STATISTICAL ANALYSIS PLAN

A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY DARIGABAT IN PARTICIPANTS WITH PANIC DISORDER

Protocol Number: CVL-865-PA-2001

Compound: Darigabat (CVL-865)

Trial Phase: 2

Short Title: A Placebo-controlled Trial of Darigabat in Participants With Panic Disorder

Sponsor Name: Cerevel Therapeutics, LLC

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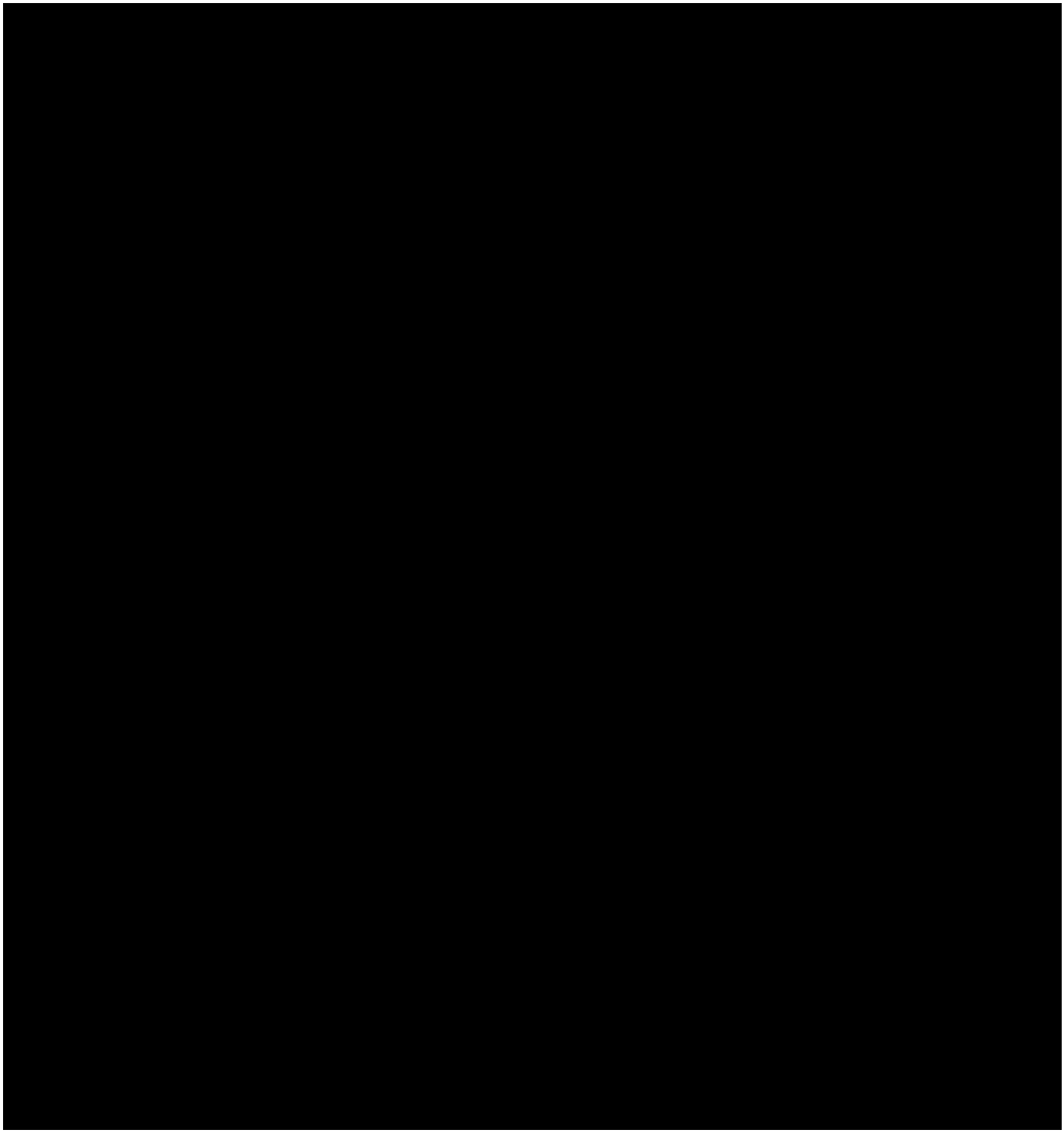
STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL



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1. INTRODUCTION

This document describes the statistical methods and data presentations planned for the analysis of efficacy and safety data from Protocol CVL-865-PA-2001. The table, listing and figure shells supporting the Statistical Analysis Plan (SAP) can be found in a separate SAP shell document.

Analysis methods described herein are based on the Clinical Study Protocol (CSP) amendment Version 3.0, dated 24 January 2024. In February 2025, the sponsor made a decision to close this exploratory study. This decision was not associated with any safety concerns. As a result, the analyses described in this SAP have been revised from those described in the CSP to reflect the adjusted scope applicable to the available data. Planned analyses described in this SAP will supersede those described in the CSP. This document will be finalized prior to database lock and unblinding.

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 Phase 2, randomized, double-blind, placebo-controlled, parallel-group, 14-week treatment period trial to evaluate the efficacy, safety, and tolerability of darigabat 25 mg twice daily (BID) in male and female participants aged 18 to 65 years, inclusive, who have a primary diagnosis of panic disorder based on the Diagnostic And Statistical Manual Of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) criteria (present for at least 6 months prior to the Screening Visit) and confirmed by the Mini International Neuropsychiatric Interview (MINI). Panic attacks will be defined per the DSM-5-TR criteria (APA, 2022). For an event to meet the definition of a panic attack, the participant must report experiencing 4 or more of the symptoms described in the DSM-5-TR definition of a panic attack and document the symptoms in the eDiary. The definition of panic attack per DSM-5-TR (APA, 2022) is an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes, and during which time 4 (or more) of the following symptoms occur:

- Palpitations, pounding heart, or accelerated heart rate
- Sweating
- Trembling or shaking
- Sensations of shortness of breath or smothering
- Feeling of choking
- Chest pain or discomfort
- Nausea or abdominal distress
- Feeling dizzy, unsteady, lightheaded, or faint
- Derealization (feelings of unreality) or depersonalization (being detached from oneself)

- Fear of losing control or "going crazy"
- Fear of dying
- Paresthesias (numbness or tingling sensation)
- Chills or hot flashes

The trial will include the following:

- Screening Period of at least 14 days and up to 28 days
  - Baseline Period of at least 14 days
- 14-week Treatment Period, including an initial two-week Titration Period and a 1 two-week Maintenance Period
- Approximately 4-week Safety Follow-up Period

Each participant will participate in the trial for up to 25 weeks. Participants who complete the 14-week Treatment Period of the trial may have the opportunity to receive post-trial supportive therapy offered via the sponsor.

Details of schedule of assessments are provided in Section 9.1.

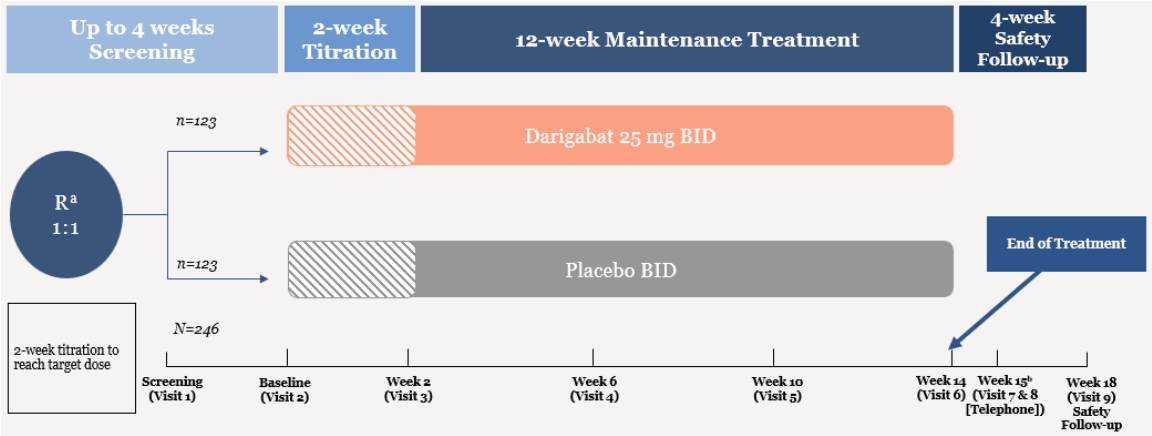
Approximately 246 participants who satisfy all inclusion/exclusion criteria and thus are eligible for the trial will be randomized in a 1:1 ratio to receive treatment with darigabat 25 mg BID or placebo BID. The randomization will be stratified by evidence-based psychotherapy for the treatment of anxiety disorders including panic disorder with 2 strata: receiving evidence-based psychotherapy (initiated >3 months prior to the Screening Visit) or not receiving evidence-based psychotherapy. Examples of evidence-based psychotherapy may include, but are not limited to, the following: Cognitive Behavioral Therapy (CBT), Mindfulness Based Cognitive Therapy (MBCT), Exposure and Response Prevention, Behavioral Activation, Acceptance and Commitment Therapy (ACT), Interpersonal Psychotherapy, Psychodynamic Therapy, Dialectical Behavioral Therapy, and/or Motivational Interviewing/Therapy.

Participants will initiate outpatient dosing beginning on Day 1 (the day after the Baseline Visit). During the two-week Titration Period, the participant's dose will be increased in a blinded fashion up to the randomized dose level (darigabat 25 mg BID or placebo BID). In the darigabat 25 mg BID group, darigabat will be administered as 5 mg BID for 1 week followed by 12.5 mg BID for another week during the Titration Period, and then 25 mg BID during the 1two-week Maintenance Treatment Period. The investigational medicinal product (IMP) will be taken orally.

Participants will continue to record all requested information in the eDiary for each day during both the two-week Titration and 1two-week Maintenance Treatment Periods.

The trial design is depicted in Figure 1.

Figure 1: Trial Schematic



Abbreviations: BID=twice daily; R=randomization.
Note: A summary of the dosing schedule, including doses during the Titration Period, is provided in Section 9.1
[a] Randomization occurs at Baseline (Visit 2).
[b] Visit 7 (Telephone) and Visit 8 (Telephone) will occur 3±1 days and 7±3 days after Visit 6, respectively.

1.2. Sample Size Considerations

A sample size of 114 participants per group (total of 228 participants) will provide at least 80% power to detect a difference of approximately 20% in proportion of participants (e.g., 60% of darigabat group versus 40% of placebo group) free of panic attacks at Week 14 at α=0.05 (2-sided).

Two-hundred forty-six participants will be randomized to account for 18 participants whose panic attack assessments were made prior to implementation of protocol eDiary requirements (i.e., assessments recorded contemporaneous to the day being assessed [minimizing any potential recall bias] and records of the presence as well as the absence of each DSM-5-TR panic attack symptom associated with a given panic attack [distinguishing between missing data and the absence of a specific symptom]).

1.3. Measures to Minimize Bias: Randomization and Blinding

1.3.1. Participant Assignment to Treatment

All participants will be centrally randomized in a 1:1 ratio to 1 of 2 treatment groups (placebo or darigabat 25 mg BID) at the Baseline Visit (Day -1) via an Interactive Response Technology (IRT) according to a computer-generated randomization scheme. Participants will be sequentially assigned to the next available randomization number and will receive the IMP that corresponds to that randomization number. Once a randomization number has been assigned, it will not be reassigned.

The randomization will be stratified by evidence-based psychotherapy for the treatment of anxiety disorders including panic disorder with 2 strata: receiving evidence-based psychotherapy (initiated >3 months prior to the Screening Visit) or not receiving evidence-based psychotherapy.

1.3.2. Blinding

The darigabat and placebo tablets will be identical in appearance and will be packaged in identically appearing blister packs and/or bottles. During the entire trial, treatment will be blinded such that participants, the blinded sponsor members/designee, raters for clinician-administered scales, the investigator, and other site and trial personnel will not have knowledge of the treatment assignment. Access to the treatment codes or unblinded kit assignments will be restricted to personnel who are responsible for generating and maintaining the randomization code, analyzing the pharmacokinetic (PK) blood samples, or unblinded sponsor personnel (for the purposes of packaging/managing IMP supply, supporting IRT, or reporting serious adverse events (SAEs) or adverse events of special interest (AESI) to regulatory agencies). Unblinded personnel are documented in the trial level Blinding Plan.

At the initiation of the trial, investigators and site personnel will be instructed on the method for breaking the blind. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of the treatment assignment for an individual participant is warranted. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the medical monitor before unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. The medical monitor must be notified within 24 hours after breaking the blind for a trial participant.

Documentation of unblinding should be recorded in the participant's medical record, including 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 participant, treatment with the IMP may not be reinitiated for that participant.

1.4. Treatment Period

Participants will initiate outpatient dosing beginning on Day 1 (the day after the Baseline Visit). During the two-week Titration Period, the participant's dose will be increased in a blinded fashion up to the randomized dose level (darigabat 25 mg BID or placebo BID). In the darigabat 25 mg BID group, darigabat will be administered as 5 mg BID for 1 week followed by 12.5 mg BID for another week during the Titration Period, and then 25 mg BID during the 1two-week Maintenance Treatment Period.

The dosing schedule is shown in Table 1.

Table 1: Dosing Schedule

Blinded Treatment Assignment	Titration Period		Begin Target Dose
	Day 1-7	Day 8-14	Day 15
Darigabat 25 mg BID	5 mg BID	12.5 mg BID	25 mg BID
Placebo	Matching Placebo	Matching Placebo	Matching Placebo

Abbreviation: BID=twice daily.

Participants will continue to record all requested information in the eDiary for each day during both the two-week Titration and 1two-week Maintenance Treatment Periods.

Follow-up telephone contacts will be performed within 3 days and 7 days after the last dose of IMP and an in-clinic follow-up visit will be performed approximately 33 days after the last dose of IMP. The Penn Physician Withdrawal Checklist (PWC) (Rickels et al, 2008).

will be used to monitor withdrawal symptoms approximately 3 days and 7 days after the last dose of IMP. Participants will continue to record all requested information in the eDiary for each day up to 7 days after the last dose of IMP. Participants should not begin taking their standard-of-care treatment for up to 7 days after the last dose of IMP, if possible.

2. OBJECTIVES AND ENDPOINTS

The trial objectives and endpoints are summarized in Table 2.

Table 2: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of darigabat as monotherapy in adult participants with panic disorder	Primary Efficacy Endpoint: • Proportion of participants free of panic attacks as assessed by participant daily eDiary during the last two weeks of the Maintenance Treatment Period Key Secondary Efficacy Endpoints: • Change from Baseline in the PDSS total score at Week 14 • Change from Baseline in panic attack frequency during the last two weeks of the Maintenance Treatment Period Secondary Efficacy Endpoints: • Analysis at all time points in the proportion of participants free of panic attacks as assessed by participant daily eDiary • Change from Baseline at all time points in the PDSS total score and subscores • Change from Baseline at all time points in panic attack frequency • Change from Baseline in the CGI-S score at all time points • Change from Baseline in the HAM-A total score at all time points
Secondary	
• To evaluate the safety and tolerability of darigabat as monotherapy in adult participants with panic disorder	• Treatment-emergent AEs • Clinically significant changes in ECGs, clinical laboratory assessments, vital sign measurements, and physical and neurological examination results • Suicidality assessed using the C-SSRS • Withdrawal symptoms assessed using the PWC

Objectives	Endpoints
Exploratory	
• To evaluate the pharmacokinetics of darigabat as monotherapy in adult participants with panic disorder	• Darigabat plasma concentrations
• To evaluate the quality of life and functional impairment of symptoms following treatment with darigabat as monotherapy in adult participants with panic disorder	• Change from Baseline in the EQ-5D-5L at all time points • Change from Baseline in the SDS total score at all time points

Abbreviations: AE=adverse event; CGI-S=Clinical Global Impressions-Scale; C-SSRS=Columbia–Suicide Severity Rating Scale; ECG=electrocardiogram; EQ-5D-5L=European Quality of Life Questionnaire 5 Dimensions 5 Levels; HAM-A=Hamilton Anxiety Scale; PDSS=Panic Disorder Severity Scale; PWC=Physician Withdrawal Checklist; SDS=Sheehan Disability Scale.

3. KEY ASSESSMENTS AND DERIVATIONS

3.1. Efficacy Assessments

3.1.1. Panic Attack Assessments

Panic attack frequency will be assessed using an eDiary that will be completed by participants each day. Participants will record the presence/absence of panic attacks along with associated symptoms for a given day in an eDiary. For participants operating under Protocol versions 1.0 and 2.0, information can be recorded for the current day as well as two days prior. Participants under Protocol version 3.0 are limited to eDiary recordings with a recall time of immediate to end of day on that same day. For each panic attack, reporting the presence or absence of each symptom referenced in the DSM-5-TR criteria will be recorded in the eDiary.

Participants will train on eDiary use at the Screening Visit and will start recording their daily frequency of panic attacks; participants must complete a minimum of 11 eDiary day entries, including days free of panic attacks, in the 14 days preceding the Baseline Visit. The panic attack frequency recorded for the 14 days prior to randomization and dosing will be used as the baseline. During the double-blind randomized treatment period, the panic attack frequency per each two-week period will be the basis of the repeated measure assessments.

3.1.1.1. Derivation of Panic Attack Frequency

For an event to meet the definition of a panic attack, the participant must report experiencing four or more of the symptoms described in the DSM-5-TR. Panic attack frequency is defined as the total number of panic attacks over each two-week interval divided by the total number of days the eDiary was completed in the same analysis period multiplied by 14. Participants with a minimum of 7 completed diary days in a two-week interval will be considered for panic attack frequency, otherwise will be considered missing.

3.1.1.2. Participants Free of Panic Attacks

A participant is considered to be panic free within a two-week interval if during each two-week interval, there is a minimum of 12 days of the eDiary completed and there is no presence of panic attacks associated with 4 symptoms as specified in DSM-5-TR. The outcome for participants who do not report a panic attack associated with four symptoms but have fewer than 12 completed eDiary days, will be considered missing for efficacy analysis.

A modified definition will be used in supportive analyses. Under the modified definition, a participant is considered to be panic free within a two-week interval if during each two-week interval, there are no missing eDiary days and there is no presence of panic attacks associated with 4 symptoms as specified in DSM-5-TR. The outcome for participants who do not report a panic attack associated with 4 symptoms but have missing eDiary days, will be considered missing for efficacy analysis.

3.1.1.3. Derivation of Proportion of Participants Free of Panic Attacks

The proportion of participants free of panic attacks is derived as the number of participants who do not experience any panic attacks (defined by DSM-5-TR) over a two-week interval divided by the total number of participants in the treatment group. Calculations will be derived initially for weeks where at least 12 days reported on a diary per two-week interval (>80%). Participants with fewer than 12 days of completed eDiary entries who have not reported a panic attack will be considered missing from this analysis. Calculations will also be derived for weeks were all 14 days were reported on a diary per two-week interval (100%). Participants with fewer than 14 days of completed eDiary entries who have not reported a panic attack will be considered missing from this analysis.

3.1.2. Panic Disorder Severity Scale

The Panic Disorder Severity Scale (PDSS) (Shear et al, 1997) is a 7-item, clinician-administered measure of panic disorder severity that covers multiple dimensions of the disorder and has become a widely used standard measure. The first 5 items of the PDSS assess the core DSM-5-TR symptoms of panic disorder, and 2 additional items assess impairment in social and occupational functioning. Each item is scored on a 0 to 4 scale.

3.1.2.1. Handling of Missing PDSS Data

If individual items are missing from a given subscale of PDSS for an individual participant at a given time point, the subscale total will be calculated by prorating the total of non-missing items if the number of missing items is no more than one item of the total number of items in the subscale. The PDSS total score for an individual participant at a given time point will be similarly calculated by prorating the total of non-missing items if the number of missing items is less than or equal to 3. 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 participant for the given subscale, and U is the number of total items in the given subscale.

If the number of missing items exceeds the specifications above, the subscale score or the total score for the individual participant at that time point will be considered missing.

3.1.2.2. Derivation of PDSS Total Score

The PDSS total score is defined as the sum of scores per participant per visit. The total score will range from 0 to 28 with higher scores indicating a higher severity of panic disorder.

3.1.3. Clinical Global Impression-Severity of Symptoms Scale

The global severity of panic disorder symptoms for each participant will be rated using the Clinical Global Impression Severity of Symptoms Scale (CGI-S) (Guy, 1976). 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 0=not assessed; 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. Participants with a score of 0 will be set to missing in the derived dataset.

3.1.4. Hamilton Anxiety Rating Scale

The Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959) is a clinician interview-administered scale designed to measure the signs and symptoms of anxiety states in an adult population. It has 14 items and a recall period of the past week. There are 2 domains covered within the questionnaire, a Somatic factor (made up of 8 items including somatic muscular, somatic sensory, cardiovascular symptoms, respiratory symptoms, gastrointestinal symptoms, genitourinary symptoms, automatic symptoms and behavior) and a Psychic factor (made up of 6 items including anxious mood, tension, fears, insomnia, intellectual and depressed mood). Each item is scored on the following scale: 0=Not Present, 1=Mild, 2=Moderate, 3=Severe, and 4=Very Severe. A total score (ranging from 0 to 56) can be calculated in addition to the 2-dimension scores. If more than 3 individual items are missing per domain, the HAM-A total score will not be calculated and will be left as missing. If less than or equal to 3 individual item scores are missing, the missing item scores will be imputed by the mean of all other available item scores, or the maximum possible values for the missing responses, whichever is smaller, to calculate the HAM-A total score. Lower scores indicate less anxiety.

3.2. Safety Assessments

3.2.1. Adverse Event

Adverse Events (AE) is defined as any untoward medical occurrence in a patient or clinical trial participant, temporally associated with the use of trial intervention, whether considered related to the trial intervention. NOTE: Signs and symptoms and/or abnormal laboratory test results 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 toxicity 'Grade 3' 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.

3.2.1.1. Adverse Event of Special Interest

AESIs are defined as any event meeting the following criteria:

- AEs that result in the discontinuation of IMP
- AEs potentially related to abuse (refer to the Abuse Potential Monitoring Plan [APMP] document for details)
- AEs of suicidality
- C-SSRS (Since Last Visit) "Yes" answer to Suicidal Ideation Items #4 or #5 or any Suicidal Behaviors
- Corrected QT values using Fridericia's method (QTcF) >500 ms or an increase >60 ms from Baseline
- Liver enzymes:
  - ALT or AST ≥3 × Upper Limit of Normal (ULN) and serum bilirubin ≥2 × ULN (suspected Hy's Law)
  - ALT ≥5 × ULN
- Hematologic abnormalities:
  - Absolute neutrophil count <1.5 × 10^9/L
  - Platelet count <100 × 10^9/L
  - Hemoglobin <10 g/dL

These events will be noted by the investigator in the ADVERSE EVENT/ADVERSE EVENT OF SPECIAL INTEREST eCRF.

3.2.1.2. Treatment-Emergent Adverse Event (TEAE)

Any event reported on the eCRF that occurs on or after the initiation of IMP and through the follow-up contact (i.e., date of Visit 9) is considered treatment-emergent. Additionally, it is an Adverse Event which was reported to have started on Day 1 without an associated onset time is assumed to be treatment emergent.

3.2.2. 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 (Section 9.1). All laboratory tests with values considered clinically significantly abnormal during participation in the trial should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the medical monitor notified.

3.2.2.1. 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 through the last follow up contact.

A treatment-emergent laboratory toxicity is defined as an increase of at least one toxicity grade (Section 9.5) from the baseline assessment at any post baseline visit which occurs after the first administration of IMP and through last follow up contact. If a laboratory assessment obtained on Day 1 has unknown collection times, it will be assumed to be an assessment prior to the initiation of IMP. If the relevant baseline assessments are missing for a given participant, then any post-baseline graded toxicity (i.e., at least Grade 1) is considered a treatment-emergent laboratory toxicity.

3.2.3. Columbia-Suicide Severity Rating Scale

Suicidality will be monitored during the trial using the Columbia-Suicide Severity Rating Scale (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 participant 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 participants at screening to determine eligibility and confirmed at baseline.

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 participant to continue in the trial. If a participant 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 participant should continue in or be discontinued from the trial.

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

3.2.4. Vital Signs

Vital signs include systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature. At the Screening Visit, triplicate blood pressure and heart rate measurements will be obtained after the participant has been supine and at rest for at least 3 minutes. Measurements will be obtained at approximately 1-minute intervals at the time points indicated in the Schedule of Assessments (Section 9.1).

Duplicate supine heart rate and blood pressure measurements will be taken at all other time points. The values will be individually recorded, and the values will be averaged by the sponsor for all time point assessments following confirmation of eligibility. For determination of eligibility, the average of the last 2 values will be used.

The supine heart rate and blood pressure measurements will be followed by a single measurement after approximately 2 minutes in a standing position to allow for orthostatic assessments.

3.2.5. Electrocardiograms

At Screening, triplicate 12-lead electrocardiograms (ECGs) are required to assess participant eligibility. A triplicate set of ECGs is 3 consecutive ECGs collected 1 to 2 minutes apart over a 5-minute period. The central ECG service will provide the QTcF corrections and average of the 3 ECGs performed to determine eligibility. At all other specified time points in the Schedule of Assessments where an ECG recording must be performed, only a single ECG is required.

All ECG recordings will be obtained after the participant has been supine and at rest for approximately 3 minutes. Additional 12-lead ECGs may be obtained at the investigator's discretion and should always be obtained in the event of an early termination. The ECG will be repeated if any results are considered to be clinically significant. Any clinically significant changes occurring during the trial will be recorded in the AE section of the eCRF.

3.2.6. Prior and Concomitant Medications

Prior medications are those medications taken prior to and ended prior to the initiation of IMP. 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. These medications will be recorded in the PRIOR AND CONCOMITANT MEDICATIONS eCRF. Medications that start after the last dose of IMP will be classified as taken post last dose and will not be considered as concomitant.

3.2.7. Prior and Concomitant Non-Drug Therapy/Procedures

Prior non-drug therapy/procedures are those medications taken prior to and ended prior to the initiation of IMP. Concomitant non-drug therapy/procedures are those non-drug therapy/procedures taken on or after the initiation of IMP. These therapy/procedures include those non-drug therapy/procedures started before the initiation of IMP and continuing post Day 1. The investigator will record all therapies (including vaccines, over the counter or prescription medicines, vitamins, and/or herbal supplements) taken by the participant from 30 days prior to signing the ICF through the end of the evaluation period (defined as the time period during which participants are evaluated for primary and/or secondary objectives). These non-drug therapy/procedures will be recorded in the NON-DRUG THERAPY/PROCEDURES eCRF.

3.2.8. Physical/Neurological Examinations

The full physical examination will include a review of the following body systems: head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, and musculoskeletal systems.

The limited physical examinations will include evaluation of cardiovascular, pulmonary, and gastrointestinal systems.

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

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

3.2.9. Penn Physician Withdrawal Checklist

The PWC is a 20-item scale to measure discontinuation symptoms (e.g., loss of appetite, nausea-vomiting, diarrhea, anxiety-nervousness, irritability, etc.) after stopping a medication for anxiety disorders (Rickels et al, 2008). All 20 items are rated on a 4-point numeric-rating scale ranging from 0 (not present), 1 (mild), 2 (moderate), to 3 (severe). A total score, ranging from 0 to 60, can be calculated in addition to the individual scores for each item. If more than 4 individual items are missing, the PWC total score will not be calculated and will be left as missing. If less than or equal to 4 individual item scores are missing, the missing item scores will be imputed by the mean of all other available item scores or the maximum possible values for the missing responses, whichever is smaller, to calculate the PWC total score. Lower scores indicate less severity in discontinuation symptoms.

3.3. Pharmacokinetics

With participants maintaining their normal BID dosing routine, a single daytime venous blood sample for determination of plasma darigabat concentration will be collected as specified in the Schedule of Assessments.

During each PK sampling, an approximately 4-mL venous blood sample will be collected into appropriately labeled tubes. The blood samples will be used to provide approximately 2 × 1-mL plasma samples (one primary and the other as backup) for separate quantifications in plasma.

A fully validated bioanalytical method will be used to quantitate the concentrations of darigabat in plasma. Plasma samples collected in this trial may be used for further development of the bioanalytical method or identification of metabolites. The backup samples may be stored for a duration of approximately up to 1 year after the date of the final CSR.

3.4. Other Assessments

3.4.1. Sheehan Disability Scale

The Sheehan Disability Scale (SDS) instrument is patient rated with the first 3 items in a numeric rating scale and the last 2 questions asking for number of days impacted (Sheehan et al, 1996; Sheehan, 1983). The first 3 items, one for each of the 3 domains, are rated on an 11-point numeric rating scale ranging from 0 (not at all), 1 to 3 (mildly), 4 to 6 (moderately), 7 to 9 (markedly), to 10 (very severely). The sum score from the first 3 items, ranging from 0 (unimpaired) to 30 (highly impaired), will be used to evaluate global functional impairment.

Individual subscores from the first 3 items will also be reported to assess the impact of panic disorder on work, social life/leisure activities, and family life/home responsibilities.

Two additional items measuring "days lost" and "days unproductive" during the last week further quantify the lost and reduced productivity in school or work.

If one item is missing to evaluate global functional impairment, the scores from the other two items will be averaged and used in the summation. If two or more items are missing, then the SDS total score will be missing.

3.4.2. European Quality of Life (EQ-5D-5L)

The European Quality of Life (EQ-5D-5L) is a generic estimate of health status with 2 parts (EQ-5D-5L User Guide, 2019). The first part, the descriptive system, was designed to assess decrement of health in terms of 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of these dimensions has a self-rated 5 level response: no problem (level 1), slight problems (level 2), moderate problems (level 3), severe problems (level 4), and unable to/extreme problems (level 5). Thus, a health profile consisting of a 5-digit code based on respondent's selected levels for each of the 5 dimensions will be generated. For example, a respondent with a health profile code of 12345 would have no problem with mobility, slight problems with self-case, moderate problems with usual activities, severe problems with pain/discomfort, and extreme problems with anxiety/depression. For each participant 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 et al, 2012).

The second part of EQ-5D-5L is the EQ Visual Analog Scale (EQ VAS), a self-rated vertical visual analog 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'.

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.

4.1.2. Day 1

Study Day 1 is the day IMP is first initiated.

4.1.3. Study Day of an Event

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

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

4.1.4. 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 CRF.

4.1.5. Days on Treatment

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 CRF.

4.1.6. Date of Diagnosis

Date of Initial Diagnosis will be taken from the Mini International Neuropsychiatric Interview CRF. Partial dates will be imputed as instructed in Section 4.1.19.

4.1.7. Years Since Initial Diagnosis

Years since initial diagnosis will be calculated as the difference between the date of Informed Consent and the date of Initial Diagnosis.

4.1.8. Days on IMP

Days on IMP is the number of days from Study Day 1 to the date of last dose of IMP as recorded on the END OF TREATMENT CRF.

4.1.9. Baseline Value

The baseline value is defined as the last non missing value obtained prior to initiation of the first dose of IMP.

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.

The panic attack frequency recorded for the 14 days prior to randomization and dosing will be used as the baseline.

4.1.10. Change from Baseline

Change from baseline for a given endpoint is defined as the value on a given Study Day minus the Baseline Value.

4.1.11. 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, date and timepoint, 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, date, and timepoint will be used.

4.1.12. Last Dose of IMP

Last Dose of IMP is defined as the last date that the participant received IMP.

4.1.13. Last Two Weeks of Maintenance Treatment

The last two weeks of maintenance treatment for an individual participant is defined as the 14 days leading up to and including the last dose of IMP. For aggregate analysis, the last two weeks of maintenance treatment is defined as two weeks prior to Visit 6 (Week 14). A participant must have a minimum of 14 days of treatment in the maintenance phase to be considered for this metric.

4.1.14. Diary Days

Diary days are defined as days with completed eDiary assessments, i.e. panic attack diary fields were recorded on that date.

4.1.15. Panic Attack Occurrence

Panic attack occurrence is defined as a panic attack eDiary entry associated with at least 4 panic attack symptoms. Associated field (CE.CEOCCUR) for event occurrence is recorded as either “Y” or missing.

4.1.16. eDiary Compliance

eDiary compliance will be calculated as 100 times the number of diary days (i.e., days with completed diary assessments) during a period divided by the expected number of completed diary days in that same period.

4.1.17. Compliance with Study Drug

Dosing compliance based on daily dose of IMP as recorded in the OVERALL DOSING - BLINDED CRF will be defined by the dosing compliance ratio: the number of doses actually taken by the participant divided by the number of doses that were expected to be taken during the same period multiplied by 100. Subjects were to have taken 4 tablets/day during the titration period and 2 tablets/day during the Maintenance Treatment Period.

4.1.18. Definition of Completed Participant

A participant is considered to be a treatment completer if he/she has completed the Treatment Period of the trial including the last visit in the Maintenance Treatment Period (Visit 6, Day 98) as captured in the eCRF.

A participant is considered to have completed the study if he/she has completed all periods of the trial including the last scheduled procedure in the Safety Follow-up (Visit 9, Day 131) as shown in the Schedule of Assessments in Section 9.1 and as captured in the eCRF.

Table 3: Two-Week Intervals

Two-Week Interval	Study Days in Interval
Maintenance Week 1-2	Days 15-28
Maintenance Week 3-4	Days 29-42
Maintenance Week 5-6	Days 43-56
Maintenance Week 7-8	Days 57-70
Maintenance Week 9-10	Days 71-84
Maintenance Week 11-12 (no-panic attack endpoint)	Two weeks prior to end of treatment
Maintenance Week 11-12 (panic attack frequency endpoint)	Days 85-last day in treatment period

4.1.19. Handling of Incomplete or Missing Dates

Incomplete or missing start and end dates will be imputed for adverse events to determine treatment-emergence and for medications/non-drug therapies to determine when the medication/non-drug therapy was taken (i.e., pre-dose, concomitant, or post last dose of IMP). Incomplete dates will also be imputed for date of Initial Diagnosis where required.

An incomplete date occurs when the exact date an event occurred or ended cannot be obtained from a participant. 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.

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 in the 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 an 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), for adverse events 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 the 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 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 imputed for the date. In participant data listings, start and stop date of events will be displayed as reported on the eCRF (i.e., imputed values will not be listed).

4.1.20. Handling of Alphanumeric Data

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

For incorporation in quantitative summaries (except for concentration data), the following imputation rules will be employed:

- The lower limit of quantification (LLOQ) will be replaced with ½ the value of the lower limit. For example, < 0.1 will be replaced with 0.05.
- The upper limit of quantitation will be increased by one level of precision that precedes the value. For example, ">0.1" will be imputed to "0.11", and ">10" will be imputed to "10.1".
- Additionally, the ULN/lower limit of normal (LLN) values may be reported as alphanumeric (e.g., '<5', '≤5', '>5', '≥5'). In these cases, if the ULN or LLN is necessary for determination of the laboratory severity grade, the following conventions will be employed:
  - If the value is in the form of ≤5, the ULN will be populated with the value after removing the symbol (i.e., the ULN is set to 5). If the value is in the form of <5, 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 value is in the form of ≥5, the LLN will be populated with the value after removing the symbol (i.e., the LLN is set to 5). If the value is in the form of >5, the 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. Analysis Periods

The start and ends dates of each analysis period (following the study design) are used for the classification of efficacy data and will be assigned sequentially according to the study day of the event.

Table 4: Definition of Analysis Periods for Efficacy Data

Analysis Period	Duration	Start Day	End Day
Baseline Period	~2 Weeks	The greater of: Study Day -14 or Informed consent	Study Day, -1
Titration Period	~2 Weeks	Study Day, 1	The lesser of: Day 15 minus 1 or **Early termination (minus 1) or End of Treatment

Analysis Period	Duration	Start Day	End Day
Maintenance Period	~12 Weeks	Day 15	The lesser of: Day 98 (Visit 6) or Early Termination (if > Day 15)

** If a participant experiences early termination from the study and continues to Maintenance Period, end dates will be bound by early termination minus 1, while the start of Maintenance Period will begin on the date of early termination.

4.3. Analysis Visit Windows

Data collected longitudinally across visits will be summarized and analyzed by visit. Assessments made on scheduled visits will be mapped to an appropriate analysis visit that corresponds to the nominal visit. Early termination and unscheduled visits will be assigned to visit windows based on the study day of the event according to Table 5-Table 9.

If assessments are collected multiple times within a given visit, the scheduled visit, if available, will be used for summary presentations. If no scheduled visit is available, then the result closest to the scheduled visit date will be used for summary presentations. If two unscheduled measurements (discharge or unscheduled visit) have the same distance to the expected date, the earlier value will be used. If a participant has multiple non-missing unscheduled values on the same date, then the last one is used, as determined by the time collected, if available.

Table 5: Visit Windows for PDSS

Study Day of Early Termination or Unscheduled Visit	Analysis Visit	Analysis Visit Target Day
< 1 Predose	Baseline	1
≥ 1 to 56 (PDSS only)	Day 42 (Visit 4)	42
57 to 84 (PDSS only)	Day 70 (Visit 5)	70
> 84 (PDSS only)	Day 98 (Visit 6)	98

Table 6: Visit Windows for SDS

Study Day of Early Termination or Unscheduled Visit	Analysis Visit	Analysis Visit Target Day
< 1 Predose	Baseline	1
≥ 1 to 70	Day 42 (Visit 4)	42
> 70	Day 98 (Visit 6)	70

Table 7: Visit Windows for EQ-5D-5L

Study Day of Early Termination or Unscheduled Visit	Analysis Visit	Analysis Visit Target Day
< 1 Predose	Baseline	1
≥ 1	Day 98 (Visit 6)	98

Table 8: Visit Windows for ECG

Study Day of Early Termination or Unscheduled Visit	Analysis Visit	Analysis Visit Target Day
< 1 Predose	Baseline	1
≥ 1 to 70	Day 42 (Visit 4)	42

Table 9: Visit Windows for Vital Signs, C-SSRS, HAM-A, CGI-S and Urine Drug Screening

Study Day of Early Termination or Unscheduled Visit	Analysis Visit	Analysis Visit Target Day
< 1 Predose	Baseline	1
≥ 1 to 28	Day 14 (Visit 3)	14
> 28 to 56	Day 42 (Visit 4)	42
> 56 to 84	Day 70 (Visit 5)	70
> 84	Day 98 (Visit 6)	98

Table 10: Visit Windows for PWC

Study Day of Early Termination or Unscheduled Visit	Analysis Visit	Analysis Visit Target Day
> 84 to 100	Baseline (Visit 6)	98
≥ 100 to 102	Day 101 (Visit 7)	101
> 102 to 108	Day 105 (Visit 8)	105

Table 11: Visit Windows for Safety Laboratory Blood Sample Assessments and Urine Pregnancy Tests

Study Day of Early Termination or Unscheduled Visit	Analysis Visit	Analysis Visit Target Day
< 1 Predose	Baseline	1
≥ 1 to 28	Day 14 (Visit 3)	14
> 28 to 56	Day 42 (Visit 4)	42
> 56 to 84	Day 70 (Visit 5)	70
> 84 to 100	Day 98 (Visit 6)	98
> 100	Day 131 Follow-up (Visit 9)	131

Table 12: Visit Windows for Safety Laboratory Urine Sample Assessments

Study Day of Early Termination or Unscheduled Visit	Analysis Visit	Analysis Visit Target Day
< 1	Baseline	1
≥ 1	Day 98 (Visit 6)	98

Table 13: Visit Windows for PK Sampling

Study Day of Early Termination or Unscheduled Visit	Analysis Visit	Analysis Visit Target Day
1 to 21	Day 14 (Visit 3)	14
22 to 49	Day 42 (Visit 4)	42
50 to 77	Day 70 (Visit 5)	70
>77	Day 98 (Visit 6)	98

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 participants (N), number of observations (n), arithmetic mean, median, standard deviation (SD), 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: 25 mg darigabat and placebo. All data collected from participants 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 participant number and then by date within each participant number.

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

5.2. Analysis Sets

The analysis sets are defined as follows:

Table 14: Analysis Set Descriptions

Term	Description	Analysis
All Screened Participants	All Screened Participants includes all participants who signed the informed consent form.	Disposition
Intent-to-Treat Analysis Set (ITT)	All randomized participants.	Demographic and Baseline Characteristics
Safety Analysis Set	All randomized participants who receive at least 1 dose of IMP.	Safety analysis
Full Analysis Set (FAS)	FAS: Panic Attack Endpoints All randomized participants who receive at least 1 dose of IMP and have valid baseline panic attack assessments and have recorded all baseline/post-baseline panic attack assessments in an eDiary that requires collection of reports contemporaneous to the day being assessed and collection of the presence/absence of each associated symptom (i.e. eDiary Version 2). Participants who have not met all inclusion/exclusion criteria but are randomized in error will not be included.	All efficacy analysis (including primary) related to panic attack events captured by eDiary

Term	Description	Analysis
	FAS: Expanded All randomized participants who receive at least 1 dose of IMP and have valid baseline panic attack assessments. Participants who have not met all inclusion/exclusion criteria but are randomized in error will not be included.	Sensitivity efficacy analysis (including primary) related to panic attack events as specified
PK Analysis Set	All randomized participants who receive at least 1 dose of IMP and have at least 1 measurable darigabat concentration.	PK analysis

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

5.3. Statistical Hypotheses

The hypotheses of interest for the efficacy endpoints are 2-sided tests of superiority comparing the darigabat (DAR) with placebo.

$$H0: \mu_{placebo} = \mu_{DAR} \text{ vs } H1: \mu_{placebo} \neq \mu_{DAR}$$

5.4. Multiplicity Adjustment

No multiplicity adjustments will be made for this Phase 2 study.

5.5. Strata and Covariates

The randomization will be stratified by evidence-based psychotherapy for the treatment of anxiety disorders including panic disorder with 2 strata: receiving evidence-based psychotherapy (initiated >3 months prior to the Screening Visit) or not receiving evidence-based psychotherapy. The baseline value of each efficacy variable will be included as a covariate in the efficacy analyses based off collection in CRF. For analysis of freedom from panic attacks and panic attack frequency, baseline PDSS score will also be included as a covariate.

5.6. Participant Disposition, Demographic and Baseline Characteristics

Participant disposition will be based on all participants randomized with tabulation of the number of participants who completed the study, the number who completed treatment, the number of participants discontinued from the study/treatment, and the reasons by treatment group. Additionally, the number of days on study will be summarized.

Participant disposition data will also be tabulated for all participants screened to include the number of participants screened, the number of screen failures, and the reason for screen failure.

The number of participants in each analysis set will be summarized.

Additionally, the number of participants randomized will be summarized by treatment group and overall.

A listing of randomization number, randomization date, participant, treatment randomized, treatment received, and inclusion in each analysis set will be prepared.

Demographic data and baseline characteristics including age at screening, sex, fertility status, race, ethnicity, height at screening, weight at screening and baseline, body mass index (BMI) at screening and baseline, years since initial diagnosis of panic disorders, baseline panic attack frequency, proportion of participants free of panic attacks at baseline, proportion of participants receiving evidence-based psychotherapy baseline PDSS total score, , baseline CGI-S score, and baseline HAM-A total score will be summarized by treatment using descriptive statistics for the ITT Analysis Set.

5.7. Medical and Psychiatric History

Medical and psychiatric history events will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) versions 27.0 and 27.1 preferred term and system organ class. Medical and psychiatric history will be summarized by treatment group for the ITT Analysis Set using preferred terms and system organ classes. All events will be listed for the ITT Analysis Set.

5.8. Exposure to Treatment

The number of participants who received IMP, number of days on IMP, number of treatment discontinuations, reasons for treatment discontinuation, and treatment compliance will be summarized by treatment group for the FAS: Expanded Analysis Set. Drug accountability data will be listed.

5.9. eDiary Compliance

Primary, secondary, and other efficacy variables are based on diary-collected panic attack frequencies, and as such, diary compliance will be evaluated along with treatment compliance. Participants are instructed to complete their diary entries at least once a day during the study. A diary day will be considered missing for compliance if a panic attack diary record is missing for that day. Diary compliance will be evaluated during the Screening Period, the Baseline Period, the Titration Period, the Maintenance Period, the entire Treatment Period, and the last two weeks of Maintenance Treatment.

eDiary compliance will be calculated as 100 times the number diary days (days with diary completed) during the period and dividing this quantity by the expected number of diary days that should have been completed during this period of time. Compliance is computed for actual time of participation in the study through Visit 8 follow-up. If a participant did not enter an analysis period, the diary compliance for the analysis period will not be calculated.

eDiary compliance data will be listed by treatment then participant for each diary type and summarized by treatment group and version of diary used.

5.10. Mini International Neuropsychiatric Interview

Participants MINI summary will be listed.

5.11. Primary Efficacy Analysis

5.11.1. Primary Analysis

The primary estimand has the following attributes:

1. Treatments as randomized
2. The population defined by the inclusion/exclusion criteria of the trial as the primary population of interest
3. The proportion of participants who are free of panic attacks during the last two weeks of the Maintenance Treatment as the primary endpoint of interest
4. The population level summary of interest is the estimated odds ratio of freedom from panic attack between treatments and the corresponding 95% confidence intervals (CI)
5. Handling of intercurrent events (ICEs)
   - The treatment policy strategy will be used to handle the ICE of use of concomitant medications during the study for primary analysis of the primary efficacy endpoint, which will include the collected data in the analyses regardless of the use of medications
   - The hypothetical strategy will be used to handle the ICEs of discontinuation from treatment/study participation for primary analysis of the primary efficacy endpoint, which will only include collected data through the discontinuation visit

5.11.2. Main Analytical Approach

The number and proportion of participants who are free of panic attacks during the last two weeks of the Maintenance Treatment will be summarized by analysis period and treatment group. The binomial repeated measures will be analyzed using the SAS® GENMOD procedure with logit link. The Baseline PDSS total score will be included as a covariate, and the treatment group, analysis periods, evidence-based psychotherapy use, and interaction between treatment group and analysis period will be included as fixed effects. Model diagnostics will be performed to explore the goodness-of-fit. An unstructured covariance matrix will be used for the repeated measures model. If the sparseness of the data results in model convergence or other issues, affecting reliability of estimates, efficacy conclusions will be based on the sensitivity analysis using the Fisher's exact test described in Section 5.11.3. The odds ratio of active dose to placebo at the endpoint analysis period will be estimated based on the least squares mean difference in logit between the treatment groups from the GENMOD model with the associated 95% CI and p-values.

5.11.3. Sensitivity Analyses

A sensitivity analysis using Fisher's exact test and 95% exact CI about the difference in treatment groups will be performed to assess the robustness of the conclusion from the logistic regression and the impact of potential use of a structured covariance matrix on the estimation of treatment effect.

Participants will be assessed based on the final two weeks of treatment in the Maintenance Period. Those with less than 12 eDiary days and no reported panic attacks will be imputed as missing.

Additional sensitivity analysis will include the model-based analysis described in Section 5.11.2 conducted using all participants regardless of panic attack eDiary version used.

Lastly, two sensitivity analyses will be performed using modified definitions of the efficacy endpoint, free of panic attacks. Under the first modified definition, a participant is considered to be panic free within a two-week interval if during each two-week interval, there are no missing eDiary days and there is no presence of panic attacks associated with 4 symptoms as specified in DSM-5-TR. The second definition will require 10 or more eDiary days without a reported panic attack (per DSM-5-TR). The outcome for participants who do not report a panic attack associated (per DSM-5-TR) but have missing eDiary days, will be considered missing for efficacy analysis. Analysis using the model-based approach described in Section 5.11.2 will be performed using the 14/14 eDiary day definition and the Fisher's exact test will be performed using the both modified definitions.

5.12. Key Secondary Efficacy Analyses

5.12.1. First Key Secondary Analyses

5.12.1.1. Estimand

The first key secondary estimand has the following attributes:

1. Treatments as randomized
2. The population defined by the inclusion/exclusion criteria of the trial as the primary population of interest
3. The change from baseline in PDSS total score at Week 14 as the endpoint of interest
4. The population level summary of interest is the estimated treatment differences and the corresponding 95% confidence interval based on a mixed model for repeated measures (MMRM)
5. Handling of intercurrent events (ICEs)
    - The treatment policy strategy will be used to handle the ICE of use of concomitant medications during the study for primary analysis of the primary efficacy endpoint, which will include the collected data in the analyses regardless of the use of medications
    - The hypothetical strategy will be used to handle the ICEs of discontinuation from treatment/study participation for primary analysis of the primary efficacy endpoint, which will only include collected data through the discontinuation visit

5.12.1.2. Analytic Method

The change from Baseline to each trial visit in PDSS total score will be summarized by visit and treatment group. An MMRM analysis will be used with fixed effects of treatment group, visits, evidence-based psychotherapy use, and interaction between treatment group and visit. The baseline value of PDSS total score will be included as a covariate. Participant will be included as a random effect. An unstructured covariance structure will be used for the repeated measures. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. If the unstructured covariance matrix results in convergence issue, the Fisher scoring algorithm may be used to obtain the initial values of covariance parameters. If convergence issues still cannot be resolved, a structured covariance matrix may be used with the heterogeneous Toeplitz covariance structure followed by the heterogeneous first-order autoregressive (AR[1]) structure. In the case that a structured covariance matrix needs to be used, a robust sandwich variance estimator will be used to address the potential adverse impact of covariance matrix misspecification. The difference between active dose and placebo at the endpoint visit will be estimated based on the least squares mean difference between the treatment groups at the endpoint visit from the MMRM with the associated 95% CI and p-values. The LS Mean (±SE) from the model will be plotted for change in PDSS total score during each visit by treatment group. Similarly, the mean (±SD) of absolute values and change from Baseline PDSS total score will be presented by visit and treatment group.

5.12.2. Second Key Secondary Efficacy Analysis

5.12.2.1. Estimand

The second key secondary estimand has the following attributes:

1. Treatments as randomized
2. Full analysis set as the primary population of interest
3. The change from baseline in panic attack frequency during the last two weeks of the Maintenance Treatment as the endpoint of interest
4. The population level summary of interest is the estimated treatment differences in median and the 95% confidence interval using Hodges-Lehmann estimation
5. While-on-treatment strategy with data prior to treatment discontinuation used in the analysis

5.12.2.2. Main Analytic Method

The change from Baseline to each analysis period in frequency of panic attacks will be summarized by analysis period and treatment group using descriptive statistics. Estimated treatment differences in median and the 95% confidence interval using Hodges-Lehmann estimation will also be reported. A non-parametric analysis using Mann-Whitney test performed on the change from Baseline during the last two weeks of the Maintenance Treatment will be the basis for comparison between the two treatment groups.

Panic attack frequency over two-week intervals will be plotted. Similarly, the mean (±SD) absolute values and changes from baseline will be plotted by study analysis period and treatment group.

5.12.2.3. Sensitivity Analyses

Sensitivity analysis will include all participants regardless of panic attack eDiary version used.

5.13. Summary of Primary and Key Secondary Efficacy Analyses

ICE Strategy	Primary Analysis	Sensitivity Analysis
Primary Endpoint: Proportion of participants who are free of panic attacks during the last two weeks of the Maintenance Treatment Period		
Hypothetical strategy with data prior to treatment discontinuation used in a repeated measures analysis last two weeks	• The population defined by the inclusion/exclusion criteria of the trial • Treatment as randomized • Binomial repeated measures described in Section 5.11.2	• Fisher's exact test • Include all participants regardless of panic attack eDiary version used • Analysis using modified definition of outcome requiring complete eDiary compliance
Key Secondary Endpoint: Change from baseline in PDSS total score at Week 14 as the endpoint of interest		
Hypothetical strategy with data prior to treatment discontinuation used in a repeated measures analysis	• The population defined by the inclusion/exclusion criteria of the trial • Treatment as randomized • MMRM described in Section 5.12.1.2	• None
Second Key Secondary Endpoint: Change from Baseline in panic attack frequency during the last two weeks of the Maintenance Treatment Period		
While-on-treatment strategy with data prior to treatment discontinuation used in the analysis	• The population defined by the inclusion/exclusion criteria of the trial as the primary population of interest • Treatment as randomized • Non-parametric analysis using Mann-Whitney test, median difference and 95% CI using Hodges-Lehmann estimation described in Section 5.12.2.2	• Include all participants regardless of panic attack eDiary version used.

5.14. Other Secondary Efficacy and Exploratory Analyses

All other secondary efficacy endpoints will be summarized using descriptive statistics by treatment group and visit, if appropriate. Statistical comparisons for each endpoint will be constructed without adjustment for multiple endpoints.

The other secondary efficacy endpoints are:

- Analysis at all time points in the proportion of participants free of panic attacks as assessed by participant daily diary. The baseline PDSS score will be used as the covariate.
- Change from baseline at all time points in the PDSS total score and subscores. The baseline PDSS total score will be used as the covariate.
- Change from baseline at all time points in panic attack frequency. The baseline panic attack frequency will be used as the covariate.
- Change from baseline in the CGI-S score at all time points. The baseline CGI-S score will be used as the covariate and derived as the score obtained
- Change from baseline in the HAM-A total scores. The baseline HAM-A total score will be used as the covariate.
- Change from baseline in the EQ-5D-5L at all time points. The baseline EQ-5D-5L index score will be used as the covariate.
- Change from baseline in the SDS total score at all time points. The baseline SDS total score will be used as the covariate.

5.15. Summary of Analyses of Other Efficacy and Exploratory Endpoints

Endpoint	Analysis Method
Analysis at all time points in the proportion of participants free of panic attacks as assessed by participant daily diary	Repeated measure logistic regression described in Section 5.11.2
Change from baseline at all time points in the PDSS total score and subscores	MMRM model described in Section 5.12.1.2
Change from baseline at all time points in panic attack frequency	Same methods described in Section 5.12.2.2
Change from baseline in the CGI-S score at all time points	MMRM model described in Section 5.12.1.2
Change from baseline in the HAM-A total score at all time points	MMRM model described in Section 5.12.1.2
Change from baseline in the EQ 5D-5L at all time points	MMRM model described in Section 5.12.1.2
Change from baseline in the SDS total score at all time points	MMRM model described in Section 5.12.1.2

5.16. Interim Analysis

The trial is designed to be conducted to full completion without interim analyses. If any interim analysis becomes necessary, all plans will be prespecified prior to the conduct of such analyses.

5.17. Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Should any participants receive a treatment other than their randomized treatment, the treatment as received will be used in the safety presentation.

5.17.1. Adverse Events

Adverse events will be mapped to the most current MedDRA version preferred term and system organ class. If a participant 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. Summaries of treatment-emergent AEs will include any AEs reported beginning with the initiation of study drug on Day 1 through last follow-up. The occurrence of TEAEs will be summarized by treatment group using preferred terms, system organ classes, and severity. 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 events leading to the discontinuation of study will be generated respectively.

Presentations of AEs by onset titration versus maintenance period will be prepared.

All adverse events will be included in the listings.

Missing onset dates will be imputed as previously outlined in Section 4.1.19.

5.17.2. Medications and Non-Drug Therapy/Procedures

Prior medications, concomitant medications, and medications taken post last dose of IMP will be coded using the World Health Organization (WHO) drug dictionary (WHODrug) (Version: March 2024). Prior medications and concomitant medications will be summarized by treatment group, frequency of drug classification, and generic drug name. All medications will be presented in a data listing.

Non-drug therapy/procedures will be coded using MedDRA Versions 27.0 and 27.1. Concomitant 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.

5.17.3. Clinical Laboratory Assessments

Descriptive summaries of selective (quantitative) clinical laboratory results and change from baseline will be presented by study visit.

Additionally, for hematology, blood chemistry, coagulation, and urinalysis parameters, toxicity grade will be determined for laboratory tests with toxicity grade specified in Section 9.5. Shifts from baseline to greatest (worst) post-baseline laboratory grade will be presented. For parameters not graded as described above, laboratory values outside the normal range for each systematically collected hematology, blood chemistry, and urinalysis parameters defined in Protocol Section 10.2 will be identified using shift tables. 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 values will be flagged as "normal" or "abnormal". Shifts from baseline to high/normal/low status for the hematology, blood chemistry, and urinalysis parameters will be presented to for the maximum post-baseline value and the minimum post-baseline value for each laboratory test. Shifts from baseline to normal/abnormal status for urinalysis parameters will be presented to the maximum post-baseline value and the minimum post-baseline value for each laboratory test.

The number and percentage of participants 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 participant may be counted once per elevation criteria using the worst-case result. That is, a participant 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 participant had that met the > 5 × ULN and > 3 × 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, a Hy's law 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 using the format recommended by the Food and Drug Administration (FDA)/Industry/Academia Safety Graphics working group (https://www.ctspedia.org/do/view/CTSpedia/StatGraphHome). 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.

5.17.4. Vital Signs

Vital signs and corresponding changes from baseline will be summarized by position (if applicable), visit, and timepoint using descriptive statistics. Vital signs results, including orthostatic changes, will be listed.

Out of range vital signs occurring post study baseline will be summarized. For supine blood pressure and heart rate, only averages of duplicates will be used. If an average is not available, the single reading will be used for summary.

The following out-of-range criteria will be summarized for post study baseline assessments:

- Systolic Blood Pressure (Supine)
  - ≤ 90 mmHg
  - ≥ 140 mmHg
- Orthostatic Change in Systolic Blood Pressure
  - ≥ 20 mmHg decrease upon standing compared with supine position
- Diastolic Blood Pressure (Supine)
  - ≤ 60 mmHg
  - ≥ 90 mmHg
- Orthostatic Change in Diastolic Blood Pressure
  - ≥ 10 mmHg decrease upon standing compared with supine position
- Heart Rate
  - < 60 bpm
  - > 100 bpm
- Respiratory Rate
  - < 12 breaths/min
  - > 20 breaths/min
- Temperature
  - < 36° C
  - > 38° C
- Body weight
  - ≥ 7% increase
  - ≥ 7% decrease

5.17.5. 12-Lead Electrocardiograms

Single or triplicate 12-lead electrocardiograms (ECGs) will be obtained during the trial. 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.

The number and percentage of participants who experience any post-baseline occurrence of potentially clinically significant 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.

Additionally, a distribution plot of QTcF over time may be produced using the format recommended by the FDA/Industry/Academia Safety Graphics working group (https://www.ctspedia.org/do/view/CTSpedia/StatGraphHome). The graph format to be used is the same graph provided for the distribution of ALT by time and treatment.

5.17.6. Physical and Neurological Examinations

Physical and neurological examination data will be listed.

5.17.7. Missing Visits and Assessments due to COVID-19

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 participants with any such missing visits, assessments, or remote visits in each treatment group if required

5.18. Other Analyses

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

The baseline and 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.

5.18.2. HAM-A Scores

The HAM-A domain scores and total score will be listed by treatment group and study visit. The total score will be summarized by treatment group.

5.18.3. Penn Physician Withdrawal Checklist

The PWC individual items and total score will be listed by treatment group and study visit. The total score will be summarized by treatment group.

5.18.4. EQ-5D-5L

The EQ-5D-5L individual scores of the 5 dimensions, the total index score, health state and VAS score will be listed by treatment group and study visit. The total index score and VAS score and changes from baseline will be summarized by treatment group.

5.18.5. Sheehan's Disability Scale

The SDS scores will be listed by treatment group and study visit. The SDS score and change from baseline will be summarized by treatment group.

5.19. Pharmacokinetics

All PK listings and individual plasma concentration-time profiles will be presented using the Safety Analysis Set. PK summary tables, mean figures and all statistical analyses will be presented using the PK Analysis Set.

5.19.1. Pharmacokinetic Sampling

With participants maintaining their normal BID dosing routine, a single daytime blood sample for determination of plasma darigabat concentration will be collected at Visits 3, 4, 5, and 6. The date and time of the PK sample, as well as the time of ingestion of previous dose of IMP, will be recorded in the source documentation.

5.19.2. Pharmacokinetic Data Handling

Concentration values that are below the level of quantification (BLQ) will be set to zero for summary tables. Individual values that are BLQ will be presented as "BLQ" in the concentration data listing.

5.19.3. Pharmacokinetic Analysis

Darigabat plasma concentrations will be summarized by dose and day, where applicable, using descriptive statistics including the arithmetic mean, median, standard deviation, coefficient of variation, minimum and maximum values, and geometric mean.

Plasma concentrations will also be pooled with data from other trials in a population PK analysis to describe the time course of plasma concentrations of darigabat and the influence of covariates (e.g., body weight, age, sex, race, concomitant medications) on PK parameters. Plasma concentration may also be pooled with data from other trials in a physiologically based PK model. The results of these analyses are outside the scope of this SAP.

5.20. Protocol Deviations

All protocol deviations will be reviewed by the project team prior to unblinding to identify participants with important protocol deviations. Summaries of important deviations will be presented by category and subcategory of deviation for the FAS: Expanded Analysis Set. All deviations from the protocol will be listed by category along with a description and any additional comments.

6. CHANGES IN THE PLANNED ANALYSES

Analysis methods described here reflect revisions to strategic focus and scope and will supersede those described in the protocol. In addition to changes corresponding to protocol amendments, the analysis plan differs from the statistical analysis section of the protocol as described below:

- As a result of early closure of enrollment and early treatment discontinuation of ongoing participants, planned sample size will not be achieved and proportion of participants with treatment discontinuation will be increased. The resulting sample size will have insufficient power for hypothesis tests and thus, efficacy analysis will be exploratory.
  - The following changes were made to the protocol-specified statistical analysis to reflect the strategic shift to an exploratory evaluation of efficacy
    - Multiplicity adjustments were removed
    - Most sensitivity analyses were removed
    - Supportive analyses involving panic attack-related endpoints were added using an expanded FAS population including all participants regardless of eDiary version used
- Description of handling of ICEs was expanded and revised for the primary and key secondary endpoints:
  - Additional detail was provided for different types of ICEs (eg, administration of rescue medication and treatment discontinuation)
  - Composite strategy was replaced with treatment policy and while on treatment strategies for handling ICEs for analysis of primary and key secondary endpoints
- Added description of missing diary data handling:
  - For the primary efficacy outcome (proportion of participants free of panic attacks), outcome for participants who did not report a panic attack and had <12/14 days of completed eDiary was set to missing, unless otherwise indicated
  - For key secondary efficacy outcome (change from baseline in the frequency of panic attacks), outcome for participants with <7/14 days of completed eDiary was set to missing
- The SAP replaced the SAS® procedure GLIMMIX (specified in protocol) with GENMOD to fit binomial repeated measures model to estimate the proportion of participants that were free of panic attack and the treatment difference. Although both procedures can fit binomial repeated measures model, model-fitting is more efficient with the GENMOD procedure.

Should any deviations from the analyses pre-specified in the authorized statistical analysis plan arise, such deviations will be documented in the final clinical study report.

7. REVISION HISTORY

Only one version of the Statistical Analysis Plan was finalized. There were no subsequent amendments to the original version.

8. REFERENCES

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9. APPENDICES

9.1. Schedule of Assessments

Trial Periods/Phases	Screening (2 weeks)[a]		Treatment									Follow-up (4 weeks)		
			Titration (2 weeks)			Maintenance (12 weeks)								
Visit/Contact	**Screening/ Visit 1**	**Baseline/ Visit 2**		**Telephone Contact**	**Visit 3**	**Telephone Contact**	**Visit 4**	**Telephone Contact**	**Visit 5**	**Telephone Contact**	**Visit 6**	**Visit 7 (Telephone)**	**Visit 8 (Telephone)**	**Visit 9**
Day	**-16 to -2**	**-1**	**1**	**7**	**14**	**28**	**42**	**56**	**70**	**84**	**98/ET[b]**	**101**	**105**	**131**
Window				**±3 days**								**±1 day**	**±3 days**	
Entrance and History														
Informed consent	X													
Review inclusion/exclusion criteria	X	X[c,d]												
Medical and psychiatric history[e]	←----------	----------→												
MINI	X													
Demography	X													
History of drug and alcohol use	X													
Nicotine use and history	X	X			X		X		X		X			
Review of birth control methods	X	X			X		X		X		X			X
Breathalyzer test for alcohol[f]	X	X												
Dispense diary and train on use	X													
Efficacy Assessments														
Review diary including compliance with use of diary		X		X	X	X	X	X	X	X	X	X	X[g]	
PDSS	X	X					X		X		X			

Trial Periods/Phases	Screening (2 weeks)[a]		Treatment									Follow-up (4 weeks)		
			Titration (2 weeks)			Maintenance (12 weeks)								
Visit/Contact	**Screening/ Visit 1**	**Baseline/ Visit 2**		**Telephone Contact**	**Visit 3**	**Telephone Contact**	**Visit 4**	**Telephone Contact**	**Visit 5**	**Telephone Contact**	**Visit 6**	**Visit 7 (Telephone)**	**Visit 8 (Telephone)**	**Visit 9**
Day	**-16 to -2**	**-1**	**1**	**7**	**14**	**28**	**42**	**56**	**70**	**84**	**98/ET[b]**	**101**	**105**	**131**
Window				**±3 days**								**±1 day**	**±3 days**	
CGI-S		X			X		X		X		X			
Other Assessments														
SDS		X					X				X			
HAM-A		X			X		X		X		X			
EQ-5D-5L		X									X			
Safety Assessments														
Height (Screening only) and weight	X	X					X				X			
Physical/neurological examination[h]	X	X									X			
ECG[i]	X	X					X				X			
Vital signs[j]	X	X			X		X		X		X			
C-SSRS	X	X			X		X		X		X			
PWC											X[k]	X	X	
Prior/concomitant treatments[l]	←----------													----------→
Adverse event monitoring[m]			←----------											----------→
Laboratory														
Blood for safety laboratory	X	X			X		X		X		X			X
Serum pregnancy test[n]	X													
Urine pregnancy test[n]		X			X		X		X		X			X

Trial Periods/Phases	Screening (2 weeks)[a]		Treatment									Follow-up (4 weeks)		
			Titration (2 weeks)			Maintenance (12 weeks)								
Visit/Contact	**Screening/ Visit 1**	**Baseline/ Visit 2**		**Telephone Contact**	**Visit 3**	**Telephone Contact**	**Visit 4**	**Telephone Contact**	**Visit 5**	**Telephone Contact**	**Visit 6**	**Visit 7 (Telephone)**	**Visit 8 (Telephone)**	**Visit 9**
Day	**-16 to -2**	**-1**	**1**	**7**	**14**	**28**	**42**	**56**	**70**	**84**	**98/ET[b]**	**101**	**105**	**131**
Window				**±3 days**								**±1 day**	**±3 days**	
Urine for safety laboratory	X	X									X			
Urine drug screening[o]	X	X			X		X		X		X			
Screening only laboratory tests: hepatitis B, C, HIV, and serum FSH[p,q]	X													
PK blood sample[r]					X		X		X		X			
Blood sample for future biospecimen research[s]		X												
Other														
IMP dispensing		X[t]			X		X		X					
Dosing starts			X											

Abbreviations: BID=twice daily; CGI-S=Clinical Global Impression-Severity of Symptoms Scale; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EQ-5D-5L=European Quality of Life; ET=early termination; FSH=follicle-stimulating hormone; HAM-A=Hamilton Anxiety Scale; HIV=human immunodeficiency virus; IMP=investigational medicinal product; MINI=Mini International Neuropsychiatric Interview; PCR=polymerase chain reaction; PDSS=Panic Disorder Severity Scale; PK=pharmacokinetic; PWC=Physician's Withdrawal Checklist; SDS=Sheehan Disability Scale.

[a] Participants will enter a Screening Period of approximately 2 weeks (minimum 14 days). The Screening Period may be extended up to 28 days if needed following consultation with the medical monitor.

[b] If a participant discontinues early, the participant should follow the safety follow-up procedures (Visits 7-9).

[c] Review of inclusion/exclusion criteria includes review of diary data to assess panic attack frequency.

[d] Inclusion/exclusion criteria will be assessed at Baseline to ensure ongoing participant eligibility, with the exception of age or assessments that are only scheduled during Screening (eg, height for body mass index calculation).

[e] Medical occurrences that begin before the start of dosing with IMP but after obtaining informed consent should be collected as medical and/or psychiatric history.

[f] A breathalyzer alcohol test is required at the Screening Visit and at Baseline. The alcohol test (breathalyzer or blood/urine) can be conducted at any time during the trial at the discretion of the investigator.

[g] The diary will be collected through Visit 8 (Day 105). Physical devices will be collected at the last in-person visit.
[h] Full physical and neurological examinations should be completed at Screening. Limited examinations (cardiovascular, pulmonary, and gastrointestinal) should be completed at all other specified time points. Symptom-driven physical and/or neurological examinations may be done at any time during the trial at the investigator's discretion.
[i] 12-lead ECG assessments will be performed after the participant has been at rest for approximately 3 minutes. At Screening, the average of 3 consecutive ECGs collected 1 to 2 minutes apart will be used to determine participant eligibility; at Baseline, only 1 reading is required for determination of eligibility. Single ECGs will be obtained at all other time points. Additional ECGs can be performed at the investigator's discretion (eg, if abnormalities are noted).
[j] Blood pressure and heart rate assessments should be performed in order to confirm eligibility (see Exclusion Criterion in Protocol Section 5.2). Triplicate supine heart rate and blood pressure measurements should be taken at approximately 1-minute intervals at the Screening Visit. Duplicate supine heart rate and blood pressure measurements will be taken at all other time points. The supine heart rate and blood pressure measurements will be followed by a single measurement after approximately 2 minutes in a standing position to allow for orthostatic assessments. Additional time points can be added at the investigator's discretion (eg, if abnormalities are noted). Further details are provided in Protocol Section 8.2.3 and in the Operations Manual.
[k] Visit 6 will be considered the baseline assessment for the PWC.
[l] Prior and concomitant medications, including cannabis products, should be recorded from Screening through the participant's last visit/contact.
[m] Adverse events (serious and nonserious) should be recorded from the first dose of IMP on Day 1 (eg, the day after Baseline) through the participant's last visit/contact.
[n] For women of childbearing potential only. Pregnancy tests can be performed at any time during the trial at the discretion of the investigator if pregnancy is suspected. Any urine pregnancy tests that are positive must be confirmed using a serum test.
[o] Additional urine drug screening can be conducted at any time during the trial at the discretion of the investigator.
[p] Reflex viral hepatitis C PCR testing if hepatitis C antibody is positive or indeterminate.
[q] A confirmatory FSH is required for all postmenopausal women.
[r] With participants maintaining their normal BID dosing routine, a single daytime blood sample for determination of plasma darigabat concentration will be collected at Visits 3, 4, 5, and 6. The date and time of the PK sample, as well as the time of ingestion of previous dose of IMP, will be recorded in the source documentation.
[s] Future biospecimen research sample is optional and is only to be collected if signed consent is obtained from the participant. Sample can be collected at any time following confirmation of participant eligibility and prior to initiation of first dose.
[t] Randomization will occur at Baseline and IMP will be dispensed after randomization. Participants will start taking IMP on Day 1 (eg, the day following their Baseline Visit). Dosing will continue through Visit 6 (Day 98) or ET.

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 participant 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 CRF 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 participant 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 participant 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 participant 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 participant 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 participant 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 participants 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 participants actually summarized within any given summary module; some participants 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 participants actually contributing to the summary statistics presented in any given summary module. As mentioned above, this may be less than the number of participants 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, participant 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:
    - 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.
- Means 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.

- 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 participant 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. 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	-

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 = 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

The baseline criterion will only apply to post-baseline assessments.

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
Alkalosis 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

9.6. Abbreviations

Abbreviation	Definition
ACT	Acceptance and Commitment Therapy
AE	Adverse event
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APMP	Abuse Potential Monitoring Plan
AR[1]	First-order Autoregressive Structure
AST	Aspartate aminotransferase
BID	Twice daily
BLQ	Below the level of quantification
CBT	Cognitive Behavioral Therapy
CGI-S	Clinical Global Impression Severity of Symptoms Scale
CI	Confidence interval
CRF	Case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology of Criteria for Adverse Events
CV%	Coefficient of variation
DSM-5-TR	Diagnostic And Statistical Manual Of Mental Disorders, Fifth Edition, Text Revision
eCFR	Electronic case report form
ECG	Electrocardiograms
EQ-5D-5L	European Quality of Life
EQ-VAS	EQ Visual Analog Scale
HAM-A	Hamilton Anxiety Rating Scale
ICE	Intercurrent event
IMP	Investigational medicinal product
IRT	Interactive Response Technology
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
MAR	Missing at random
MNAR	Missing not at random
MBCT	Mindfulness Based Cognitive Therapy

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
MMRM	Mixed model for repeated measures
n	Number of observations
N	Number of participants
PDSS	Panic Disorder Severity Scale
PK	Pharmacokinetic
PWC	Physician Withdrawal Checklist
Q1	First quartile
Q3	Third quartile
QTcF	Corrected QT values using Fridericia's method
SAE	Serious adverse event
SDS	Sheehan Disability Scale
SE	Standard error of the mean
TEAE	Treatment-emergent adverse events
TESAE	Treatment-emergent serious adverse event
ULN	Upper limit of normal
VAS	Visual analog scale
WHO	World Health Organization