221	0.689
43222	0.625
43223	0.608
43224	0.500
43225	0.389
43231	0.673
43232	0.605
43233	0.587
43234	0.482
43235	0.372
43241	0.551
43242	0.489
43243	0.473
43244	0.389
43245	0.301
43251	0.367
43252	0.316
43253	0.302
43254	0.249
43255	0.195
43311	0.748
43312	0.693
43313	0.679
43314	0.566
43315	0.448
43321	0.680
43322	0.612
43323	0.594
43324	0.488
43325	0.379
43331	0.663
43332	0.591
43333	0.573

Health State (5L profile)	US
43334	0.469
43335	0.362
43341	0.542
43342	0.477
43343	0.461
43344	0.378
43345	0.293
43351	0.361
43352	0.306
43353	0.292
43354	0.241
43355	0.189
43411	0.684
43412	0.635
43413	0.623
43414	0.526
43415	0.426
43421	0.622
43422	0.559
43423	0.543
43424	0.455
43425	0.363
43431	0.606
43432	0.540
43433	0.523
43434	0.437
43435	0.347
43441	0.500
43442	0.440
43443	0.425
43444	0.353
43445	0.279
43451	0.339
43452	0.290
43453	0.277
43454	0.228
43455	0.177
43511	0.554
43512	0.516
43513	0.507
43514	0.445
43515	0.382
43521	0.503
43522	0.452
43523	0.438
43524	0.385
43525	0.330
43531	0.490
43532	0.435
43533	0.421
43534	0.370

Health State (5L profile)	US
43535	0.318
43541	0.412
43542	0.364
43543	0.352
43544	0.303
43545	0.252
43551	0.295
43552	0.257
43553	0.248
43554	0.201
43555	0.152
44111	0.712
44112	0.678
44113	0.669
44114	0.558
44115	0.442
44121	0.664
44122	0.618
44123	0.605
44124	0.502
44125	0.395
44131	0.653
44132	0.602
44133	0.589
44134	0.488
44135	0.384
44141	0.534
44142	0.490
44143	0.479
44144	0.394
44145	0.306
44151	0.355
44152	0.322
44153	0.313
44154	0.253
44155	0.190
44211	0.691
44212	0.644
44213	0.632
44214	0.529
44215	0.422
44221	0.630
44222	0.570
44223	0.554
44224	0.459
44225	0.361
44231	0.615
44232	0.551
44233	0.535
44234	0.442
44235	0.346

Health State (5L profile)	US
44241	0.503
44242	0.446
44243	0.431
44244	0.355
44245	0.276
44251	0.335
44252	0.288
44253	0.276
44254	0.224
44255	0.170
44311	0.686
44312	0.636
44313	0.622
44314	0.521
44315	0.417
44321	0.622
44322	0.558
44323	0.541
44324	0.449
44325	0.352
44331	0.606
44332	0.539
44333	0.521
44334	0.430
44335	0.336
44341	0.496
44342	0.435
44343	0.419
44344	0.345
44345	0.268
44351	0.330
44352	0.279
44353	0.266
44354	0.217
44355	0.165
44411	0.631
44412	0.586
44413	0.574
44414	0.487
44415	0.396
44421	0.572
44422	0.514
44423	0.499
44424	0.419
44425	0.337
44431	0.558
44432	0.496
44433	0.480
44434	0.403
44435	0.322
44441	0.458

Health State (5L profile)	US
44442	0.403
44443	0.389
44444	0.323
44445	0.255
44451	0.309
44452	0.264
44453	0.252
44454	0.204
44455	0.154
44511	0.518
44512	0.485
44513	0.476
44514	0.416
44515	0.353
44521	0.471
44522	0.424
44523	0.411
44524	0.360
44525	0.306
44531	0.460
44532	0.409
44533	0.395
44534	0.346
44535	0.294
44541	0.382
44542	0.338
44543	0.327
44544	0.279
44545	0.229
44551	0.266
44552	0.233
44553	0.224
44554	0.178
44555	0.131
45111	0.502
45112	0.481
45113	0.476
45114	0.404
45115	0.330
45121	0.468
45122	0.434
45123	0.425
45124	0.362
45125	0.296
45131	0.459
45132	0.422
45133	0.412
45134	0.351
45135	0.287
45141	0.373
45142	0.342

Health State (5L profile)	US
45143	0.334
45144	0.275
45145	0.213
45151	0.243
45152	0.223
45153	0.217
45154	0.160
45155	0.101
45211	0.495
45212	0.460
45213	0.452
45214	0.388
45215	0.322
45221	0.447
45222	0.399
45223	0.387
45224	0.332
45225	0.274
45231	0.435
45232	0.384
45233	0.370
45234	0.318
45235	0.263
45241	0.355
45242	0.311
45243	0.299
45244	0.248
45245	0.195
45251	0.235
45252	0.201
45253	0.193
45254	0.144
45255	0.093
45311	0.493
45312	0.455
45313	0.446
45314	0.384
45315	0.320
45321	0.441
45322	0.390
45323	0.377
45324	0.324
45325	0.269
45331	0.429
45332	0.374
45333	0.360
45334	0.309
45335	0.257
45341	0.350
45342	0.303
45343	0.291

Health State (5L profile)	US
45344	0.242
45345	0.191
45351	0.233
45352	0.196
45353	0.187
45354	0.140
45355	0.091
45411	0.464
45412	0.432
45413	0.424
45414	0.364
45415	0.302
45421	0.418
45422	0.373
45423	0.361
45424	0.310
45425	0.256
45431	0.407
45432	0.358
45433	0.345
45434	0.296
45435	0.245
45441	0.330
45442	0.288
45443	0.277
45444	0.229
45445	0.180
45451	0.215
45452	0.183
45453	0.175
45454	0.129
45455	0.082
45511	0.406
45512	0.386
45513	0.380
45514	0.323
45515	0.263
45521	0.372
45522	0.337
45523	0.328
45524	0.280
45525	0.229
45531	0.363
45532	0.325
45533	0.316
45534	0.269
45535	0.220
45541	0.289
45542	0.258
45543	0.250
45544	0.205

Health State (5L profile)	US
45545	0.158
45551	0.177
45552	0.156
45553	0.150
45554	0.108
45555	0.064
51111	0.442
51112	0.429
51113	0.426
51114	0.349
51115	0.268
51121	0.416
51122	0.396
51123	0.391
51124	0.318
51125	0.242
51131	0.409
51132	0.388
51133	0.382
51134	0.310
51135	0.235
51141	0.318
51142	0.300
51143	0.295
51144	0.227
51145	0.156
51151	0.181
51152	0.168
51153	0.165
51154	0.102
51155	0.037
51211	0.442
51212	0.422
51213	0.417
51214	0.344
51215	0.268
51221	0.409
51222	0.377
51223	0.368
51224	0.303
51225	0.235
51231	0.400
51232	0.365
51233	0.356
51234	0.293
51235	0.226
51241	0.313
51242	0.284
51243	0.276
51244	0.215
51245	0.150

Health State (5L profile)	US
51251	0.181
51252	0.161
51253	0.156
51254	0.097
51255	0.036
51311	0.442
51312	0.421
51313	0.415
51314	0.343
51315	0.268
51321	0.407
51322	0.372
51323	0.363
51324	0.299
51325	0.233
51331	0.398
51332	0.360
51333	0.350
51334	0.288
51335	0.224
51341	0.311
51342	0.280
51343	0.272
51344	0.211
51345	0.149
51351	0.181
51352	0.160
51353	0.154
51354	0.096
51355	0.036
51411	0.410
51412	0.391
51413	0.386
51414	0.317
51415	0.245
51421	0.378
51422	0.347
51423	0.340
51424	0.277
51425	0.213
51431	0.369
51432	0.337
51433	0.328
51434	0.268
51435	0.205
51441	0.285
51442	0.258
51443	0.251
51444	0.193
51445	0.132
51451	0.158

Health State (5L profile)	US
51452	0.140
51453	0.135
51454	0.080
51455	0.023
51511	0.344
51512	0.331
51513	0.327
51514	0.264
51515	0.199
51521	0.318
51522	0.297
51523	0.292
51524	0.233
51525	0.173
51531	0.311
51532	0.289
51533	0.283
51534	0.226
51535	0.166
51541	0.232
51542	0.213
51543	0.208
51544	0.154
51545	0.099
51551	0.112
51552	0.099
51553	0.096
51554	0.047
51555	-0.003
52111	0.413
52112	0.392
52113	0.387
52114	0.314
52115	0.238
52121	0.379
52122	0.346
52123	0.338
52124	0.272
52125	0.204
52131	0.371
52132	0.335
52133	0.325
52134	0.262
52135	0.196
52141	0.283
52142	0.253
52143	0.246
52144	0.184
52145	0.120
52151	0.151
52152	0.131

Health State (5L profile)	US
52153	0.126
52154	0.068
52155	0.007
52211	0.406
52212	0.373
52213	0.364
52214	0.299
52215	0.231
52221	0.359
52222	0.313
52223	0.301
52224	0.244
52225	0.185
52231	0.347
52232	0.298
52233	0.285
52234	0.230
52235	0.173
52241	0.266
52242	0.223
52243	0.212
52244	0.159
52245	0.104
52251	0.144
52252	0.112
52253	0.103
52254	0.052
52255	-0.001
52311	0.404
52312	0.368
52313	0.358
52314	0.295
52315	0.230
52321	0.354
52322	0.305
52323	0.292
52324	0.237
52325	0.180
52331	0.341
52332	0.289
52333	0.275
52334	0.222
52335	0.167
52341	0.262
52342	0.216
52343	0.204
52344	0.153
52345	0.100
52351	0.143
52352	0.107
52353	0.097

Health State (5L profile)	US
52354	0.049
52355	-0.002
52411	0.374
52412	0.344
52413	0.336
52414	0.274
52415	0.210
52421	0.330
52422	0.286
52423	0.275
52424	0.221
52425	0.165
52431	0.319
52432	0.272
52433	0.259
52434	0.208
52435	0.154
52441	0.240
52442	0.200
52443	0.189
52444	0.140
52445	0.088
52451	0.123
52452	0.092
52453	0.084
52454	0.037
52455	-0.012
52511	0.314
52512	0.294
52513	0.289
52514	0.230
52515	0.170
52521	0.280
52522	0.248
52523	0.239
52524	0.189
52525	0.136
52531	0.272
52532	0.236
52533	0.227
52534	0.178
52535	0.128
52541	0.196
52542	0.167
52543	0.159
52544	0.112
52545	0.064
52551	0.083
52552	0.062
52553	0.057
52554	0.013

Health State (5L profile)	US
52555	-0.032
53111	0.407
53112	0.385
53113	0.379
53114	0.307
53115	0.232
53121	0.372
53122	0.336
53123	0.327
53124	0.263
53125	0.197
53131	0.363
53132	0.324
53133	0.314
53134	0.252
53135	0.188
53141	0.276
53142	0.244
53143	0.236
53144	0.176
53145	0.113
53151	0.145
53152	0.124
53153	0.118
53154	0.061
53155	0.001
53211	0.398
53212	0.363
53213	0.353
53214	0.290
53215	0.224
53221	0.349
53222	0.300
53223	0.287
53224	0.232
53225	0.175
53231	0.337
53232	0.284
53233	0.271
53234	0.218
53235	0.162
53241	0.257
53242	0.211
53243	0.199
53244	0.148
53245	0.094
53251	0.137
53252	0.102
53253	0.092
53254	0.043
53255	-0.008

Health State (5L profile)	US
53311	0.396
53312	0.357
53313	0.347
53314	0.286
53315	0.222
53321	0.343
53322	0.291
53323	0.277
53324	0.224
53325	0.169
53331	0.330
53332	0.275
53333	0.260
53334	0.209
53335	0.156
53341	0.252
53342	0.203
53343	0.191
53344	0.141
53345	0.090
53351	0.135
53352	0.096
53353	0.086
53354	0.039
53355	-0.010
53411	0.367
53412	0.334
53413	0.325
53414	0.265
53415	0.203
53421	0.320
53422	0.274
53423	0.261
53424	0.210
53425	0.156
53431	0.308
53432	0.259
53433	0.246
53434	0.196
53435	0.144
53441	0.232
53442	0.188
53443	0.177
53444	0.129
53445	0.079
53451	0.116
53452	0.083
53453	0.074
53454	0.028
53455	-0.019
53511	0.308

Health State (5L profile)	US
53512	0.287
53513	0.281
53514	0.224
53515	0.164
53521	0.273
53522	0.238
53523	0.229
53524	0.180
53525	0.129
53531	0.264
53532	0.226
53533	0.216
53534	0.169
53535	0.120
53541	0.189
53542	0.158
53543	0.149
53544	0.104
53545	0.057
53551	0.077
53552	0.055
53553	0.049
53554	0.006
53555	-0.038
54111	0.368
54112	0.348
54113	0.343
54114	0.273
54115	0.200
54121	0.335
54122	0.303
54123	0.295
54124	0.232
54125	0.167
54131	0.327
54132	0.292
54133	0.283
54134	0.222
54135	0.159
54141	0.242
54142	0.213
54143	0.206
54144	0.147
54145	0.086
54151	0.114
54152	0.094
54153	0.089
54154	0.034
54155	-0.024
54211	0.361
54212	0.330

Health State (5L profile)	US
54213	0.321
54214	0.259
54215	0.194
54221	0.316
54222	0.271
54223	0.259
54224	0.205
54225	0.149
54231	0.305
54232	0.256
54233	0.244
54234	0.192
54235	0.138
54241	0.226
54242	0.184
54243	0.173
54244	0.123
54245	0.071
54251	0.107
54252	0.076
54253	0.068
54254	0.020
54255	-0.030
54311	0.360
54312	0.325
54313	0.316
54314	0.256
54315	0.193
54321	0.311
54322	0.263
54323	0.251
54324	0.198
54325	0.144
54331	0.299
54332	0.248
54333	0.234
54334	0.184
54335	0.132
54341	0.222
54342	0.177
54343	0.166
54344	0.117
54345	0.067
54351	0.106
54352	0.071
54353	0.062
54354	0.016
54355	-0.032
54411	0.332
54412	0.303
54413	0.295

Health State (5L profile)	US
54414	0.236
54415	0.175
54421	0.289
54422	0.246
54423	0.235
54424	0.185
54425	0.132
54431	0.278
54432	0.232
54433	0.220
54434	0.172
54435	0.121
54441	0.202
54442	0.163
54443	0.153
54444	0.106
54445	0.057
54451	0.088
54452	0.059
54453	0.051
54454	0.006
54455	-0.040
54511	0.276
54512	0.257
54513	0.252
54514	0.197
54515	0.140
54521	0.243
54522	0.212
54523	0.204
54524	0.156
54525	0.106
54531	0.235
54532	0.201
54533	0.192
54534	0.146
54535	0.098
54541	0.162
54542	0.134
54543	0.126
54544	0.082
54545	0.037
54551	0.053
54552	0.033
54553	0.027
54554	-0.013
54555	-0.055
55111	0.247
55112	0.234
55113	0.230
55114	0.167

Health State (5L profile)	US
55115	0.102
55121	0.221
55122	0.200
55123	0.195
55124	0.136
55125	0.076
55131	0.214
55132	0.192
55133	0.186
55134	0.129
55135	0.069
55141	0.135
55142	0.116
55143	0.111
55144	0.057
55145	0.002
55151	0.016
55152	0.003
55153	-0.001
55154	-0.050
55155	-0.100
55211	0.247
55212	0.227
55213	0.222
55214	0.163
55215	0.102
55221	0.214
55222	0.181
55223	0.173
55224	0.122
55225	0.069
55231	0.205
55232	0.170
55233	0.160
55234	0.111
55235	0.060
55241	0.129
55242	0.100
55243	0.092
55244	0.045
55245	-0.004
55251	0.015
55252	-0.005
55253	-0.010
55254	-0.054
55255	-0.100
55311	0.247
55312	0.226
55313	0.220
55314	0.162
55315	0.102

Health State (5L profile)	US
55321	0.212
55322	0.176
55323	0.167
55324	0.118
55325	0.067
55331	0.203
55332	0.164
55333	0.154
55334	0.107
55335	0.058
55341	0.128
55342	0.096
55343	0.088
55344	0.042
55345	-0.005
55351	0.015
55352	-0.006
55353	-0.012
55354	-0.055
55355	-0.100
55411	0.224
55412	0.206
55413	0.201
55414	0.146
55415	0.089
55421	0.192
55422	0.162
55423	0.154
55424	0.106
55425	0.057
55431	0.184
55432	0.151
55433	0.142
55434	0.096
55435	0.049
55441	0.111
55442	0.084
55443	0.077
55444	0.033
55445	-0.012
55451	0.002
55452	-0.016
55453	-0.021
55454	-0.061
55455	-0.103
55511	0.178
55512	0.165
55513	0.162
55514	0.113
55515	0.063
55521	0.152

Health State (5L profile)	US
55522	0.132
55523	0.127
55524	0.083
55525	0.037
55531	0.145
55532	0.124
55533	0.118
55534	0.075
55535	0.030
55541	0.078
55542	0.060
55543	0.055
55544	0.015
55545	-0.026
55551	-0.024
55552	-0.037
55553	-0.040
55554	-0.074
55555	-0.109

9.10. Abbreviations

Abbreviation	Definition
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
APMP	Abuse Potential Monitoring Plan
AST	Aspartate aminotransferase
BLQ	Below limit of quantification
BUN	Blood urea nitrogen
C_{max}	Maximum observed plasma concentration
cAMP	Cyclic adenosine monophosphate
CFR	Code of Federal Regulations
CI	Confidence interval
CGI-I	Clinical Global Impressions - Improvement
CGI-S	Clinical Global Impressions – Severity of Illness
CIOMS	Council for International Organizations of Medical Sciences
COMT	Catechol-O-methyltransferase
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
C-QT	Concentration-QT
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
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
ICE	Intercurrent event
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IOP	Intraocular pressure
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
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LSMean	Least square mean
MAO	Monoamine oxidase
MAO-B	Monoamine oxidase B
MAR	Missing at random
MCAR	Missing completely at random
MNAR	Missing not at random
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
PGIC	Patient Global Impression of Change
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
TEAE	Treatment-emergent adverse event
THC	Tetrahydrocannabinol
TQT	Thorough QT
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
VAS	Visual analog scale
WBC	White blood cell