CLINICAL PROTOCOL

Title:	A Phase 2, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy, Safety, and Tolerability of Darigabat in Participants With Panic Disorder (ADAPT Trial)
Trial Number:	CVL-865-PA-2001
Trial Phase:	2
Compound:	Darigabat (CVL-865)
Sponsor Name:	Cerevel Therapeutics, LLC
Legal Registered Address:	222 Jacobs Street, Suite 200 Cambridge, MA 02141 US
Health Authority Identifier Number(s):	IND 162,966

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

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

CONFIDENTIAL – PROPRIETARY INFORMATION

Version 3.0: 24 Jan 2024

Version 2.0: 17 Jul 2023

Version 1.0: 04 Jan 2023

SPONSOR SIGNATORIES

PROTOCOL VERSION 3.0 SUMMARY OF CHANGES TABLE

Document History	
Protocol Version	**Date**
3.0	24 Jan 2024
2.0	17 Jul 2023
1.0	04 Jan 2023

Amendment: Protocol Version 3.0 (24 Jan 2024)

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

Overall Rationale for the Amendment:

The overall rationale for this amendment is to extend the Screening Period to provide adequate time for participants to become competent in eDiary use and to clarify trial procedures based on feedback from sites. The amendment also incorporates items communicated in the Sponsor's protocol clarification letter dated 28 Sep 2023.

Section # and Name	Description of Change	Brief Rationale
Sponsor Signatories	Medical Lead and Biostats Lead changed.	Updated due to change in personnel
Section 1.1 Synopsis	Updated the synopsis to reflect changes made in the body.	Change made for internal consistency
Section 1.2 Schema	Updated "2-week Screening" to "up to 4 weeks Screening"; updated number of participants; added a visual to identify the titration period within each group and updated the footnote to reference the dosing schedule table; added a footnote to indicate that randomization occurs at Baseline	Change made to align with extending the Screening Period for at least 14 days and up to 28 days; sample size revised to ensure adequate number of participants complete to achieve trial objectives; visually identifying the Titration Period within each group, referencing the dosing schedule table, and specifying that randomization occurs at Baseline provides additional clarity
Section 1.3 Schedule of Assessments	Changed Trial Period for Screening from "2 weeks" to "up to 4 weeks" and updated footnote "a" accordingly.	Change made to align with extending the Screening Period for at least 14 days and up to 28 days

Section # and Name	Description of Change	Brief Rationale
	Changed Screening/Visit 1 Day from "-16 to -2" to "-28 to -2"	
Section 4.1 Overall Design	Added the DSM-5-TR definition of a panic attack	To clarify the existing protocol text
Section 4.1 Overall Design	Updated the trial duration to up to 25 weeks	Change made to align with extending the Screening Period for at least 14 days and up to 28 days
Section 4.1 Overall Design and Section 4.1.1 Screening Period	Extended the Screening Period to up to 28 days	To provide participants with sufficient time to learn and practice the eDiary to increase the accuracy and compliance of eDiary data entry by participants
Section 4.1.1 Screening Period	Clarified that participants will train on eDiary use and on the definition of panic attack and associated symptoms at the Screening Visit	Change made to clarify that participants will receive adequate instruction and training to become competent in eDiary use
Section 4.1.1 Screening Period	Added details about the requirements in the new version of the eDiary (eg, panic attack presence/absence recorded contemporaneous to the day being assessed; the presence as well as the absence of each DSM-5-TR panic attack symptom associated with a given panic attack).	To specify eDiary information as the requirements in the new version of the eDiary should minimize any potential recall bias and clearly distinguish between missing data and the absence of a panic attack or a specific symptom
Section 4.1.1 Screening Period	Added that the participant must have a minimum of 11 eDiary day entries during the 14 days preceding the Baseline Visit	To ensure that enrolled participants can comply with eDiary completion, the minimum number of eDiary day entries that must be completed for assessing panic attack eligibility during the Screening Period was specified
Section 4.1.1 Screening Period	Described the panic attack eligibility criteria and assessment period if the Screening window is extended	Additional clarity for site personnel as panic attack eligibility criteria will be based on the 14-day period prior to the Baseline Visit even if the Screening window is extended
Section 4.1.1 Screening Period	Removed Progressive Exposure as an example of evidence-based	Change made to reduce confusion with terms

Section # and Name	Description of Change	Brief Rationale
	psychotherapy that is allowed in the trial if initiated >3 months prior to the Screening Visit	
Section 4.1.2 Treatment Period and Section 4.1.3 Follow-up Period	Clarified that participants will continue to record requested information in the eDiary during both the Titration and Maintenance Treatment Periods and during the Follow-up Period for up to 7 days after last dose of IMP	Change made to clarify the duration of eDiary use throughout the trial
Section 4.1.3 Follow-up Period	Added that participants will be monitored for withdrawal symptoms approximately 3 days and 7 days after last dose of IMP	Clarification made to align with the Schedule of Assessments
Section 5.1 Inclusion Criteria	Added a clarifying note to inclusion criterion #3 indicating that the participant must complete a minimum of 11 eDiary day entries in the 14 days preceding the Baseline Visit	To clarify the minimum number of eDiary day entries that must be completed for assessing panic attack eligibility during the Screening Period
Section 6.7.2 Prohibited Therapy	Clarified in Table 5 that the washout duration is based on the period prior to the Baseline Visit and that the Screening Period may be extended if needed to accommodate a washout duration that is longer than 28 days following consultation with the medical monitor	To clarify the required washout durations
Section 6.7.2 Prohibited Therapy	Clarified in Table 6 that topical cannabidiol (CBD) will be evaluated on an individual basis	To clarify that topical CBD used for muscle spasms or massages may be permitted upon discussion with the medical monitor
Section 6.7.2 Prohibited Therapy	Added systemic steroids are prohibited to Table 6. Any	To correct an inadvertent omission

Section # and Name	Description of Change	Brief Rationale
	steroid that is not systemic is permitted.	
Section 7.2 Participant Discontinuation/Withdrawal From the Trial	Added a clarifying statement for procedures that should be conducted if a participant discontinues investigational medicinal product	Additional clarity for site personnel
Section 8.1.1 Panic Attack Frequency	Removed "duration" from information recorded in the eDiary; added details about the requirements in the new version of the eDiary (eg, panic attack presence/absence recorded contemporaneous to the day being assessed; the presence as well as the absence of each DSM-5-TR panic attack symptom associated with a panic attack); added that the participant must have a minimum of 11 eDiary day entries during the 14 days preceding the Baseline Visit	To specify eDiary information as the requirements in the new version of the eDiary should minimize any potential recall bias and clearly distinguish between missing data and the absence of a panic attack or a specific symptom. To ensure that enrolled participants can comply with eDiary completion, the minimum number of eDiary day entries that must be completed for assessing panic attack eligibility during the Screening Period was specified.
Section 8.1.3 Clinical Global Impression-Severity of Symptoms Scale	Changed "mentally ill" to "ill with panic disorder symptoms"	Change made to focus specifically on the severity of panic disorder symptoms
Section 9.2 Analysis Sets	Defined Full Analysis Set (FAS) to be used for analysis of endpoints related to panic attacks assessments captured by eDiary. In addition to FAS criterion defined in the previous protocol version, inclusion in FAS requires that panic attack assessments are made using an eDiary, which implements the requirements described in the current protocol version.	To update the FAS definition in accordance with the changes in the new version of the eDiary

Section # and Name	Description of Change	Brief Rationale
	The definition of the second efficacy analysis population remains as in the previous protocol version and will be used for analysis of efficacy endpoints not collected by eDiary.	
Section 9.3.2 Primary Endpoint/Estimand Analyses and Section 9.3.3.2 Change From Baseline in Panic Attack Frequency During the Last 2 Weeks of the Maintenance Treatment Period	Specified that additional sensitivity analyses will include all participants regardless of panic attack eDiary version used	To reflect revisions to the analysis population as 18 participants whose panic attack assessments were made prior to implementation of the new eDiary requirements will be excluded from the primary efficacy analysis
Section 9.3.5 Safety Analyses	Clarified that severity will be assessed by National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE)	To clarify the existing protocol text
Section 9.5 Sample Size Determination	Updated number of participants to be randomized to 246 in order to achieve the required sample size of 228.	This update was made to reflect revisions to the analysis population to be used for primary efficacy analysis as described in the current protocol version. Eighteen participants whose panic attack assessments were made prior to implementation of the eDiary requirements will be excluded from the primary efficacy analysis but included in other efficacy analyses that are not based on eDiary assessments
Section 10.2 Clinical Laboratory Tests	Language added to clarify that fasting for at least 8 hours prior to obtaining laboratory tests is requested (but not required)	Additional guidance for site personnel as fasting is requested (but not required) prior to laboratory tests
Overall	Minor grammatical and wording corrections/clarifications made throughout protocol	Correct errors or provide further clarification

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase 2, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy, Safety, and Tolerability of Darigabat in Participants With Panic Disorder (ADAPT Trial)

Short Title:

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

Rationale:

Darigabat (previously referred to as CVL-865; PF-06372865) is a novel, small molecule, brain penetrable, positive allosteric modulator (PAM) of α2, α3, and α5 subunit-containing gamma-amino-butyric-acid type A ($GABA_A$) receptors with minimal functional activity at α1 subunit-containing receptors. Darigabat is being developed for the treatment of epilepsy and anxiety-related disorders, including panic disorder. Based on the mechanism of action and emerging clinical evidence demonstrating darigabat reduces acute panic and fear symptoms induced by carbon dioxide (CO_2) inhalation in healthy participants (Trial CVL-865-HV-001), darigabat could be a potential effective treatment for patients with panic disorder.

The aim of this trial is to investigate the efficacy, safety, and tolerability of darigabat in participants with panic disorder.

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 2 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 2 weeks of the Maintenance Treatment Period Secondary Efficacy Endpoints: • Change from Baseline 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
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.

Brief Summary (Lay Language):

The purpose of this trial is to measure the efficacy, safety, and tolerability of darigabat (25 mg twice daily [BID]) compared with placebo in participants with panic disorder. Trial details include:

- Trial duration for an individual participant: up to 25 weeks
- Treatment duration: up to 14 weeks
- Visit frequency: all eligible participants will visit the clinical site at regular intervals (approximately 4-week intervals for the majority of trial with more frequent visits during the early part of trial)

Overall Design:

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 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

Participants will enter a Screening Period of at least 14 days and up to 28 days to provide participants with sufficient time to learn and practice the eDiary to increase accuracy and compliance of eDiary data entry by participants. In addition, the increased time may allow for washout from prior prohibited medications that require a period of longer than 2 weeks.

At the Screening Visit, participants will train on eDiary use and on the definition of panic attack and associated symptoms. Participants will record the presence/absence of panic attacks along with associated symptoms for a given day with a recall time of immediate to end of day on that same day. For each panic attack, the presence or absence of each symptom referenced in the DSM-5-TR criteria will be recorded in the eDiary. Prior to the 14-day eligibility period, participants will be strongly encouraged to practice the eDiary at home to ensure compliance and accuracy throughout the eligibility period and the trial. Entries during the 14-day eligibility period prior to the Baseline Visit will be used to assess panic attack eligibility.

During the Screening Period, participants should complete an eDiary entry each day, including days free of panic attacks, and must have a minimum of 11 eDiary day entries completed during the 14 days preceding the Baseline Visit. The recommendation is for all participants to complete the eDiary every single day (14 days). If a participant misses more than 3 days of eDiary entries during the 14 days preceding the Baseline Visit, the participant will result in a Screen Failure. Should there be unprecedented circumstances (eg, phone stops working), please consult the trial medical monitor. If a participant has their Screening window extended, panic attack eligibility will be assessed based on the 14 days prior to the Baseline Visit; the participant must have at least 4 panic attacks with at least 4 associated symptoms per DSM-5-TR criteria within the new 14-day window, with no week free of panic attacks, prior to the Baseline Visit.

On Day -1 (Baseline), 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. The medical monitor should be consulted regarding any psychotherapy that is not listed.

Participants will initiate outpatient dosing beginning on Day 1 (the day after the Baseline Visit). During the 2-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 12-week Maintenance Treatment Period.

Participants will continue to record all requested information in the eDiary for each day during both the 2-week Titration and 12-week Maintenance Treatment Periods.

Follow-up telephone contacts will be performed within 3 days and 7 days after the last dose of investigational medicinal product (IMP) and an in-clinic follow-up visit will be performed approximately 33 days after the last dose of IMP. The Physician Withdrawal Checklist (PWC) will be used to monitor for 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.

Number of Participants:

Approximately 246 participants who satisfy all inclusion/exclusion criteria and thus are eligible for the trial will be randomized to treatment (approximately 123 participants per group).

In the event of higher than anticipated early terminations, Cerevel may extend enrollment to achieve trial objectives.

Key Entry Criteria:

- Men and women 18 to 65 years of age, inclusive, with a primary diagnosis of panic disorder based on the DSM-5-TR criteria (present for at least 6 months prior to the Screening Visit) and confirmed by the MINI
- Participants with a minimum of 8 panic attacks, with no week free of panic attacks, in the month prior to the Screening Visit. In the 14 days preceding the Baseline Visit, the participant must have had at least 4 panic attacks and no week free of panic attacks. Note: Participant must complete a minimum of 11 eDiary day entries, including days free of panic attacks, in the 14 days preceding the Baseline Visit.
- Participants with a Panic Disorder Severity Scale (PDSS) total score ≥12 at the Screening and Baseline Visits

Intervention Groups and Duration:

Participants will receive treatment with darigabat 25 mg BID or placebo during the Treatment Period of the trial.

The trial will include a Screening Period of at least 14 days and up to 28 days, a 14-week Treatment Period that includes a 2-week Titration Period to target dose, and a 33-day Follow-up Period. Each participant will participate in the trial for up to 25 weeks.

Statistical Considerations:

Sample Size Estimate

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 (eg, 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 (ie, 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]).

Statistical Methods

Efficacy 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 2 weeks of the Maintenance Treatment Period 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% CI
5. A composite strategy will be used to address missing values due to ICEs regardless of whether they are considered as treatment related. Specifically, participants who fail to achieve panic attack free in the last 2 weeks of treatment prior to ICE will be considered as failure for all following time points.

For the primary efficacy endpoint, the number and proportion of participants who are free of panic attacks during the last 2 weeks of the Maintenance Treatment Period will be summarized by visit and treatment group. The binomial repeated measures will be analyzed using the SAS® GLIMMIX procedure with logit link. The Baseline PDSS total score will be included as a covariate, and the treatment group, visits, evidence-based psychotherapy use, and interaction between treatment group and visit will be included as fixed effect. An unstructured covariance structure will be used for the repeated measures. The odds ratio of active dose to placebo at the endpoint visit will be estimated based on the least squares mean difference in logit between the treatment groups from the GLIMMIX model with the associated 95% CI and p-values. A sensitivity analysis using Fisher's exact test and 95% exact CI will be performed to assess the robustness of the conclusion from the logistic regression.

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% CI based on a mixed model for repeated measures (MMRM) model
5. Missing values due to ICEs to be addressed by a hypothetical strategy followed by tipping point analyses

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 effect 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. Subject 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. 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 second 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 panic attack frequency during the last 2 weeks of the Maintenance Treatment Period as the endpoint of interest
4. The population level summary of interest is the estimated treatment differences in median and the 95% Hodges-Lehmann CI
5. A composite strategy will be used to handle missing values due to ICEs. The cases of potential treatment-related ICEs will be assigned the worst rank and other cases of missing outcomes from ICEs will be assigned the second worst rank

The change from Baseline to each trial visit in frequency of panic attacks, will be summarized by visit and treatment group. A non-parametric analysis using Mann-Whitney test performed on the change from Baseline during the last 2 weeks of the Maintenance Treatment Period will be the basis for comparison between the 2 treatment groups. A supportive analysis of frequency of panic attacks recorded at each visit will be performed using a Poisson or negative binomial regression with fixed effect of treatment group, visits, evidence-based psychotherapy use, and interaction between treatment group and visit. The Baseline panic attack frequency will be included as a covariate. Subject will be included as a random effect.

Safety Analysis

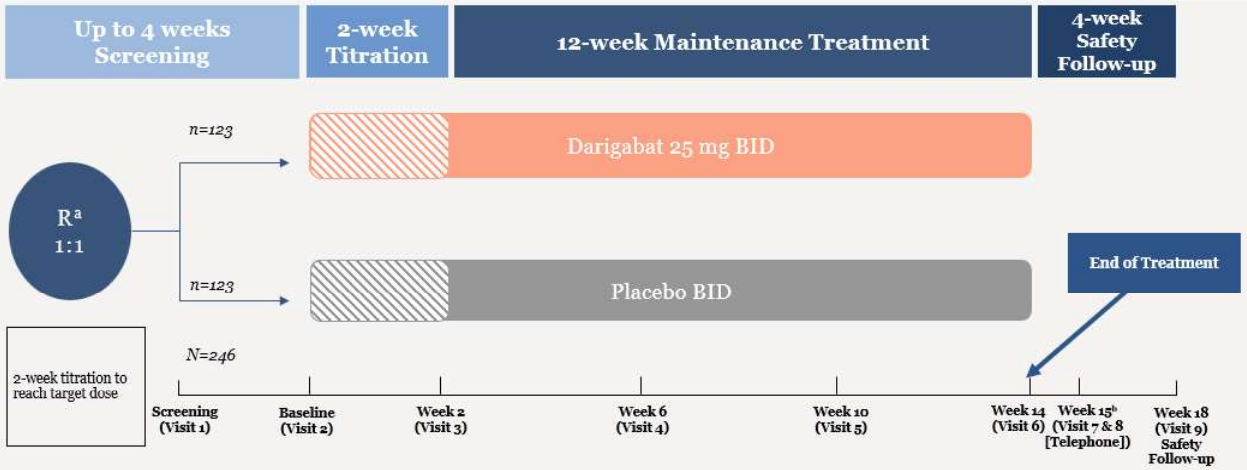
Treatment-emergent adverse events (serious and nonserious) will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by treatment group, system organ class, and preferred term. Further summaries will be done by severity (assessed by National Cancer Institute-Common Terminology Criteria for Adverse Events), relationship to IMP, and dose at the time of onset. The frequency (or incidence) of abuse potential will be summarized by treatment group. Other safety endpoints will be summarized with descriptive statistics by treatment group, including suicidality monitored during the trial using the Columbia-Suicide Severity Rating Scale (C-SSRS) and withdrawal symptoms using the PWC.

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.

1.2. Schema

A schematic of the trial design is provided 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 Table 3.
[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.

1.3. Schedule of Assessments

Trial procedures and their timing are summarized in the Schedule of Assessments provided in Table 1.

Table 1: Schedule of Assessments

Trial Periods/Phases	Screening (up to 4 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	**-28 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												
eDiary training	X													
Efficacy Assessments														
Review eDiary including compliance with use of eDiary		X		X	X	X	X	X	X	X	X	X	X[g]	
PDSS	X	X					X		X		X			
CGI-S		X			X		X		X		X			
Other Assessments														
SDS		X					X				X			

Trial Periods/Phases	Screening (up to 4 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	**-28 to -2**	**-1**	**1**	**7**	**14**	**28**	**42**	**56**	**70**	**84**	**98/ET[b]**	**101**	**105**	**131**
Window				**±3 days**								**±1 day**	**±3 days**	
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
Urine for safety laboratory	X	X									X			
Urine drug screening[o]	X	X			X		X		X		X			

Trial Periods/Phases	Screening (up to 4 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	**-28 to -2**	**-1**	**1**	**7**	**14**	**28**	**42**	**56**	**70**	**84**	**98/ET[b]**	**101**	**105**	**131**
Window				**±3 days**								**±1 day**	**±3 days**	
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 at least 14 days and up to 28 days.

[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 eDiary 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 eDiary 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 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 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.

2. INTRODUCTION

2.1. Trial Rationale

Darigabat (previously referred to as CVL-865; PF-06372865) is a novel, small molecule, brain penetrable, positive allosteric modulator (PAM) of α2, α3, and α5 subunit-containing $GABA_A$ receptors with minimal functional activity at α1 subunit-containing receptors. Darigabat is being developed for the treatment of epilepsy and anxiety-related disorders, including panic disorder. Based on the mechanism of action and emerging clinical evidence demonstrating darigabat reduces acute panic and fear symptoms induced by CO_2 inhalation in healthy participants (Trial CVL-865-HV-001), darigabat could be a potential effective treatment for patients with panic disorder.

The aim of this trial is to investigate the efficacy, safety, and tolerability of darigabat in participants with panic disorder.

2.2. Background

2.2.1. Panic Disorder Overview

Panic disorder is a serious condition that can cause significant psychological and physical distress. Panic disorder manifests as recurrent, unexpected panic attacks, and a persistent fear of future panic attacks and their consequences with subsequent maladaptive behavioral changes (NIMH Panic Disorder). According to the DSM-5, the average 12-month prevalence of panic disorder is 2% to 3% in the US and EU across adults and adolescents. Another US-focused survey of 9,282 adults reported a lifetime panic disorder prevalence of 4.7% according to the DSM-IV diagnostic criteria, with a prevalence rate of 3.7% for panic disorder without agoraphobia and 1.1% for panic disorder with agoraphobia (Kessler et al, 2006). Unfortunately, many patients with panic disorder remain symptomatic despite initial intervention.

Current pharmacological treatments for panic disorder consist mainly of benzodiazepines (BZDs), selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, and monoamine oxidase inhibitors, with overall no evidence for the superiority for any one of the classes (Chawla et al, 2022; APA Work Group on Panic Disorder, 2009). Although monotherapy with SSRIs or SNRIs is the recommended first-line option for patients with panic disorder, BZDs may also be used as a monotherapy for patients without a co-occurring mood disorder when rapid control of distressing or impairing symptoms is critical (APA Work Group on Panic Disorder, 2009). In addition, the side effects associated with SSRIs and their delayed onset of effects are contributing factors for suboptimal adherence to and discontinuation of therapy, which may occur before efficacy is observed (Cowley et al, 1997).

BZDs are PAMs of $GABA_A$ receptors and non-selectively modulate α1, α2, α3, and α5 subunit-containing receptors and have widespread utility in neurology and psychiatry. However, the use of BZDs is also associated with significant adverse effects that limit their clinical utility, including sedation, psychomotor impairment, and other adverse effects such as the risk of

physical dependence (Schweizer et al, 1993; Rickels et al, 1983). Due to this increased risk, FDA in 2020 required a class-wide, boxed warning labeling change for BZDs to include the risk of abuse, misuse, addiction, physical dependence, and withdrawal reactions to help improve the safe use of BZDs.

Despite the availability of therapies, 56% of patients with panic disorder are not receiving therapy (Manjunatha and Ram, 2022). For those on treatment, a significant proportion of patients with panic disorder have an incomplete or partial response to available treatments with a low likelihood of complete and persistent remission (Manjunatha and Ram, 2022; Teismann et al, 2018; Scholten et al, 2013; Bruce et al, 2005; Pollack and Marzol, 2000; Keller et al, 1994). The various undesirable side effect profiles of available therapies contribute to suboptimal adherence and early discontinuation of therapy, which increases the probability of relapse. In addition, there have been limited new treatment options with no recent drug approvals for the treatment of panic disorder in the US since venlafaxine was approved in 2005 (BioSpace, 2005). Taken together, there is a clear unmet need for new treatments for panic disorder that can deliver symptomatic relief while maintaining a favorable tolerability profile.

2.2.2. Darigabat

Darigabat, a PAM of α2, α3, and α5 subunit-containing $GABA_A$ receptors that is structurally distinct from BZDs, has shown high affinity binding to the BZD site, but exhibits activity at α2, α3, and α5 subunits and minimal activity at the α1 subunit. The α2 and α3 subunits of $GABA_A$ receptors are thought to mediate the anxiolytic effects of BZDs without the BZD-associated adverse effects that are mediated via the $GABA_A$ α1 subunits (Rudolph et al, 1999). Evidence based on molecular genetic approaches, as well as testing subtype selective compounds in a range of other rodent and non-human primate models, also suggests that $GABA_A$ α2/3 receptors are associated with the anxiolytic effects of BZDs and that the α1 subtype is responsible for the sedative properties of BZDs. Studies in mouse models have supported the involvement of α2-containing $GABA_A$ receptors in anxiety and that drug binding to these α2-containing $GABA_A$ receptors is required for anxiolytic effects of GABAergic drugs, including diazepam (Löw et al, 2000; Smith et al, 2012; Engin et al, 2012). In adult rhesus monkeys, the anxiolytic effects of BZD-like drugs involved α2, α3, and α5 $GABA_A$ receptors, while the sedative properties of these drugs were likely mediated by the α1 subunit (Rowlett et al, 2005). Therefore, darigabat is a candidate for development as a treatment of panic disorder that is not expected to mediate effects via the α1 subunit.

2.2.2.1. Nonclinical Experience

Nonclinical studies have been conducted to assess darigabat's potential anxiolytic-like effects and motor function effects. Darigabat was tested in C57B1/6 mice in the elevated plus maze to characterize potential anxiolytic-like effects, with darigabat oral doses of 3.2 mg/kg and 10 mg/kg producing anxiolytic-like effects similar in magnitude to 3 mg/kg diazepam. At the minimally effective darigabat dose (3.2 mg/kg), plasma exposure levels were estimated to correlate with approximately 50% RO.

Darigabat oral doses up to 10 mg/kg in the mouse rotarod assay did not result in any motor impairment (comparable to vehicle group) while diazepam (10 mg/kg) resulted in motor impairment as indicated by a statistically significant reduction in mean fall latency time.

Darigabat has been tested in a battery of in vitro and in vivo genetic toxicity studies, single- and repeat-dose toxicity studies up to 6 months' duration in rats and up to 9 months' duration in dogs by oral gavage, and tested in a battery of cardiovascular, respiratory, and CNS safety pharmacology studies. The nonclinical studies conducted to date with darigabat support long-term dosing in clinical trials, including this Phase 2 trial in participants with panic disorder.

Please refer to the darigabat Investigator's Brochure for a summary of available nonclinical safety data.

2.2.2.2. Clinical Experience

Darigabat has been evaluated in 8 completed Phase 1 trials and 3 completed Phase 2 proof-of-concept trials. In the completed Phase 1 trials, darigabat was safe and well tolerated. There were no TEAEs leading to discontinuation attributed to darigabat. There were no safety signals.

In the 3 completed Phase 2 trials, there were no safety signals. Four participants (all in the darigabat treatment groups) were permanently discontinued due to treatment-related AEs (severe panic attack; mild severity AEs of increased ALT, increased AST, and muscle aches and moderate severity AEs of fatigue, dizziness, and drowsiness, which occurred throughout the trial; moderate severity macular papular rash over the entire body; and severe TIA). The severe panic attack occurred on Day 4 while on the first week of titration, and the participant was discontinued from the trial.

In the combined Phase 1 and 2 trials, a total of 6 SAEs have been reported. No treatment-related SAEs were reported in the completed Phase 1 trials. One SAE in the completed Phase 2 trials was considered by the investigator to be related to darigabat and the participant was discontinued (TIA in Trial B7431006 in a participant with a history of high serum cholesterol levels, high blood pressure, and a high BMI and was diagnosed with diabetes mellitus after onset of the TIA).

Clinically, the first investigation of the anxiolytic potential of darigabat was in participants with GAD (Trial B7431007) showing an incomplete response to current standard-of-care pharmacotherapy (Simen et al, 2019). Two doses of darigabat (2.5 mg BID and 7.5 mg BID) were compared against placebo in a total of 90 of planned 384 participants in a trial that was terminated early for non-safety reasons. Neither dose of darigabat differentiated from placebo on the efficacy endpoints (the Hamilton Anxiety Rating Scale total score [primary] or Sheehan Disability Scale total score [secondary]). Factors potentially contributing to the negative primary and secondary efficacy results include the limited sample size and a failure to explore a higher occupancy range (ie, the maximum RO achieved at the higher dose was approximately 50%).

The anxiolytic effects of multiple doses of darigabat (7.5 mg BID and 25 mg BID) were more specifically evaluated in Trial CVL-865-HV-001 using a CO_2 inhalation model that is associated with symptoms of anxiety/panic and is known to be sensitive to the effects of anxiolytic BZDs (Salvadore et al, 2020; Colasanti et al, 2008; Woods et al, 1988; Woods et al, 1986; Gorman et al, 1984; Van den Hout and Griez, 1984). Alprazolam XR 1 mg BID was included as a positive

control. Both doses of darigabat exhibited an anxiolytic effect compared with placebo on PSL-IV total score (primary endpoint). Darigabat 7.5 mg BID also demonstrated an anxiolytic effect on Fear VAS (key secondary endpoint). The effect on Fear VAS for darigabat 25 mg BID was a 7.8-millimeter reduction (improvement) versus placebo. Plasma concentrations of darigabat were dose related and corresponded with estimated $GABA_A$ α2 receptor occupancy of approximately 50% and 80% for the 7.5 mg BID and 25 mg BID doses, respectively.

Additional details about the safety of darigabat for the completed clinical trials can be found in the darigabat Investigator's Brochure.

2.3. Benefit/Risk Assessment

This trial is designed primarily to evaluate the efficacy, safety, and tolerability of darigabat 25 mg BID in the target patient population.

There are no identified risks for darigabat at this time. Somnolence and dizziness, fetal toxicity, bone marrow suppression, impairment of spermatogenesis and on male fertility, and increased mitoses are considered potential risks; however, these potential risks will be minimized during the trial by monitoring AEs, monitoring cell blood counts, and requiring the use of appropriate contraception and regular pregnancy testing.

Based on available safety data for darigabat, the proposed dose of 25 mg darigabat BID is considered to be safe.

More detailed information regarding benefit/risk assessment for darigabat is available in the Investigator's Brochure.

3. OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints are summarized in Table 2.

Banked biospecimens will be collected from consenting participants and stored for potential exploratory research.

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 2 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 2 weeks of the Maintenance Treatment Period Secondary Efficacy Endpoints: • Change from Baseline 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
Exploratory	
• To evaluate the pharmacokinetics of darigabat as monotherapy in adult participants with panic disorder	• Darigabat plasma concentrations

Objectives	Endpoints
• 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.

4. TRIAL DESIGN

4.1. Overall Design

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 BID in male and female participants aged 18 to 65 years, inclusive, who have a primary diagnosis of panic disorder based on the DSM-5-TR criteria (present for at least 6 months prior to the Screening Visit) and confirmed by the 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/Baseline Period of at least 14 days and up to 28 days
- 14-week Treatment Period, including an initial 2-week Titration Period and a 12-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 through the 14-week Treatment Period of the trial may have the opportunity to receive post-trial supportive therapy offered via the sponsor.

4.1.1. Screening Period

Participants will enter a Screening Period of at least 14 days and up to 28 days to provide participants with sufficient time to learn and practice the eDiary to increase accuracy and compliance of eDiary data entry by participants. In addition, the increased time may allow for washout from prior prohibited medications that require a period of longer than 2 weeks.

At the Screening Visit, participants will train on eDiary use and on the definition of panic attack and associated symptoms. Participants will record the presence/absence of panic attacks along with associated symptoms for a given day with a recall time of immediate to end of day on that same day. For each panic attack, the presence or absence of each symptom referenced in the DSM-5-TR criteria (see Section 4.1) will be recorded in the eDiary. Prior to the 14-day eligibility period, participants will be strongly encouraged to practice the eDiary at home to ensure compliance and accuracy throughout the eligibility period and the trial. Entries during the 14-day eligibility period prior to the Baseline Visit will be used to assess panic attack eligibility.

During the Screening Period, participants should complete an eDiary entry each day, including days free of panic attacks, and must have a minimum of 11 eDiary day entries completed during the 14 days preceding the Baseline Visit. The recommendation is for all participants to complete the eDiary every single day (14 days). If a participant misses more than 3 days of eDiary entries during the 14 days preceding the Baseline Visit, the participant will result in a Screen Failure. Should there be unprecedented circumstances (eg, phone stops working), please consult the trial medical monitor. If a participant has their Screening window extended, panic attack eligibility will be assessed based on the 14 days prior to the Baseline Visit; the participant must have at least 4 panic attacks with at least 4 associated symptoms per DSM-5-TR criteria within the new 14-day window, with no week free of panic attacks, prior to the Baseline Visit.

On Day -1 (Baseline), 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. The medical monitor should be consulted regarding any psychotherapy that is not listed.

4.1.2. Treatment Period

Participants will initiate outpatient dosing beginning on Day 1 (the day after the Baseline Visit). During the 2-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 12-week Maintenance Treatment Period. A summary of the dosing schedule is provided in Table 3.

Table 3: 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 Placebos	Matching Placebo

Abbreviation: BID=twice daily.

Participants will continue to record all requested information in the eDiary for each day during both the 2-week Titration and 12-week Maintenance Treatment Periods.

4.1.3. Follow-up Period

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 PWC will be used to monitor for 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.

4.1.4. 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).

A participant is considered to have completed the trial 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 1.3.

4.2. Scientific Rationale for Trial Design

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

The 12-week Maintenance Treatment Period is selected to allow sufficient opportunity to characterize the effect of darigabat. In addition, the Treatment Period is equivalent to or longer than the duration used in previous clinical trials evaluating treatments for panic disorder, in which the duration ranged from 6 weeks to 12 weeks (Nardi et al, 2011; Liebowitz et al, 2009; Pollack et al, 2007; Bradwejn et al, 2005; Pollack et al, 2003; Goddard et al, 2001; Michelson et al, 2001; Schweizer et al, 1990; Munjack et al, 1989; Chouinard et al, 1982).

The dose planned for investigating the efficacy of darigabat for the treatment of panic disorder is 25 mg BID based on the results from the Phase 1 Trial CVL-865-HV-001 and considering the

PK, estimated α2-receptor occupancy, and safety profile from previous trials (see Section 4.3.1). In Trial CVL-865-HV-001, the exposure-response relationship was demonstrated for PSL-IV total score in which darigabat doses, 7.5 mg BID and 25 mg BID, were tested based on the receptor occupancy. A similar exposure-response was observed for SPV, which is a putative marker for desired α2/3 $GABA_A$ receptor engagement (Nickolls et al, 2018). That is, as darigabat plasma concentrations increased, the change from Baseline in SPV decreased. Therefore, the 25 mg BID dose will be used to test the therapeutic potential of darigabat as treatment of panic disorder.

The primary endpoint in this trial is the proportion of participants who are free of panic attacks during the last 2 weeks of the Maintenance Treatment Period. It has been demonstrated that a higher proportion of patients treated with currently approved therapies were free of panic attacks than those treated with placebo at the end of treatment period (Paroxetine Prescribing Information; Fluoxetine Prescribing Information; Venlafaxine Prescribing Information; Clonazepam Prescribing Information; Alprazolam Prescribing Information). A key secondary endpoint, the 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 safety assessments are considered standard for evaluation of neurological compounds. The C-SSRS is commonly used for stringent monitoring of the risk of suicidality in clinical trials (Posner et al, 2011). The PWC is an instrument used to assess BZD-like withdrawal and will be used to monitor for withdrawal symptoms for up to 7 days after the last dose of IMP during the Follow-up Period (Rickels et al, 2008).

4.3. Justification for Dose

4.3.1. Dosing Rationale

Single doses of darigabat up to 100 mg have been safe and well tolerated and associated with mild AEs. No clinically significant findings in ECGs, laboratory results, vital signs, and physical examinations have been observed at doses up to 100 mg. Multiple doses of darigabat up to 42.5 mg BID (2 weeks at target dose) have also been found to be safe and well tolerated in healthy adult participants. At the 25 mg BID dosing level, the common AEs (>25%) reported higher than placebo have been bradyphrenia, dizziness, somnolence, disturbance in attention, fatigue, headache, and constipation. Most AEs were mild. Dose titration may mitigate the occurrence of central nervous system AEs.

The results from Trial CVL-865-HV-001 demonstrated an exposure-response for PSL-IV total score. As darigabat plasma exposure increased, the placebo-corrected change in PSL-IV total score decreased, reflecting the anxiolytic effect of darigabat. This response appeared to plateau at higher concentrations suggesting higher doses may not provide additional benefit considering the exposure in this trial was estimated to achieve α2 and whole brain receptor occupancy of approximately 74% and 85%, respectively, in the 25 mg BID group. A similar exposure response was observed for SPV, which is a putative marker for desired α2/3 $GABA_A$ receptor engagement (Nickolls et al, 2018). That is, as darigabat plasma concentrations increased, the change from Baseline in SPV decreased.

Based on the safety, tolerability, PK/PD profile, and anxiolytic results from completed Phase 1 and 2 trials, the dose that will be used in this trial is a maintenance dose of 25 mg BID after an initial approximately 2-week titration period to target dose (see Table 3).

4.4. End of Trial Definition

The end of the trial is defined as the date of the last visit (including the Safety Follow-up Visit) of the last participant in the trial.

The definition of a completed participant is provided in Section 4.1.4.

5. TRIAL POPULATION

Men and women, 18 to 65 years of age, inclusive, with a primary diagnosis of panic disorder will be enrolled into the trial.

5.1. Inclusion Criteria

Individuals are eligible for participation in this trial only if all of the following criteria apply:

1.	Male and female participants, ages 18-65 years, inclusive, at the time of Screening.
2.	Primary diagnosis of panic disorder based on the DSM-5-TR criteria (present for at least 6 months prior to the Screening Visit) and confirmed by the MINI; additional primary diagnosis of agoraphobia is allowed and secondary diagnosis of GAD and/or SAD is allowed.
3.	Participant has had a minimum of 8 panic attacks, with no week free of panic attacks, in the month prior to the Screening Visit. In the 14 days preceding the Baseline Visit, the participant must have had at least 4 panic attacks and no week free of panic attacks. Note: Participant must complete a minimum of 11 eDiary day entries in the 14 days preceding the Baseline Visit.
4.	Participants with a PDSS total score ≥12 at the Screening and Baseline Visits
5.	Body mass index of 17.5 to 40.0 kg/m^2 and a total body weight >48 kg at Screening.
6.	A female participant of childbearing potential who is sexually active with a nonsterilized male partner must agree to use a highly effective method of contraception (defined in Section 10.4.1.2) from signing of informed consent throughout the duration of the trial until the last dose of IMP and for an additional 33 days after the last dose. A male participant with a pregnant or a nonpregnant partner of childbearing potential must agree to use a condom during treatment and until the last dose of IMP and for an additional 93 days. In addition, male participants should not donate sperm for a minimum of 93 days following last dose of IMP.
7.	Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in the trial protocol.
8.	Ability, in the opinion of the investigator, to understand the nature of the trial and comply with protocol requirements, including the prescribed dosage regimens, scheduled visits, laboratory tests, and other trial procedures.

5.2. Exclusion Criteria

Individuals are not eligible for participation in this trial if any of the following criteria apply:

Target Disease	
1.	Participants who have a current DSM-5-TR diagnosis of major depressive disorder, dysthymia, bipolar I or II, or other bipolar disorder not specified, posttraumatic stress disorder, obsessive compulsive disorder, eating disorder, phobia (except for agoraphobia), schizophrenia, schizoaffective disorder, other psychotic disorder, delirium, dementia, amnestic disorder, or other cognitive disorder. Participants with a DSM-5-TR personality

	diagnosis. In addition, participants with any other psychiatric illness, not otherwise specified above, of sufficient severity as to make them inappropriate for the trial are excluded. Per investigator's discretion, the medical monitor should be contacted to discuss individual cases, as needed. • Participants with symptoms of depression/dysphoria are allowed if not a primary diagnosis and not requiring medical management. • Participants with a history of alcohol use disorder or substance use disorder within the 6 months prior to Screening will be excluded.
2.	Any newly initiated (within 3 months prior to the Screening Visit) evidence-based psychotherapy, including CBT. • Any exposure-based therapy is prohibited throughout the duration of the trial
Medical History and Concurrent Diseases	
3.	Participants with a current history of significant cardiovascular, pulmonary, gastrointestinal, renal, hepatic, metabolic, hematological, immunological, or neurological disease that, in the opinion of the investigator or medical monitor, could compromise either participant safety or the results of the trial. Medical conditions that are minor or well-controlled with non-prohibited concomitant medication(s) may be considered acceptable if the condition does not expose the participant to an undue risk of a significant AE or interfere with the assessments of safety or efficacy during the course of the trial. • The medical monitor should be contacted in any instance where the investigator is uncertain regarding the stability of a participant's medical condition(s) or non-prohibited concomitant medication(s) and the potential impact of the condition(s) on trial participation.
4.	Have recently been hospitalized for COVID-19 within 6 months prior to signing the ICF or report a positive test result (ie, using PCR or rapid antigen test) for SARS-CoV-2 within 15 days prior to the Screening Visit.
5.	Participants who answer "Yes" on the following C-SSRS Suicidal Ideation Items (within the last 6 months) • Suicidal Ideation Item 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) OR • Suicidal Ideation Item 5 (Active Suicidal Ideation with Specific Plan and Intent) OR Participants who answer "Yes" on any of the 5 C-SSRS Suicidal Behavior Items (within the last 2 years) • Any of the Suicidal Behavior items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) OR Participants who, in the opinion of the investigator, present a serious risk of suicide.

Physical Examination and Clinical Laboratory Results	
6.	Positive result for HIV antibody, hepatitis B surface antigen, or hepatitis C antibody at Screening. • Positive or indeterminate test result for hepatitis C antibody should follow with HCV PCR RNA test. If result is positive, the participant is excluded.
7.	Positive test for alcohol at Screening or Baseline (note: Individuals who test positive for alcohol may be rescreened with approval from the medical monitor).
8.	Participants with a positive drug screen result at Screening are excluded. • Participants with a positive urine drug screen resulting from use of any THC containing products, prescription medications (with valid current prescription), or over the counter medications or products who do not meet the criteria for abuse in the investigator's documented opinion may be rescreened after 1 month following consultation and approval by the medical monitor.
9.	Participants with a 12-lead ECG demonstrating any of the following at Screening: • QTcF >450 msec • QRS interval >120 msec • Second-degree (Type 2) or third-degree atrioventricular block • Clinically significant abnormal heart rhythm (such as atrial fibrillation or flutter, ventricular tachycardia) Note: at Screening, eligibility will be based on the average of a centrally read triplicate set of ECGs. At the Baseline Visit, if any of the above criteria are met on the machine read of the ECG, the medical monitor should be consulted to determine whether the participant is eligible for randomization. The medical monitor should be contacted in any instance where the investigator is uncertain regarding the interpretation of ECG results.
10.	Blood pressure measurements demonstrating any of the following at Screening: • Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg ○ Blood pressure will be measured in triplicate at approximately 1-minute intervals in a supine position after at least 3 minutes of rest. The triplicate measures will be individually recorded and the average of the last 2 measurements will be used to determine eligibility. • Orthostatic hypotension, defined as a decrease of ≥20 mmHg in systolic blood pressure and/or ≥10 mmHg in diastolic blood pressure after at least 2 minutes of standing compared with the average of the resting supine blood pressure measurements • Symptomatic postural dizziness (with or without orthostatic hypotension) • Heart rate <45 bpm or >100 bpm on vital signs assessment (not ECG)

11.	Participants with any of the following abnormalities in clinical laboratory tests at the Screening Visit, as assessed by the central laboratory and confirmed by a single repeat measurement, if deemed necessary: • AST or ALT ≥2 × ULN • Total bilirubin ≥1.5 × ULN. If Gilbert's syndrome is suspected, total bilirubin >1.5 × ULN is acceptable if the conjugated or direct bilirubin fraction is <20% of total bilirubin • eGFR <60 mL/min/1.73 m^2 (as estimated by the CKD-EPI 2021 equation [Levey et al, 2009; Delgado et al, 2022]) and as reported by the central laboratory • TSH < LLN • Hemoglobin < LLN • WBC count < LLN or >ULN • Neutrophil count < LLN or >ULN • Platelet count < LLN or >ULN
12.	Any other abnormal safety findings unless, based on the investigator's judgment, the findings are not medically significant and would not impact the safety of the participant or the interpretation of the trial results. The medical monitor should be contacted to discuss individual cases, as needed. Tests with abnormal results that are potentially exclusionary should be repeated to ensure reproducibility of the result before excluding a potential participant based on criteria provided in the protocol.
Prior or Concomitant Therapies	
13.	Use of prohibited medications prior to randomization within the required wash-out period or likely to require prohibited concomitant therapy during the trial (see Section 6.7).
Other	
14.	Female participants who are breastfeeding or who have a positive pregnancy test result prior to receiving IMP.
15.	Any condition possibly affecting drug absorption, including bowel resections, bariatric weight loss surgery, or gastrectomy (this does not include gastric banding). Considering or scheduled to undergo any surgical procedure during the trial.
16.	Any other condition that would preclude IMP administration (eg, difficulty swallowing) or trial participation (eg, poor venous access).
17.	Participants who are known to be allergic or hypersensitive to the IMP or any of its components.
18.	Participants who have participated in any clinical trial within 60 days prior to signing the ICF or who have participated in more than 2 interventional clinical trials within 12 months prior to signing the ICF. Note: Prior participation in an interventional trial and a rollover extension trial with the same IMP within the last 12 months is permitted.
19.	Any participant who, in the opinion of the sponsor, investigator, or medical monitor, should not participate in the trial.

	• Employee of the investigator, clinic, or sponsor with direct involvement in the proposed trial or other trials under the direction of the investigator or clinic, as well as family members of the employee or investigator.
20.	Refusal to abstain from grapefruit-containing foods or beverages or Seville orange-containing foods or beverages from 7 days prior to dosing through the end of the trial.

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; bpm=beats per minute; CBT=cognitive behavioral therapy; COVID-19=coronavirus disease-2019; C-SSRS=Columbia-Suicide Severity Rating Scale; DSM-5-TR=Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision; ECG=electrocardiogram; GAD=generalized anxiety disorder; eGFR=estimated glomerular filtration rate; HCV=hepatitis C virus; HIV=human immunodeficiency virus; ICF=informed consent form; IMP=investigational medicinal product; LLN=lower limit of normal; MINI=Mini International Neuropsychiatric Interview; PCR=polymerase chain reaction; PDSS=Panic Disorder Severity Scale; QRS=Q wave, R wave, S wave; QTcF=QT interval corrected for heart rate using Fridericia's formula; RNA=ribonucleic acid; SAD=social anxiety disorder; SARS-CoV-2=severe acute respiratory syndrome coronavirus-2; THC=tetrahydrocannabinol; TSH=thyroid stimulating hormone; ULN=upper limit of normal; WBC=white blood cell.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Participants will not be allowed to eat or drink food/food products that are strong/moderate inhibitors or inducers of cytochrome P450 3A4 (including but not limited to grapefruit, grapefruit juice, or grapefruit-related citrus fruits/juices [eg, Seville oranges, pomelos]) from 7 days prior to dosing through the end of trial.

5.3.2. Caffeine, Alcohol, and Tobacco

Participants should adhere to their usual regimen of caffeine and tobacco, if applicable. As the potential for interactions between IMP and alcohol have not yet been evaluated, participants are strongly discouraged from consuming alcohol for the duration of the trial.

5.3.3. Activity

Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this trial (screen failure) at Screening may be rescreened. Individuals may be rescreened once at the discretion of the investigator and after consultation with the sponsor unless screen failure is due to a positive urine drug screen for illicit substances. Rescreened participants should be assigned a new participant number.

6. TRIAL INTERVENTION AND CONCOMITANT THERAPY

Trial intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a trial participant according to the trial protocol.

In this protocol, the trial interventions are referred to as IMPs. An IMP is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.

6.1. Trial Interventions Administered

A summary of the IMP to be administered during this trial is presented in Table 4.

Table 4: Investigational Medicinal Products

IMP	Darigabat 25 mg BID	Placebo BID
Type	Drug	Placebo
Dose Formulation	Tablet	Matching tablet
Unit Dose Strength(s)	5 mg, 7.5 mg, 25 mg	Matching
Dosage Level(s)	• 5 mg BID (Days 1 to 7) • 12.5 mg BID (Days 8 to 14) • 25 mg BID (Day 15 to end of treatment)	0 mg
Route of Administration	Oral	Oral
Sourcing	Provided centrally by Cerevel	
Packaging and Labeling	IMP will be provided in blister packs and/or bottles. Each blister pack or bottle will be labeled as required per country requirement.	

Abbreviations: BID=twice daily; IMP=investigational medicinal product.

6.2. Preparation, Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit (original shipment and/or moving of IMP supply from 1 office or facility to another within the trial site's network) for all IMP received and any discrepancies are reported and resolved before use of the IMP.

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

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

Further guidance and information for the preparation, handling, storage, accountability, and disposition of unused IMP are provided in the pharmacy manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. 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 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 (see Section 4.1.1 for additional details).

6.3.2. Blinding

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 PK blood samples, or unblinded sponsor personnel (for the purposes of packaging/managing IMP supply, supporting IRT, or reporting SAEs or 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. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the 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.

6.4. Trial Intervention Compliance

Responsible trial personnel will dispense the IMP. Participants will be counseled on the importance of taking the IMP as directed and will be instructed to bring all used and unused IMP to each visit for assessment of accountability and compliance.

Compliance will be assessed by direct questioning and by counting returned tablets. Compliance will be documented in the source documents and the eCRF, including any deviations from the prescribed dosage regimen.

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

6.5. Dose Modification

No dose modifications are permitted during the trial.

6.6. Intervention After the End of the Trial

There will be no provision of darigabat for participants after they complete or discontinue treatment in this trial.

Participants who complete through the 14-week Treatment Period of the trial may have the opportunity to receive post-trial supportive therapy offered via the sponsor. Additional details are provided in the Operations Manual.

6.7. Prior and Concomitant Therapy

6.7.1. Time Period for Recording Prior and Concomitant Therapy

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).

For concomitant medications, the following information will be recorded in the eCRF: medication, indication, dose, frequency, route, start date, and end date. For nondrug therapies or procedures, the following information will be recorded in the eCRF: therapy/procedure name, indication, start date, and end date.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.7.2. Prohibited Therapy

Participants are required to discontinue use of prohibited medications in accordance with predefined washout periods, as shown in Table 5.

Table 5: Prohibited Prior Medications

Prohibited Prior Medications	Washout[a] (if applicable)
Moderate or strong inducers of CYP3A4 metabolism (see Section 10.7)	5 weeks
Moderate or strong inhibitors of CYP3A4, including Paxlovid (see Section 10.7)	14 days or 5 half-lives, whichever is longer
P-gp substrates with a narrow therapeutic index (eg, digoxin, dabigatran)	14 days
BCRP substrate rosuvastatin	5 days
All psychoactive substances other than antidepressants (unless otherwise noted) including but not limited to: • Opiates • Anxiolytics (eg, benzodiazepines, non-benzodiazepine anxiolytics) • Beta receptor antagonists used for any indication • Antiseizure/neuropathic pain medications used for any indication (eg, gabapentin, pregabalin, topiramate, phenytoin, phenobarbital) • Hypnotics ○ Sleep medications (eg, zolpidem, zaleplon, eszopiclone, trazodone, and suvorexant or other orexin receptor antagonists) are permitted if medically prescribed at doses labeled for insomnia and used no more than 3 times per week • Mood stabilizers (eg, lithium, divalproex, carbamazepine, lamotrigine) • Stimulants (eg, amphetamine, methylphenidate, modafinil) • Antipsychotics	14 days
Antidepressants	14 days, except for fluoxetine and Symbyax, which require a washout of 28 days
D2/3 agonist (eg, pramipexole)	14 days or 5 half-lives, whichever is longer
Any investigational agent	60 days

Abbreviations: BCRP=breast cancer resistance protein; CYP=cytochrome P450; D2/3=dopamine D2/D3 receptor agonist; ICF=informed consent form; P-gp=P-glycoprotein.

[a] The required washout duration is based on the period prior to the Baseline Visit. Once the participant signs the ICF, the participant has up to 28 days prior to the Baseline Visit to washout. If the participant happened to washout prior to the Screening Visit for their own reasons and out of their own will, this is acceptable and must be documented in the medical records. Following consultation with the medical monitor, the Screening Period may be extended if needed to accommodate a washout duration that is longer than 28 days.

The concomitant medications that are prohibited during the trial are listed in Table 6.

The medical monitor should be contacted regarding the appropriateness of a participant's continued participation in the trial in the event that initiation of therapy with a prohibited

concomitant medication is deemed necessary, in the investigator's opinion, for the treatment of a TEAE.

The medical monitor should be contacted if a participant tests positive for cannabis products/THC during the trial to determine whether participation in the trial should continue.

Table 6: Prohibited Concomitant Medications and/or Therapies

Prohibited Concomitant Medications/Therapies During Trial Conduct
All psychoactive substances (unless otherwise noted) including but not limited to: • Antidepressants • Opiates • Anxiolytics (eg, benzodiazepines, non-benzodiazepine anxiolytics) • Beta receptor antagonists used for any indication • Antiseizure/neuropathic pain medications used for any indication (eg, gabapentin, pregabalin, topiramate, phenytoin, phenobarbital) • All first-generation antihistamines are prohibited for all indications, except for diphenhydramine, which is permitted only if medically indicated for insomnia and used no more than 3 times per week. • Hypnotics   ○ Sleep medications (eg, zolpidem, zaleplon, eszopiclone, trazodone, and suvorexant or other orexin receptor antagonists) are permitted if medically prescribed at doses labeled for insomnia and used no more than 3 times per week • Mood stabilizers (eg, lithium, divalproex, carbamazepine, lamotrigine) • Stimulants (eg, amphetamine, methylphenidate, modafinil) • Antipsychotics
D2/3 agonists (eg, pramipexole)
Any OTC treatments for the treatment of panic disorder or anxiety disorder(s) (eg, cannabis products/THC, CBD [a], herbal supplements, including but not limited to valerian root, St. John's wort, and GABA supplements)
Investigational agents
Any drug or product that is a moderate to strong inducer of CYP3A4 metabolism, which has the potential to lower darigabat exposure levels. An example list of strong (>80% reduction in AUC) and moderate (50% to 80% reduction in AUC) inducers is provided in Section 10.7.
Any drug or product that is classified as a significant (ie, strong or moderate) inhibitor of the CYP3A4 metabolic pathway, which has the potential to increase darigabat exposure levels. An example list of strong (eg, >5-fold increase in AUC) and moderate (eg, 2-to 5-fold increase in AUC) inhibitors is provided in Section 10.7.
BCRP substrate rosuvastatin
Exposure-based therapy
Systemic steroids are prohibited. Any steroid that is not systemic (eg, topical or inhaled) is permitted.

Abbreviations: AUC=area under the concentration-time curve; BCRP=breast cancer resistance protein; CBD=cannabidiol; CYP=cytochrome P450; D2/3=dopamine D2/D3 receptor agonist; eCRF=electronic case report form; GABA=gamma-aminobutyric acid; IMP=investigational medicinal product; OTC=over-the-counter; THC=tetrahydrocannabinol.

Note: In the event that rescue therapy with a benzodiazepine is required at the discretion of the investigator, the medical monitor should be contacted to determine whether the participant remains eligible to continue participation in the trial.

Note: Non-benzodiazepine sleep aids (eg, zolpidem, zaleplon, eszopiclone, trazodone, and suvorexant or other orexin receptor antagonists) are permitted for the treatment of insomnia, but not within 10 hours of administration of IMP, regardless of indication. For the non-benzodiazepine sleep aids, site personnel should utilize one of the listed medications that are approved for this indication and the specific prescribing information should be used to determine the maximum allowable daily dose for the treatment of insomnia. Non-benzodiazepine sleep aids must not be administered within 12 hours prior to scheduled efficacy scale and safety assessments. Investigators are encouraged to delay scale administration until 12 hours have elapsed, if at all possible. However, if delaying the administration of efficacy and safety scales is not feasible, the scales should still be administered and the use of the sleep aid documented, including a notation of the drug name, dose, and time of administration on the eCRF.

[a] Topical CBD (eg, oil or lotion) used for muscle spasms or massages will be evaluated upon discussion with the medical monitor.

7. DISCONTINUATION OF TRIAL INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Details on discontinuation of individual trial sites or of the trial as a whole are provided in Section 10.1.8.

7.1. Discontinuation of Trial Intervention

For QTcF, liver enzymes, and/or hematological abnormalities meeting AESI criteria as described in Section 8.3.7, a repeat evaluation should be immediately performed for confirmation and the medical monitor notified.

If the repeat evaluation is confirmed abnormal, the treatment with study drug should be discontinued and the early termination visit should be completed.

If a participant permanently discontinues IMP, refer to the Schedule of Assessments (Section 1.3) for data to be collected following IMP discontinuation.

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

7.2. Participant Discontinuation/Withdrawal From the Trial

All participants have the right to withdraw from the trial at any time without prejudice. Participants cannot withdraw consent for use of data already collected as part of the trial, but can withdraw consent for future participation. The investigator can also discontinue a participant from the trial at any time for safety, behavioral, or compliance reasons. Unless a participant provides written withdrawal of consent or there is other written documentation by the investigator confirming the participant's verbal intent to completely withdraw from the trial, participants should be followed for all protocol-specified evaluations and assessments, if possible.

At the time of discontinuation from the trial, if possible, an early termination visit should be conducted. Unless a participant withdraws consent, an Early Termination Visit and end of trial procedures should be conducted if a participant discontinues IMP. Unless clinically necessary, the initiation of any prohibited medications should occur after the completion of all of the assessments at the Early Termination Visit and Telephone Visits 7 and 8. See the Schedule of Assessments (Section 1.3) for data to be collected at the time of discontinuation and follow-up and for any further evaluations that need to be completed.

The reason for discontinuation from the trial will be recorded in the eCRF.

7.3. Lost to Follow-up

Participants will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the trial site personnel. The following actions must be taken if a participant fails to return to the site for a required trial visit:

- Trial site personnel must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining

the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the trial.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

Participants who continue to be unreachable will be considered to have withdrawn from the trial.

8. TRIAL ASSESSMENTS AND PROCEDURES

The timing and frequency of trial procedures are provided in the Schedule of Assessments (Section 1.3). Protocol waivers or exemptions are not allowed.

At each time point during the trial, efficacy and health economics assessments should be completed before safety assessments, and every effort should be made to complete the PDSS as the first assessment. The preferred order of assessment will be specified in the Operations Manual.

Immediate safety concerns should be discussed with the medical monitor immediately upon occurrence or awareness to determine if the participant should continue or discontinue IMP.

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

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants who are screened and to confirm eligibility or record reasons for screening failure, as applicable.

The MINI for Psychotic Disorders (Sheehan et al, 1998; Sheehan et al, 1997) will be conducted at the Screening Visit to confirm the participant's diagnosis of panic disorder and to rule out exclusionary comorbid psychiatric diagnoses.

8.1. Efficacy Assessments

Trained and qualified (details provided in the rater training vendor plan or manual) clinicians should administer the efficacy assessments and the number of raters should be kept to a minimum. All efforts should be made to ensure the same clinician administers the scales for a given participant throughout the trial.

All efficacy assessments will be completed using an approved electronic data capture system.

Non-BZD sleep aids are not permitted within 12 hours of administration of clinician-administered scales (see Section 6.7).

The timing and frequency of efficacy assessments are provided in the Schedule of Assessments (Section 1.3).

8.1.1. Panic Attack Frequency

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 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 (see Section 4.1) 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 2-week period will be the basis of the repeated measure assessments.

8.1.2. Panic Disorder Severity Scale

The 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 for a total of 28 points.

8.1.3. Clinical Global Impression-Severity of Symptoms Scale

The global severity of panic disorder symptoms for each participant will be rated using the CGI-S (Guy, 1976). To perform this assessment, the investigator (or designee) will answer the following question: "Considering your total clinical experience with this particular population, how ill with panic disorder symptoms is the participant at this time?" Response choices 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 participants.

8.2. Safety Assessments

The timing and frequency of safety assessments are provided in the Schedule of Assessments (Section 1.3).

8.2.1. Height and Weight

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

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

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

8.2.2. Physical and Neurological Examinations

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

A limited physical examination 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.

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

The investigator must review the physical and neurological examination findings and document any clinically significant condition present at the post-treatment physical and neurological examinations that was not present at the baseline examination as an AE. These clinically significant findings should be followed to a satisfactory conclusion.

8.2.3. Vital Sign Measurements

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 1.3). 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 (see Section 5.2). 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 details are provided in the Operations Manual.

8.2.4. Electrocardiograms

Electrocardiogram 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 results will be evaluated at the investigational site to determine the participant's eligibility and to monitor safety during the trial. The principal investigator (or qualified designee) will review, sign, and date each ECG reading, noting whether or not any abnormal results are of clinical significance. The ECG will be repeated if any results are considered to be clinically significant. Any clinically significant changes occurring during the trial will be recorded in the AE section of the eCRF. A central ECG service will be used for reading all ECGs in order to standardize interpretations for the safety analysis. Additional guidance on collection of ECGs will be provided in the Operations Manual.

At Screening, triplicate 12-lead 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. If, during screening, according to the investigator's judgment, any abnormal ECG finding is deemed medically significant (impacting the safety of the participant or the interpretation of the trial results) or meets an exclusion criterion (see Section 5.2), the participant should be excluded from

the trial. 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 (Section 1.3) where an ECG recording must be performed, only a single ECG is required.

Exclusion criteria for screening do not apply as mandatory discontinuation criteria for participants who are already randomized. A repeat ECG should be performed in case of any clinically significant abnormality that is identified in a randomized participant during the treatment period and, in these cases, the medical monitor should be consulted on the appropriateness of the participant continuing in the trial.

8.2.5. Clinical Safety Laboratory Assessments

See Section 10.2 for the list of clinical laboratory tests to be performed and the Schedule of Assessments (Section 1.3) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the trial as an AE. The laboratory reports must be filed with the source documents.

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.

All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the Schedule of Assessments.

8.2.6. Suicidal Ideation and Behavior Risk Monitoring

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

This trial will use the “Baseline/Screening” and “Since Last Visit” versions of the scale. The “Baseline/Screening” version will be completed for all participants at Screening to determine eligibility. The exclusion criteria based on the C-SSRS are provided in Section 5.2.

The “Since Last Visit” C-SSRS form will be completed after the Screening visit. 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 has any “YES” answers on the C-SSRS for the suicidal ideation or suicidal behavior items, 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 discuss with the medical monitor whether the participant should continue in or be discontinued from the trial.

8.2.7. Penn Physician's Withdrawal Checklist

The PWC is a 20-item scale to measure discontinuation symptoms after stopping a medication for anxiety disorders (Rickels et al, 2008; Rickels et al, 1990). 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 0 to 60, can be calculated in addition to the individual scores for each item. Lower scores indicate less severity in discontinuation symptoms.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 10.3. Definitions of AESIs are provided in Section 8.3.7.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, SAE, or AESI and remain responsible for following up AESIs and AEs that are serious, considered related to the IMP or trial procedures, or that caused the participant to discontinue IMP (see Section 7.1).

Further details about AE recording and follow-up are provided in Section 10.3.

8.3.1. Time Period and Frequency for Collecting AE and SAE/AESI Information

All AEs and SAEs/AESIs will be recorded from the first dose of IMP until follow-up contact at the time points specified in the Schedule of Assessments (Section 1.3).

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

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

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

8.3.2. Method of Detecting AEs and SAEs/AESIs

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

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

8.3.3. Follow-up of AEs and SAEs/AESIs

After the initial AE/SAE/AESI report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs/AESIs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3. Further information on follow-up procedures is given in Section 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs/AESIs

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

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

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

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

8.3.5. Pregnancy

Details of all pregnancies in female participants or in female partners of male participants will be collected after the start of IMP and until final contact.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4.2.

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

8.3.6. Treatment of Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a trial participant, at a dose above that which is assigned to that individual participant according to the protocol. Please refer to the darigabat Investigator's Brochure for more detailed information about overdose.

There is no specific antidote for overdose with darigabat. In the event of overdose, treatment should consist of general supportive measures.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately.

- Closely monitor the participant for any AE/SAE and clinically significant vital sign, ECG, or laboratory abnormalities. Additional safety procedures may need to be performed at the investigator's discretion.
- Document the quantity of the excess dose as well as the duration of the overdose (if multiple time points) in the eCRF.

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

8.3.7. Adverse Events of Special Interest

All AESIs should be reported according to the procedures and timelines for SAEs (see Section 10.3.4).

The following events will be reported as AESIs:

- 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
- QTcF >500 ms or an increase >60 ms from Baseline
- Liver enzymes:
  - ALT or AST ≥3 × 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

For QTcF, liver enzymes, and/or hematological abnormalities meeting the above AESI criteria, a repeat evaluation should be immediately performed for confirmation and the medical monitor notified. See Section 10.6.1 for further details on the assessment of elevations in liver test results.

If the repeat evaluation is confirmed abnormal, the treatment with study drug should be discontinued and the early termination visit should be completed.

An APMP will be used to monitor events that may suggest that darigabat produces drug effects that could be sought out for abuse purposes. As part of the APMP, AEs potentially related to abuse and medication handling irregularities related to suspected or known abuse of IMP must be reported as AESIs. Investigators and site staff at each trial site will be trained on reporting potentially abuse-related AEs. While the investigators will be provided with examples of AE

terms as a guide during trial conduct, the analysis of potentially abuse-related AEs will be based on a search by the sponsor of all relevant MedDRA terms, all verbatim terms, and any open text fields within the AE data to identify text strings suggestive of abuse potential, consistent with US FDA guidance (US FDA Guidance for Industry, 2017).

8.4. 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 (Section 1.3).

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.

Plasma samples will be processed, stored, and shipped to the bioanalytical facility according to the instructions provided to the investigator in advance of the trial. Additional details about sample collection, processing, and shipment will be provided in the PK manual.

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.

Plasma concentration data from this trial combined with other data may also be used to build and/or update a population PK model for darigabat for the purpose of further characterizing the PK or PK/PD behavior of the compound. Any population PK assessment will be described in a separate report.

Statistical analyses of PK parameters are summarized in Section 9.3.6.

8.5. Biomarkers

Biomarkers are not evaluated in this trial.

8.6. Future Biospecimen Research

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

Future biospecimen research samples will be collected from participants who provide additional consent specifically for this sample collection. Research performed on these samples may include genetic analyses, gene expression profiling, proteomics, metabolomics and/or the

measurement of other analytes. Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial). The objective of collecting these specimens is to explore and identify biomarkers that inform the scientific understanding of diseases or their therapeutic treatments.

Additional details about future biospecimen research samples are provided in Section 10.5.

8.7. Other Assessments of Drug Effect

8.7.1. Sheehan Disability Scale

The 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.

8.7.2. Hamilton Anxiety Rating Scale

The HAM-A 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) and a Psychic factor (made up of 6 items). A total score (ranging from 0 to 56) can be calculated in addition to the 2-dimension scores. Lower scores indicate less anxiety.

8.7.3. European Quality of Life

The 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. Based on this 5-digit profile, a single summative index value can be computed according to the preferences of the general population of a given count/region. The second part of EQ-5D-5L is the EQ Visual Analog Scale (EQ VAS), a self-rated vertical visual analog scale with the top endpoint labeled as "The best health you can imagine" and the bottom endpoint labeled "The worse health you can imagine." This scale takes

a single numeric number between 0 and 100 to represent a respondent's own rating of overall health today.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

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

$$H_0: \mu_{placebo} = \mu_{DAR} \text{ vs } H1: \mu_{placebo} \neq \mu_{DAR}$$

9.1.1. Multiplicity Adjustment

The hypothesis tests will be conducted in a hierarchical order from the primary efficacy endpoint to the secondary endpoints each at a 2-sided a level of 0.05. Specifically, if the primary hypothesis test on proportion of participants free of panic attacks as assessed by participant daily eDiary during the last 2 weeks of the Maintenance Treatment Period is successful, the key secondary endpoint of change from Baseline in PDSS total score at Week 14 will be similarly tested at a level of 0.05. If the second test is successful, the hypothesis on change from baseline in panic attack frequency during the last 2 weeks of the Maintenance Treatment Period will be conducted at a level of 0.05. The overall type I error rate in the family of the primary and key secondary efficacy endpoints thus is maintained at the 0.05 level.

9.2. Analysis Sets

The analysis sets that are defined for this trial are described in Table 7.

Table 7: Analysis Set Descriptions

Term	Description	Analysis
ITT	All randomized participants.	Demographic and Baseline Characteristics
Safety Analysis Set	All randomized participants, who receive at least 1 dose of IMP. This will be the safety analysis set.	Safety analysis
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. Participants who have not met all inclusion/exclusion criteria but are randomized in error will not be included. Non-Panic Attack Endpoints 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.	All efficacy analysis (including primary) related to panic attack events captured by eDiary All other efficacy analysis
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.

9.3. Statistical Analyses

9.3.1. General Considerations

Descriptive statistical methods will be used to summarize the data from this trial, with statistical testing performed for the efficacy endpoints. All statistical analyses will be conducted with the SAS® System, version 9.4 or higher. The remainder of this section is a summary of the planned statistical analyses of the primary and secondary endpoints as well as a description of planned safety analyses. Full details of these analyses will be included in the SAP.

9.3.2. Primary Endpoint/Estimand Analyses

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 2 weeks of the Maintenance Treatment Period 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% CI
5. A composite strategy will be used to address missing values due to ICEs regardless of whether they are considered as treatment related. Specifically, participants who fail to achieve panic free in the last 2 weeks of treatment prior to ICE, including cases of missing all post-baseline assessments (other than for logistic reasons such as randomization errors) in the FAS defined in Table 7, will be considered as failure.

The number and proportion of participants who are free of panic attacks during the last 2 weeks of the Maintenance Treatment Period will be summarized by visit and treatment group. The binomial repeated measures will be analyzed using the SAS® GLIMMIX procedure with logit link. The Baseline PDSS total score will be included as a covariate, and the treatment group, visits, evidence-based psychotherapy use, and interaction between treatment group and visit will be included as fixed effect. Model diagnostics will be performed to explore the goodness-of-fit. An unstructured covariance structure will be used for the repeated measures. If the unstructured covariance matrix results in convergence issue, a structured covariance matrix such as the heterogeneous Toeplitz structure may be used. In the case that a structured covariance matrix needs to be used, a robust sandwich variance estimator will be used. The odds ratio of active dose to placebo at the endpoint visit will be estimated based on the least squares mean difference in logit between the treatment groups from the GLIMMIX model with the associated 95% CI and p-values. A sensitivity analysis using Fisher's exact test and 95% exact CI 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.

Additional sensitivity analyses will include all participants regardless of panic attack eDiary version used.

9.3.3. Secondary Endpoint/Estimand Analyses

9.3.3.1. Change From Baseline in PDSS Total Score at Week 14

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% CI based on an MMRM model
5. Missing values due to ICEs to be addressed by a hypothetical strategy followed by tipping point analyses

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 effect 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. Subject 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 following ICEs may be considered as treatment related and will be identified prior to database lock:

- Death
- Study/treatment discontinuation due to lack of efficacy
- Study/treatment discontinuation due to AEs
- Initiating evidence-based psychotherapy and continuing during double-blind treatment. Due to potential confounding effect, the observed data post ICE, if available, will be excluded.
- Initiating therapy with prohibited antidepressants or anxiolytics (eg, benzodiazepines, non-benzodiazepine anxiolytics including beta receptor antagonists) and continuing during double-blind treatment. Due to potential confounding effect, the observed data post ICE, if available, will be excluded.

For missing data due to ICEs where a treatment-related reason is identified, a pattern mixture model approach with varying level of shift parameters will be utilized. Specifically, a tipping point analysis will be performed to find a tipping point in the spectrum of shift parameter assumptions, at which the conclusion from the MMRM analysis changes. The individual cases of treatment-related ICEs will be pre-identified prior to database lock.

Further sensitivity tipping point analyses will be performed for all missing values following ICEs regardless of whether they are considered treatment related (including cases of missing all post-baseline assessments) to assess the robustness of the conclusion from the MMRM analysis.

9.3.3.2. Change From Baseline in Panic Attack Frequency During the Last 2 Weeks of the Maintenance Treatment Period

The second 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 panic attack frequency during the last 2 weeks of the Maintenance Treatment Period as the endpoint of interest
4. The population level summary of interest is the estimated treatment differences in median and the 95% Hodges-Lehmann CI
5. A composite strategy will be used to handle missing values due to ICEs. The cases of potential treatment-related ICEs described in Section 9.3.3.1 will be assigned the worst rank and other cases of missing outcomes from ICEs will be assigned the second worst rank. The individual cases of treatment-related ICEs will be pre-identified prior to database lock.

The change from Baseline to each trial visit in frequency of panic attacks will be summarized by visit and treatment group. A non-parametric analysis using Mann-Whitney test performed on the change from Baseline during the last 2 weeks of the Maintenance Treatment Period will be the basis for comparison between the 2 treatment groups. A supportive analysis of frequency of panic attacks recorded at each visit will be performed using a Poisson or negative binomial regression with fixed effect of treatment group, visits, evidence-based psychotherapy use, and interaction between treatment group and visit. The Baseline panic attack frequency will be included as a covariate. Subject will be included as a random effect.

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

9.3.4. Other Endpoints Analysis

Analysis of proportion of participants free of panic attacks at other time points will also be based on the repeated measure logistic regression described in Section 9.3.2. The PDSS total score at other time points will also be based on the MMRM model described in Section 9.3.3.1. The frequency of panic attacks at other time points will be analyzed using the same methods described in Section 9.3.3.2. Other endpoints, including change from baseline in CGI-S score, HAM-A scores, EQ-5D-5L, and SDS total score will be analyzed using similar MMRM models as described in Section 9.3.3.1.

9.3.5. Safety Analyses

Treatment-emergent adverse events (serious and nonserious) will be coded according to MedDRA and summarized by treatment group, system organ class, and preferred term. Further summaries will be done by severity (assessed by National Cancer Institute-Common Terminology Criteria for Adverse Events), relationship to IMP, and dose at the time of onset.

The frequency (or incidence) of abuse potential will be summarized by treatment group. Abuse potential will be assessed through the active monitoring of AEs related to potential abuse and AEs involving medication handling irregularities.

Other safety endpoints will be summarized with descriptive statistics by treatment group, including suicidality monitored during the trial using C-SSRS and withdrawal symptoms using the PWC.

9.3.6. Other Analyses

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 (eg, body weight, age, sex, race, concomitant medications) on PK parameters. The results of population PK analysis and response-exposure analyses may be presented separately from the main CSR. Plasma concentration may also be pooled with data from other trials in a physiologically based PK model.

9.4. Interim Analyses

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

9.5. Sample Size Determination

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 (eg, 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 (ie, 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]).

In the event of higher than anticipated early terminations, Cerevel may extend enrollment to achieve trial objectives.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Trial Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

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

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

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

The investigator will be responsible for the following:

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the trial to the participant and answer all questions regarding the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local

regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or trial center.

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

Participants must be reconsented to the most current version of the ICF(s) during their participation in the trial.

A copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF.

As described in Section 10.5, additional consent will be required for participants from whom future biospecimen research samples will be collected.

10.1.4. Data Protection

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

The participant must be informed that his/her personal trial-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

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

10.1.5. Dissemination of Clinical Trial Data

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

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

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

Cerevel posts EU Basic Results on EudraCT for all Cerevel-sponsored interventional trials that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the

primary completion date as defined in Section 4.4 for trials in adult populations or within 6 months of the primary completion date for trials in pediatric populations.

10.1.6. Data Quality Assurance

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

Guidance on completion of the eCRF will be provided in the CRF Completion Guidelines.

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

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or onsite monitoring) are provided in the Clinical Monitoring Plan.

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

The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).

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

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

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

10.1.7. Source Documents

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

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

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

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

10.1.8. Trial and Site Closure

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Total number of participants included earlier than expected

The investigator will notify the sponsor promptly if the trial is terminated by the investigator or the IRB/IEC.

If the sponsor terminates or suspends the trial for any reason, prompt notification will be given to investigators, IRBs/IECs, health authorities in accordance with regulatory requirements.

10.1.9. Publication Policy

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

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

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

10.2. Clinical Laboratory Tests

The tests detailed in Table 8 will be performed by a central laboratory.

Participants are requested, but not required, to fast for at least 8 hours prior to obtaining laboratory tests. A participant should not be rescheduled if fasting was not performed.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.

Serum pregnancy tests are required for WOCBPs at the time points indicated in the Schedule of Assessments; however, a serum pregnancy test can be done anytime during the trial at the investigator's discretion. Female participants with exclusively same sex partners may not be required to have pregnancy tests per investigator discretion; confirmation with the medical monitor is required.

Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations.

Table 8: Protocol-Required Safety Laboratory Tests

Laboratory Tests	Parameters	
Hematology	Platelet count RBC count Hemoglobin Hematocrit PTT and PT/INR MCH MCHC % Reticulocytes MCV	WBC count with differential (absolute and %): • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
Chemistry	BUN Creatinine Glucose Albumin Cholesterol (total, HDL, LDL) Triglycerides Uric acid Potassium Sodium Calcium Bicarbonate Chloride Magnesium Phosphorus	ALT AST Alkaline phosphatase GGT CPK Total bilirubin and direct bilirubin Total protein

Laboratory Tests	Parameters
Routine Urinalysis and Urine Drug Screen	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick Urine dipstick with reflex to microscopy if positive finding Urine drug screen
Pregnancy Testing	Serum pregnancy test (at Screening and as needed for women of childbearing potential) Urine dipstick pregnancy test (at all other time points and as needed for women of childbearing potential), followed by serum pregnancy test if urine dipstick test is positive
Other Screening Tests	A confirmatory FSH is required for postmenopausal women Breathalyzer test for alcohol Serology (HIV, HBsAg, total anti-HBc,[a] HBsAb,[a] hepatitis C antibody) with reflex to HCV RNA test, if HCV antibody test is positive or indeterminate TSH

Abbreviations: Ab=antibody; Ag=antigen; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CPK=creatine phosphokinase; FSH=follicle-stimulating hormone; GGT=gamma glutamyl transferase; HBc=hepatitis B core; HBs=hepatitis B surface; HCV=hepatitis C virus; HDL=high density lipoprotein; HIV=human immunodeficiency virus; INR=international normalized ratio; LDL=low density lipoprotein; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; PT=prothrombin time; PTT=partial thromboplastin time; RBC=red blood cell; RNA=ribonucleic acid; TSH=thyroid-stimulating hormone; WBC=white blood cell.
[a] HBsAb and total anti-HBc will be collected at Screening but will not be used to determine participant eligibility.

Investigators must document their review of each laboratory safety report and file appropriately.

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

10.3.1. Definition of AE

Table 9: Definition of AE

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

Table 10: Events Meeting the AE Definition

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

10.3.2. Definition of SAE

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

Table 11: Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose in the view of either the investigator or sponsor, results in any of the following outcomes:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, or blood dyscrasias.

10.3.3. Recording and Follow-up of AEs and/or SAEs/AESIs

Table 12: Recording of AEs and/or SAEs/AESIs

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

Table 13: Assessment of Severity and Causality of AEs and/or SAEs/AESIs

Severity	
All AEs, including clinically significant treatment-emergent laboratory abnormalities, will be graded according to the NCI-CTCAE, version 5.0 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf) Adverse events not listed by the NCI-CTCAE will be graded according to the criteria defined below.	
Grade	**Description**
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living.
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
4	Life-threatening consequences; urgent intervention indicated.
5	Fatal AE; an event that results in the death of the participant.
Note: Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.	
Causality	

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

Causality
• The investigator may change his/her opinion of causality in light of follow-up information and send an SAE/AESI follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements

Table 14: Follow-Up of AEs and SAEs/AESIs

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

10.3.4. Reporting of SAEs/AESIs

Table 15: SAE/AESI Reporting to the Sponsor or Designee via an Electronic Data Collection Tool

Reporting to the Sponsor or Designee via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE/AESI to the sponsor or designee will be the electronic data collection tool. • The site will enter the SAE/AESI data as soon as it becomes available within 24 hours of awareness. • If the electronic data collection tool is unavailable, then the site will use the paper form (see Table 16). • After the trial is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE/AESI from a trial participant or receives updated data on a previously reported SAE/AESI after the electronic data collection tool has been taken offline, then the site can report this information on the paper form (see Table 16) or to the sponsor or designee by telephone.

Table 16: SAE/AESI Reporting to the Sponsor or Designee via Paper Form (if needed)

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

10.4. Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions

10.4.1.1. Women of Childbearing Potential, Women of Nonchildbearing Potential, and Fertile Men

A woman is considered to be a woman of childbearing potential following menarche and until becoming postmenopausal unless permanently sterile.

A woman is considered to be of nonchildbearing potential if she fulfills either of the following criteria:

- Underwent permanent sterilization including hysterectomy, bilateral oophorectomy, or bilateral salpingectomy.
- Is in a postmenopausal state, which is defined as no menses for at least 12 consecutive months without an alternative medical cause, and confirmed with an FSH level >40 mIU/mL.

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

10.4.1.2. Highly Effective Form of Contraception (Failure Rate <1%)

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

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

in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

10.4.2. Collection of Pregnancy Information

10.4.2.1. Male Participants With Partners Who Become Pregnant

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

10.4.2.2. Female Participants Who Become Pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this trial. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-trial pregnancy-related SAE considered reasonably related to the trial intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former trial participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the trial will discontinue trial intervention and be withdrawn from the trial.

10.5. Future Biospecimen Research

Use/Analysis of DNA

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

10.6. Liver Safety: Suggested Actions and Follow-up Assessments

10.6.1. Assessment of Elevations in Liver Test Results

Elevations in liver test results occurring during a clinical trial may result from DILI. However, since DILI is a diagnosis of exclusion, it is essential to exclude other etiologies (see Section 10.6.4) that may lead to elevated results in liver tests.

When aminotransferase (ALT or AST) levels increase to ≥3 × ULN during a clinical trial, current US guidance (US FDA, 2009) recommends close observation and diagnostic workup for causes of hepatic injury (see Section 10.6.4) other than the IMP. The International Consensus Criteria for idiosyncratic DILI only uses ALT to define DILI when referring to aminotransferase levels (Watkins, 2019). The CIOMS Working Group on DILI suggests using serum ALT as it is more specific than AST to detect and monitor the liver injury, irrespective of the cause (CIOMS, 2020; EASL, 2019; Kwo et al, 2017).

The medical monitor must be consulted when ALT levels increase to ≥3 × ULN.

Table 17 describes liver test monitoring during the close observation period of elevated liver tests during a clinical trial. Close observation is required until the elevations in liver test results return to baseline levels or normalize.

Table 17: Monitoring of Liver Tests

Result	Frequency for Repeating Liver (AST, ALT, Bilirubin [Total and Direct]) and INR Tests
If either of the following: • ALT ≥3 × ULN and total bilirubin ≥2 × ULN or INR >1.5 • ALT ≥3 × ULN with symptoms and signs of hepatitis	Every 24 hours until laboratory abnormalities improve
If ALT ≥3 × ULN and total bilirubin or INR are within the normal range	Every 48 to 72 hours until laboratory abnormalities improve
If the liver test abnormalities improve AND participants' symptoms improve or participants are asymptomatic	Frequency may decrease to once weekly

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; INR=international normalized ratio; ULN=upper limit of normal.

10.6.2. Criteria for Permanent Discontinuation of Trial Intervention (Potential Hy's Law Cases)

The following criteria may suggest the presence of severe liver injury regardless of the etiology; "Hy's law" points to advanced and potentially severe DILI when other possible causes of liver injury have been excluded. When all of the following criteria are met, the IMP should be permanently discontinued and not restarted under any condition and the event should be reported as an SAE.

1. ALT increases to ≥3 × ULN

2. Total bilirubin increases to ≥2 × ULN or INR >1.5
3. Alkaline phosphatase value <2 × ULN (ie, absence of significant cholestasis)
4. No alternative cause explains the combination of the above laboratory abnormalities; important alternative causes are included in Table 19.

10.6.3. Criteria for Temporary Withholding or Permanent Discontinuation of Trial Intervention

Participants who develop abnormal results in liver tests (AST, ALT, alkaline phosphatase, total bilirubin) during the trial treatment period may meet the criteria for discontinuation of IMP treatment specified in the FDA guidance (Table 18).

Table 18: Criteria for Temporarily Withholding IMP in Association With Abnormalities in Liver Test Results

Baseline ALT Value	ALT Elevation
<3 × ULN	• >8 × ULN • >5 × ULN for more than 2 weeks • ≥3 × ULN and (total bilirubin ≥2 × ULN or INR >1.5) • ≥3 × ULN with the presence of signs and symptoms consistent with acute hepatitis and/or eosinophilia (≥500 eosinophils/µL)

Abbreviations: ALT=alanine aminotransferase; IMP=investigational medicinal product; INR=international normalized ratio; ULN=upper limit of normal.

IMP should be withheld pending an investigation (Table 20) of alternative causes of abnormalities in liver test results (Table 19). Clinical and laboratory follow-up should continue during the withholding period until the abnormalities in liver test results return to baseline values.

Resumption of IMP can only occur with the express consent of the sponsor and/or their medical designee and only if another cause for the abnormal results is identified and liver tests return to within the normal range.

10.6.4. Evaluation of Alternative Causes of Liver Test Result Abnormalities

Table 19: Alternative Causes of Abnormalities in Liver Test Results

Biliary obstruction, focal liver lesions (benign or malignant), vascular liver disease (such as portal vein thrombosis or Budd-Chiari syndrome)
Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
Autoimmune hepatitis
Exposure to hepatotoxic agents/drugs or hepatotoxins (other than IMP), including herbal and dietary supplements, plants, and mushrooms
Alcoholic hepatitis
Nonalcoholic steatohepatitis and hepatic steatosis
Congestive heart failure, hypotension, ischemic hepatitis
Others: sepsis, sinusoidal obstruction syndrome, primary biliary cholangitis, primary sclerosing cholangitis, Wilson disease, hemochromatosis, alpha-1-antitrypsin deficiency

Abbreviations: IMP=investigational medicinal product.

Table 20: Investigation of Alternative Etiologies for Elevated Liver Test Results

Initial set of tests[a]	
Complementary Tests and Parameters	**Etiologies**
Complete blood count with differential (eg, eosinophilia)	Infection (sepsis), immune-related DILI (eosinophilia), high MCV (alcoholic hepatitis)
ALT, AST, GGT, serum PEth	Alcoholic hepatitis (AST:ALT ratio ≥2)
ALP and GGT	Biliary obstruction
CPK, haptoglobin, LDH, and peripheral blood smear	Rhabdomyolysis and hemolysis
HAV IgM	Hepatitis A
HBsAg, anti-HBc IgM, total anti-HBc, anti-HBs, HBV-DNA (by PCR)	Hepatitis B (acute, reactivation of chronic or occult hepatitis B)
anti-HCV, HCV-RNA (by PCR)	Acute hepatitis C
HEV IgM and IgG	Acute hepatitis E
Liver imaging (ultrasound, CT, or MRI)	Biliary obstruction, focal lesions, vascular liver disease, hepatic steatosis
Serum total IgG, ANA, anti-smooth muscle antibody	Autoimmune hepatitis
Serum acetaminophen (paracetamol) concentration	Acetaminophen (paracetamol) overdose

Obtain a more detailed history as follows: • Prior and concurrent diseases or illness • Exposure to environmental and/or industrial chemical agents • Presence of symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting, and fever • Prior and concurrent alcohol use, recreational drug use, and special diets • Concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants, and mushrooms	
Additional set of tests[b]	
Complementary Tests and Parameters	**Etiologies**
Echocardiogram	Congestive heart failure
CMV IgM (CMV-DNA)	Acute CMV infection
EBV IgM (EBV-DNA)	Acute EBV infection
HSV IgM (HSV-DNA)	Acute HSV infection
Anti-mitochondrial autoantibodies	PBC
24 hours urine copper and serum ceruloplasmin	Wilson disease
Iron studies (serum iron and ferritin) and transferrin saturation	Hemochromatosis
Serum alpha-1 antitrypsin	Alpha-1-antitrypsin deficiency
MRI, ERCP, ANA, perinuclear anti-neutrophil cytoplasmic	PSC
Hepatology consult may be requested (a liver biopsy may be considered in consultation with a hepatologist). The medical monitor should be contacted for questions regarding adequate follow up tests.	

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; ANA=anti-nuclear antibody; anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; anti-HCV=hepatitis C virus antibody; AST=aspartate aminotransferase; CMV=cytomegalovirus; CPK=creatinine phosphokinase; CT=computed tomography; DILI= drug-induced liver injury; DNA=deoxyribonucleic acid; EBV=Epstein Barr virus; ERCP=endoscopic retrograde cholangiopancreatography; GGT=gamma glutamyltransferase; HAV=hepatitis A virus; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HEV=hepatitis E virus; HSV=herpes simplex virus; Ig=immunoglobulin; LDH=lactate dehydrogenase; MCV=mean corpuscular volume; MRI=magnetic resonance imaging; PBC=primary biliary cholangitis; PCR=polymerase chain reaction; PEth=phosphatidylethanol; PSC=primary sclerosing cholangitis; RNA=ribonucleic acid.

[a] To be done for all participants.

[b] To be done when clinically indicated.

10.7. Moderate to Strong Inducers and Inhibitors of Cytochrome P450 3A4 (not exhaustive)

Note that this may not be a complete list and that the investigator is responsible for ensuring that participants are not receiving any moderate to strong inducers or moderate to strong inhibitors of cytochrome P450 3A4 during the trial.

CYP 3A4 Inhibitors	CYP 3A4 Inducers
HIV antivirals	**HIV antivirals**
Indinavir	Efavirenz
Nelfinavir	Nevirapine
Ritonavir	Etravirine
Saquinavir	**Miscellaneous**
Boceprevir	Barbiturates
Lopinavir/ritonavir	Carbamazepine
Amprenavir	Cenobamate
Atazanavir	Eslicarbazepine
Telaprevir	Glucocorticoids (systemic)
Darunavir/ritonavir	Modafinil
Fosamprenavir	Oxcarbazepine[d]
Antibiotics	Phenobarbital
Clarithromycin	Phenytoin
Erythromycin	Pioglitazone
Telithromycin	Rifabutin
Ciprofloxacin	Rifampin
Anti-infectives	St. John's wort
Itraconazole	Troglitazone
Ketoconazole	Bosentan
Fluconazole	Nafcillin
Posaconazole	Avasimibe
Voriconazole	
Anti-anginal therapy	
Diltiazem	
Verapamil	
Anti-cancer therapy	
Crizotinib	
Imatinib	
Miscellaneous	
Nefazodone	
Aprepitant	
Grapefruit juice[a,b]	
Conivaptan	
Mibefradil[c]	

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

[a] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation dependent. Studies have shown that it can be classified as a "strong CYP3A4 inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A4 inhibitor" when another preparation was used (eg, low dose, single strength).
[b] A 7-day washout prior to dosing is required if grapefruit juice was being consumed continually.
[c] Withdrawn from the United States market.
[d] Doses >900 mg/day.

10.8. Abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
APMP	Abuse Potential Monitoring Plan
AST	aspartate aminotransferase
BID	twice daily
BMI	body mass index
BZD	benzodiazepine
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression-Severity of Symptoms Scale
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CNS	central nervous system
CO_2	carbon dioxide
CRF	case report form
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
DILI	drug-induced liver injury
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-5-TR	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EQ-5D-5L	European Quality of Life
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
$GABA_A$	gamma-amino-butyric-acid type A
GAD	generalized anxiety disorder
HAM-A	Hamilton Anxiety Scale
IB	Investigator's Brochure
ICE	intercurrent event

Abbreviation	Definition
ICF	informed consent form
IEC	Independent Ethics Committee
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
MMRM	mixed model for repeated measures
NCI-CTCAE	National Cancer Institute- Common Terminology Criteria for Adverse Events
PAM	positive allosteric modulator
PD	pharmacodynamics
PDSS	Panic Disorder Severity Scale
PK	pharmacokinetic
PSL-IV	Panic Symptom List-IV
PWC	Physician Withdrawal Checklist
QTcF	QT interval corrected for heart rate using Fridericia's formula
RO	receptor occupancy
SAE	serious adverse event
SAP	Statistical Analysis Plan
SDS	Sheehan Disability Scale
SNRI	serotonin and norepinephrine reuptake inhibitors
SPV	saccadic peak velocity
SSRI	selective serotonin reuptake inhibitors
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
TIA	transient ischemic attack
ULN	upper limit of normal
VAS	visual analog scale
WOCBP	woman of childbearing potential

10.9. Protocol Amendment History

The Document History table, which lists all versions of this protocol, and the Protocol Amendment Summary of Changes table for the current amendment are located directly before the Table of Contents.

Document History	
Protocol Version	**Date**
3.0	24 Jan 2024
2.0	17 Jul 2023
1.0	04 Jan 2023

Amendment: Protocol Version 2.0 (17 Jul 2023)

Overall Rationale for the Amendment:

The overall rationale for this amendment is to make clarifications to dosing rationale, exclusion criteria, prohibited therapy, statistical language, and AESI language.

Section # and Name	**Description of Change**	**Brief Rationale**
Title page Section 1.1 Synopsis Principal Investigator Signature Page	"(ADAPT Trial)" added to the trial title.	Change made to distinguish this trial from other trials.
Sponsor Signatories	Medical Lead changed.	Updated due to change in personnel.
Section 1.1 Synopsis	Updated the synopsis to reflect changes made in the body.	Change made for internal consistency.
Section 2.3 Benefit/Risk Assessment	Added "…at this time" to the benefit/risk language.	To clarify the existing protocol text.
Section 4.3.1 Dosing Rationale	Text explaining the dose titration was modified.	Updated to clarify the language.
Section 5.2 Exclusion Criteria	Dysthymia was added to Exclusion Criterion 1.	Change made to clarify participant eligibility criteria.
Section 5.2 Exclusion Criteria	"eGFR <60 mL/min/1.73 m^2 (as estimated by the CKD-EPI 2021 equation [Levey et al, 2009; Delgado et al, 2022]) and as reported by the central laboratory" was added to Exclusion Criterion 11.	Change made to clarify participant eligibility criteria.
Section 6.1 Trial Interventions Administered	The description of the packaging was updated to allow for blister packs to be used outside of the titration period.	Change made to provide flexibility in packaging.

Section # and Name	Description of Change	Brief Rationale
Section 6.7.2 Prohibited Therapy	Added "beta receptor antagonists used for any reason" to Table 5.	To correct an inadvertent omission.
Section 6.7.2 Prohibited Therapy	Added "Antiseizure/neuropathic pain medications used for any indication (eg, gabapentin, pregabalin, topiramate, phenytoin, phenobarbital)" to Tables 5 and 6.	Change made in order to avoid any confounding effect of these medications on the anxiolytic activity of darigabat.
Section 6.7.2 Prohibited Therapy	Hydroxyzine and diphenhydramine were removed from the bullets for hypnotics in Tables 5 and 6 and also from the footnotes of Table 6. The footnote on first-generation antihistamines was removed from Table 6 and first-generation antihistamines were instead added as a bullet under psychoactive substances in Table 6.	To correct the fact that first-generation H1-antihistamines were inadvertently excluded from the prohibited medications list and were only mentioned in a footnote. However, they have poor receptor selectivity, cross the blood-brain barrier, and interact with receptors of other biologically active amines causing antimuscarinic, anti-α-adrenergic, and antiserotonin effects.
Section 6.7.2 Prohibited Therapy	Split antidepressants into their own row in Table 5 and added text specifying that a 14-day washout is required except for fluoxetine and Symbyax, which require a 28-day washout. Text added to clarify that the prior row for psychoactive drugs does not include antidepressants.	Change made to clarify protocol text.
Section 6.7.2 Prohibited Therapy	Added a row to Table 5 specifying that investigational agents are prohibited prior medications and must have a washout of 60 days.	Change made to align with other darigabat trials.
Section 6.7.2 Prohibited Therapy	Language in Table 6 was updated to specify that beta receptor antagonists used for any indication are prohibited.	Updated to clarify the language.
Section 6.7.2 Prohibited Therapy	Updated text in Table 6 to remove fluoxetine and Symbyax.	Change made to clarify protocol text.

Section # and Name	Description of Change	Brief Rationale
Section 6.7.2 Prohibited Therapy Section 10.7 Moderate to Strong Inducers and Inhibitors of Cytochrome P450 3A4 (not exhaustive)	Updated CYP3A and cytochrome P450 3A to CYP3A4 and cytochrome P450 3A4, respectively. Section 10.7 title also modified.	Change made for internal consistency.
Section 7.1 Discontinuation of Trial Intervention Section 8.3.7 Adverse Events of Special Interest	Added treatment stopping rules for QTcF and laboratory abnormalities and removed redundant text (Section 8.3.7 only).	Change made to expand upon actions taken when AESIs occur.
Section 7.2 Participant Discontinuation/Withdrawal From the Trial	The following language was added: "Unless clinically necessary, the initiation of any prohibited medications should occur after the completion of all of the assessments at the Early Termination Visit and Telephone Visits 7 and 8."	Changes made to clarify protocol text.
Section 8.1.3 Clinical Global Impression-Severity of Symptoms Scale	Text updated to clarify that the Clinical Global Impression-Severity of Symptoms Scale applies specifically to panic disorder symptoms.	Changes made to clarify existing text.
Section 9.2 Analysis Sets	The description of the FAS was updated to specify that it will include all participants with valid baseline panic attack assessments (previously baseline and post-baseline) and to clarify that participants who have not met all inclusion/exclusion criteria but are randomized in error will not be included.	Revisions made to further clarify/define protocol text.
Section 9.3.2 Primary Endpoint/Estimand Analyses Section 9.3.3.1 Change From Baseline in PDSS Total Score at Week 14	Changed "Full analysis set" to "The population defined by the inclusion/exclusion criteria of the trial."	Revisions made to align more closely with the estimand framework.
Section 9.3.2 Primary Endpoint/Estimand Analyses	Updated the attributes of the primary estimand.	Change made to provide clarification.

Section # and Name	Description of Change	Brief Rationale
Section 9.3.2 Primary Endpoint/Estimand Analyses	Added text specifying that model diagnostics will be performed to explore goodness-of-fit.	Change made to provide additional detail.
Section 9.3.2 Primary Endpoint/Estimand Analyses	Specified that in the event of a convergence issue with the unstructured covariance matrix, a structured covariance matrix may be used and provided further details.	Change made to provide additional detail.
Section 9.3.2 Primary Endpoint/Estimand Analyses	Added details of a sensitivity analysis.	Change made to provide additional detail.
Section 9.3.3.1 Change From Baseline in PDSS Total Score at Week 14	Updated the attributes of the secondary estimand around missing values due to ICEs.	Change made to provide additional detail.
Section 9.3.3.1 Change From Baseline in PDSS Total Score at Week 14	Specified that in the event of a convergence issue with the unstructured covariance matrix, a structured covariance matrix may be used and provided further details.	Change made to provide additional detail.
Section 9.3.3.1 Change From Baseline in PDSS Total Score at Week 14	Removed the word "each" from "…each active dose."	Change made to reflect the single-dose trial design.
Section 9.3.3.1 Change From Baseline in PDSS Total Score at Week 14	Added a list of ICEs that may be considered as treatment related and added details on handling missing data due to ICEs.	Change made to provide additional detail.
Section 9.3.3.2 Change From Baseline in Panic Attack Frequency During the Last 2 Weeks of the Maintenance Treatment Period	Updated the attributes of the secondary estimand around missing values due to ICEs.	Change made to provide additional detail.
Section 9.5 Sample Size Determination	"…due to other factors" removed from the statement allowing enrollment extension in the event of higher than anticipated early terminations.	Updated to clarify the language.
Section 10.1.3 Informed Consent Process	ICF language was changed to ensure that participants who are rescreened must sign an ICF.	Changes made to correct an error in the original protocol.
Section 10.1.7 Source Documents	Text was modified to state that every effort should be made to	Changes made to clarify the prior protocol text.

Section # and Name	Description of Change	Brief Rationale
	obtain and retain current medical records.	
Section 10.2 Clinical Laboratory Tests	SARS-CoV-2 testing was removed from the list of protocol-required safety laboratory tests.	This test is not required at Screening and was removed for clarity.
Section 10.4.1.1 Women of Childbearing Potential, Women of Nonchildbearing Potential, and Fertile Men	The FSH level for confirming a postmenopausal state was updated from >40 IU/mL to >40 mIU/mL.	To correct a typo in the unit.
Overall	Minor grammatical and wording corrections/clarifications made throughout protocol.	Correction of errors from the previous version of the protocol.

Abbreviations: AESI=adverse events of special interest; ECG=electrocardiogram; FAS=full analysis set; FSH=follicle-stimulating hormone; FDA=Food and Drug Administration; eGFR=estimated glomerular filtration rate; ICE=intercurrent event; ICF=informed consent form; PDSS=Panic Disorder Severity Scale; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

11. REFERENCES

Alprazolam. Prescribing information. Pfizer Pharmacia & Upjohn Co; 2011. Accessed 17 Aug 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/018276s045lbl.pdf

American Psychiatric Association (APA). Diagnostic and statistical manual of mental disorders. Fifth ed, Text Revision. Arlington VA: American Psychiatric Publishing; 2022.

APA Work Group on Panic Disorder. Practice guideline for the treatment of patients with panic disorder. Second edition. 2009. Accessed 17 Aug 2022. https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/panicdisorder.pdf

BioSpace. Wyeth release: EFFEXOR XR approved for the treatment of panic disorder; 2005. Accessed October 13, 2022. https://www.biospace.com/article/releases/wyeth-release-effexor-xr-approved-for-the-treatment-of-panic-disorder-/

Bradwejn J, Ahokas A, Stein DJ, et al. Venlafaxine extended-release capsules in panic disorder: flexible-dose, double-blind, placebo-controlled study. Br J Psychiatry. 2005;187:352-9.

Bruce SE, Yonkers KA, Otto MW, et al. Influence of psychiatric comorbidity on recovery and recurrence in generalized anxiety disorder, social phobia, and panic disorder: A 12-year prospective study. Am J Psychiatry. 2005;162(2):1179-87.

Chawla N, Anothaisintawee T, Charoenrungrueangchai K, et al. Drug treatment for panic disorder with or without agoraphobia: systematic review and network meta-analysis of randomised controlled trials. BMJ. 2022;376:e066084.

Chouinard G, Annable L, Fontaine R, Solyom L. Alprazolam in the treatment of generalized anxiety and panic disorders: A double-blind placebo-controlled study. Psychopharmacology (Berl). 1982;77(3):229-33.

Clonazepam. Prescribing information. Genentech USA, Inc.; 2013. Accessed 17 Aug 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/017533s053,020813s009lbl.pdf

Colasanti A, Salamon E, Schruers K, van Diest R, van Duinen M, Griez EJ. Carbon dioxide-induced emotion and respiratory symptoms in healthy volunteers. Neuropsychopharmacology. 2008;33(13):3103-10.

Council for International Organizations of Medical Sciences (CIOMS). Drug-induced liver injury (DILI): Current status and future directions for drug development and the post-market setting. Geneva, Switzerland: A consensus by a CIOMS Working Group; 2020.

Cowley DS, Ha EH, Roy-Byrne PP. Determinants of pharmacologic treatment failure in panic disorder. J Clin Psychiatry. 1997;58(12):555-63.

Delgado C, Baweja M, Crews DC, et al. A unifying approach for GFR estimation: recommendations of the NKF-ASN Task Force on reassessing the inclusion of race in diagnosing kidney disease. Am J Kidney Dis. 2022;79(2):268-88.

Engin E, Liu J, Rudolph U. α2-containing GABA(A) receptors: a target for the development of novel treatment strategies for CNS disorders. Pharmacol Ther. 2012;136(2):142-52.

EQ-5D-5L User Guide. Version 3.0; Sep 2019. Accessed 03 Jan 2023. https://euroqol.org/publications/user-guides/

European Association for the Study of the Liver (EASL). EASL Clinical Practice Guidelines: Drug-induced liver injury. J Hepatol. 2019;70(6):1222-61.

Fluoxetine. Prescribing Information. Eli Lilly and Company; 1987. Accessed 17 Aug 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/018936s091lbl.pdf

Goddard AW, Brouette T, Almai A, Jetty P, Woods SW, Charney D. Early coadministration of clonazepam with sertraline for panic disorder. Arch Gen Psychiatry. 2001;58(7):681-6.

Gorman JM, Askanazi J, Liebowitz MR, et al. Response to hyperventilation in a group of patients with panic disorder. Am J Psychiatry. 1984;141(7):857-61.

Guy W. ECDEU Assessment Manual for Psychopharmacology – Revised. Rockville, MD: US Department of Health, Education, and Welfare; 1976:534-7. DHEW Publication ADM 76-338.

Keller MB, Yonkers KA, Warshaw MG, et al. Remission and relapse in subjects with panic disorder and panic with agoraphobia: a prospective short-interval naturalistic follow-up. J Nerv Ment Dis. 1994;182:290-6.

Kessler RC, Chiu WT, Jin R, Ruscio AM, Shear K, Walters EE. The epidemiology of panic attacks, panic disorder, and agoraphobia in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2006;63(4):415-24.

Kwo PY, Cohen SM, Lim JK. ACG Clinical Guideline: evaluation of abnormal liver chemistries. Am J Gastroenterol. 2017;112(1):18-35.

Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

Liebowitz MR, Asnis G, Mangano R, Tzanis E. A double-blind, placebo-controlled, parallel-group, flexible-dose study of venlafaxine extended release capsules in adult outpatients with panic disorder. J Clin Psychiatry. 2009;70(4):550-61.

Löw K, Crestani F, Keist R, et al. Molecular and neuronal substrate for the selective attenuation of anxiety. Science. 2000;290(5489):131-4.

Manjunatha N, Ram D. Panic disorder in general medical practice- A narrative review. J Family Med Prim Care. 2022;11(3):861-9.

Michelson D, Allgulander C, Dantendorfer K, et al. Efficacy of usual antidepressant dosing regimens of fluoxetine in panic disorder: randomised, placebo-controlled trial. Br J Psychiatry. 2001;179:514-8.

Munjack D J, Crocker B, Cabe D, et al. Alprazolam, propranolol, and placebo in the treatment of panic disorder and agoraphobia with panic attacks. J Clin Psychopharmacol. 1989;9(1):22-7.

Nardi AE, Valença AM, Freire RC, et al. Psychopharmacotherapy of panic disorder: 8-week randomized trial with clonazepam and paroxetine. Braz J Med Biol Res. 2011;44(4):366-73.

National Institute of Mental Health (NIMH). Panic Disorder. Accessed 17 Aug 2022. https://www.nimh.nih.gov/health/statistics/panic-disorder

Nickolls SA, Gurrell R, van Amerongen G, et al. Pharmacology in translation: the preclinical and early clinical profile of the novel α2/3 functionally selective $GABA_A$ receptor positive allosteric modulator PF-06372865. Br J Pharmacol. 2018;175(4):708-25.

Paroxetine. Prescribing information. GlaxoSmithKline; 2011. Accessed 17 Aug 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020031s067,020710s031.pdf

Pollack M, Mangano R, Entsuah R, Tzanis E, Simon NM, Zhang Y. A randomized controlled trial of venlafaxine ER and paroxetine in the treatment of outpatients with panic disorder. Psychopharmacology (Berl). 2007;194(2):233-42.

Pollack MH, Marzol PC. Panic: Course, complications and treatment of panic disorder. J Psychopharmacol. 2000;14(2_suppl1):S25-S30.

Pollack MH, Simon NM, Worthington JJ, et al. Combined paroxetine and clonazepam treatment strategies compared to paroxetine monotherapy for panic disorder. J Psychopharmacol. 2003;17(3):276-82.

Posner K, Brown GK, Stanley B, et al. The Columbia–Suicide Severity Rating Scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168(12):1266-77.

Rickels K, Case G, Downing RW, Winokur A. Long-term diazepam therapy and clinical outcome. JAMA. 1983;250(6):767-71.

Rickels K, Garcia-Espana F, Mandos LA, Case GW. Physician Withdrawal Checklist (PWC-20). J Clin Psychopharmacol. 2008;28(4):447-51.

Rickels K, Schweizer E, Case WG, Greenblatt DJ. Long-term therapeutic use of benzodiazepines. I. Effects of abrupt discontinuation. Arch Gen Psychiatry. 1990;47(10):899-907.

Rowlett JK, Platt DM, Lelas S, Atack JR, Dawson GR. Different $GABA_A$ receptor subtypes mediate the anxiolytic, abuse-related, and motor effects of benzodiazepine-like drugs in primates. Proc Natl Acad Sci U S A. 2005;102(3):915-20.

Rudolph U, Crestani F, Benke D, et al. Benzodiazepine actions mediated by specific gamma aminobutyric acid(A) receptor subtypes. Nature. 1999;401(6755):796-800.

Salvadore G, Bonaventure P, Shekhar A, et al. Translational evaluation of novel selective oresin-1 receptor antagonist JNJ-61393215 in an experimental model for panic in rodents and humans. Transl Psychiatry. 2020;10(1):308.

Scholten WD, Batelaan NM, van Balkom AJ, Wjh Penninx B, Smit JH, van Oppen P. Recurrence of anxiety disorders and its predictors. J Affect Disord. 2013;147(1-3):180-5.

Schweizer E, Pohl R, Balon R, Fox I, Rickels K, Yeragani VK. Lorazepam vs alprazolam in the treatment of panic disorder. Pharmacopsychiatry. 1990;23(2):90-3.

Schweizer E, Rickels K, Weiss S, Zavodnick S. Maintenance drug treatment of panic disorder. I. Results of a prospective, placebo-controlled comparison of alprazolam and imipramine. Arch Gen Psychiatry. 1993;50(1):51-60.

Shear KM, Brown TA, Barlow DH, et al. Multicenter collaborative Panic Disorder Severity Scale. Am J Psychiatry. 1997;154(11):1571-5.

Sheehan DV. 1983. The anxiety disease. New York: Charles Scribners.

Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. Int Clin Psychopharmacol. 1996;11(Suppl3):89-95.

Sheehan DV, Lecrubier Y, Harnett-Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59(suppl 20):22-57.

Sheehan DV, Lecrubier Y, Harnett-Sheehan K, et al. The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. Eur Psychiatry. 1997;12(5):232-41.

Simen A, Whitlock M, Qiu R, et al. An 8-week, randomized, phase 2, double-blind, sequential parallel-group comparison study of two dose levels of the GABAA positive allosteric modulator PF-06372865 compared with placebo as an adjunctive treatment in outpatients with inadequate response to standard of care for generalized anxiety disorder. J Clin Psychopharmacol. 2019;39(1):20-7.

Smith KS, Engin E, Meloni EG, Rudolph U. Benzodiazepine-induced anxiolysis and reduction of conditioned fear are mediated by distinct GABA(A) receptor subtypes in mice. Neuropharmacology. 2012;63(2):250-8.

Teismann T, Lukaschek K, Hiller TS, et al. Suicidal ideation in primary care patients suffering from panic disorder with or without agoraphobia. BMC Psychiatry. 2018;18(1):305.

US Food and Drug Administration (FDA). Guidance for Industry: Assessment of abuse potential of drugs; Jan 2017. Accessed 03 Jan 2023. https://www.fda.gov/media/116739/download

US FDA. Guidance for Industry: Drug-induced liver injury: premarketing clinical evaluation; Jul 2009. Accessed 03 Jan 2023. https://www.fda.gov/media/116737/download

US FDA. Guidance for Industry: E10 choice of control group and related issues in clinical trials; May 2001. Accessed 03 Jan 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e10-choice-control-group-and-related-issues-clinical-trials

Van den Hout MA, Griez E. Panic symptoms after inhalation of carbon dioxide. Br J Psychiatry. 1984;144:503-7.

Venlafaxine. Prescribing information. Pfizer Wyeth Pharmaceuticals Inc; 2017. Accessed 17 Aug 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020699s107lbl.pdf

Watkins PB. Idiosyncratic drug-induced liver injury in patients: Detection, severity assessment, and regulatory implications. Adv Pharmacol. 2019;85:165-93.

Woods SW, Charney DS, Goodman WK, Heninger GR. Carbon dioxide-induced anxiety: behavioral, physiologic, and biochemical effects of carbon dioxide in patients with panic disorders and healthy subjects. Arch Gen Psychiatry. 1988;45(1):43-52.

Woods SW, Charney DS, Loke J, Goodman WK, Redmond DE Jr, Heninger GR. Carbon dioxide sensitivity in panic anxiety: ventilatory and anxiogenic response to carbon dioxide in healthy subjects and patients with panic anxiety before and after alprazolam treatment. Arch Gen Psychiatry. 1986;43(9):900-9.