Official Title: A Phase II, Randomized, Double-Blind, Placebo-Controlled, Two-Arm, Parallel-Group, Multicenter Study to Evaluate the Efficacy and Safety of Balovaptan in Adults With Post-Traumatic Stress Disorder

NCT Number: NCT05401565

Document Date: Protocol Version 3: 09-January-2023

PROTOCOL

PROTOCOL TITLE:	**A PHASE II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, TWO-ARM, PARALLEL-GROUP, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF BALOVAPTAN IN ADULTS WITH POST-TRAUMATIC STRESS DISORDER**
PROTOCOL NUMBER:	BN43546
VERSION NUMBER:	3
ROCHE COMPOUND:	Balovaptan (RO5285119)
STUDY PHASE:	Phase II
EUDRACT NUMBER:	Not applicable
IND NUMBER:	158940
NCT NUMBER:	NCT05401565
SPONSOR NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL:	See electronic *signature and* date stamp *on the final page of this document*.

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
3	*See electronic date stamp on the final page of this document*
2	*23 February 2022*
1	22 December 2021

PROTOCOL AMENDMENT, VERSION 3: RATIONALE

Protocol BN43546 has been primarily amended to include Sponsor-initiated modifications including the reduction of the sample size, an update to the QT interval corrected through use of Fridericia's formula (QTcF) monitoring, and the removal of the planned interim analysis. Changes to the protocol, along with a rationale for each change, are summarized below:

- Personal identifiable information (i.e., name and telephone number) for the Medical Monitor has been removed from the protocol (Protocol title page, protocol acceptance form, and Section 8.3.8). Medical Monitor contact information has been replaced with a sentence indicating that this information will be provided separately to sites.
- The protocol synopsis has been simplified to align with Clinical Trial Regulation and other guidelines (Section 1.1).
- The sample size has been reduced from 252 participants to 30 participants to investigate the objectives of the study with a reduced scope (Sections 1.2, 4.1.2, 5, and 9.2; Appendix A1−5) and the following changes have been made as a result:
  - The objectives of this study have been revised from "evaluate" to "investigate" as the reduced sample size precludes formal comparisons (Section 3).
  - The description of the primary estimand, statistical hypothesis, and primary, secondary, and exploratory analysis methodologies have been removed as all analyses will be conducted using descriptive statistics (Section 3, 9.1, 9.4.2, 9.4.3.1, and 9.4.4).
  - The estimated time to complete enrollment has been updated from approximately 13 or 15 months to 9 months (Sections 4.1 and 4.4).
  - The planned and optional interim analyses have been removed (Sections 4.1, 9.4, 9.5.1, and 9.5.2).
  - The total length of the study has been updated from approximately 18 months to 13 months (Section 4.4).
  - The number of sites has been reduced from 25 to 12 (Appendix A1−5).
- Guidance has been added to clarify that if a participant cannot be reached during the telephone visits, at least 3 documented attempts to contact the participant must occur (Section 1.3).
- To align with the protocol text, the footnote for measurement of vital signs in the schedule of activities has been updated to include guidance that three consecutive blood pressure readings will be recorded at intervals of at least 1 minute and the average of the three blood pressure readings will be recorded on the eCRF (Section 1.3).
- Guidance has been added to provide instructions for participants who need to take their daily dose at a different time of the day and for missed doses (Sections 1.3 and 6.1).

- The exclusion criterion for ECG abnormality has been updated to clarify that the two consecutive measurements of the ECGs during screening should be taken approximately 30 minutes apart and the second measurement is only taken if it is necessary to confirm initial ECG abnormality. The exclusion criterion has also been updated to include a separate QTcF threshold of $\geq$470 ms for female participants to better reflect current standard of care QTcF thresholds (Section 5.2).
- Text has been added to specify that tobacco use is permitted during the study and to provide examples of nicotine and tobacco use (Section 5.3.2).
- As all analysis will now be conducted by the Sponsor instead of external partners, text has been added to specify that some individuals from the Sponsor *may* have access to unblinded data as needed for ongoing analysis but the core study team with direct site contact will remain blinded throughout the conduct of the study. Additionally, text regarding access to blinded data through a secure data sharing platform by the external partner has been removed (Section 6.3.2).
- The responsibilities of the investigator and the role of the Medical Monitor during study conduct have been clarified (Sections 6.8, 6.8.2.1, and 8.2.5; Appendix A6–2.2).
- It has been clarified that there is no preclinical or clinical evidence that balovaptan administration is associated with an increase in abnormal liver tests (Section 7.1.1).
- The email address for withdrawal from the Research Biosample Repository after site closure has been corrected (Section 8.11.2.6).
- A description of the technical and organizational security measures taken to protect personal data has been added to align with CTR requirements (Appendix A1–4).
- Due to certain local requirements and an alignment of Sponsor process, it has been clarified that summaries of clinical study results may be available in health authority databases for public access in addition to redacted Clinical Study Reports (Appendix A1–6).
- The Sponsor record retention policy has been clarified (Appendix A1–7).
- The descriptions of potential risks associated with balovaptan has been updated to include a clinical study in pediatric participants (Study BP30153) at 10 mg or an equivalent dose based on predicted exposure of balovaptan (Appendices A6–1.2 and A6–1.5).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOL TITLE:	**A PHASE II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, TWO-ARM, PARALLEL-GROUP, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF BALOVAPTAN IN ADULTS WITH POST-TRAUMATIC STRESS DISORDER**
PROTOCOL NUMBER:	BN43546
VERSION NUMBER:	3
ROCHE COMPOUND:	Balovaptan (RO5285119)
SPONSOR NAME:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**A PHASE II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, TWO-ARM, PARALLEL-GROUP, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF BALOVAPTAN IN ADULTS WITH POST-TRAUMATIC STRESS DISORDER**
REGULATORY AGENCY IDENTIFIER NUMBERS:	*IND Number: 158940* *EudraCT Number: Not applicable* *NCT Number: NCT05401565*

STUDY RATIONALE

The purpose of this study is to assess the efficacy and safety of balovaptan, a vasopressin 1a (V1a) receptor antagonist, in participants with post-traumatic stress disorder (PTSD). Treatment options for PTSD include trauma-focused (TF) psychological interventions, such as cognitive behavioral therapy (CBT) and pharmacological treatments, including antidepressants (selective serotonin reuptake inhibitors [SSRIs] and serotonin and norepinephrine reuptake inhibitors [SNRIs]). The overall response rate with these interventions is limited, and there continues to be a need for treatments with better benefit-risk profiles that target the core symptoms of PTSD.

OBJECTIVES AND ENDPOINTS AND ESTIMANDS

This study will evaluate the efficacy, safety, and pharmacokinetics of *10 mg once a day (QD)* balovaptan compared with placebo in participants with PTSD. Specific primary and secondary objectives and corresponding endpoints for the study are outlined below.

Primary Objective	
Efficacy Objective	**Corresponding Endpoint**
• To *investigate* the efficacy of balovaptan compared with placebo	• Change from baseline at Week 12 in the CAPS-5 total symptom severity score
Secondary Objectives	
Efficacy Objectives	**Corresponding Endpoints**
• To *investigate* the efficacy of balovaptan compared with placebo	• Change from baseline in symptom severity as measured by CGI-S after 12 weeks of treatment
• To *investigate* the efficacy of balovaptan compared with placebo in depression	• Change from baseline at Week 12 in the PHQ-9 total score
Safety Objective	**Corresponding Endpoints**
• To *investigate* the safety of balovaptan compared with placebo	Safety will be assessed through the following: • Incidence and severity of adverse events, with severity determined according to a mild/moderate/severe grading scale • Physical and neurologic examinations, vital signs, hematology, blood chemistry, including urinalysis • ECGs and Doppler echocardiograms (the latter performed only in case of confirmed cardiac biomarker elevation) • C-SSRS
Pharmacokinetic Objectives	**Corresponding Endpoints**
• To *investigate* the plasma pharmacokinetics of balovaptan	• Concentration per timepoint for balovaptan [a] • PK parameters as appropriate

CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CGI-S = Clinician-Global Impression of Severity; *M2 = metabolite 2; M3 = metabolite 3;* PHQ-9 = Patient Health Questionnaire-9; PK = pharmacokinetic*; PTSD = post-traumatic stress disorder*.

[a] Concentration of M2 and M3 may be measured if indicated (e.g., safety concern).

OVERALL DESIGN

Study BN43546 is a Phase II, randomized, double-blind, placebo-controlled, two-arm, parallel-group, multicenter study to evaluate the efficacy and safety of 10 mg of oral balovaptan QD in adults with PTSD.

Several key aspects of the study design and study population are summarized below.

Phase*:*	Phase II	**Population Type*:***	Adult patients
Control Method:	Placebo	**Population Diagnosis or Condition:**	Post-traumatic stress disorder
Interventional Model:	Parallel	**Population Age:**	18-60 years, inclusive
Test Compound:	Balovaptan	**Site Distribution:**	Multi-site
Active Comparator:	Not applicable	**Study Intervention Assignment Method:**	Randomization and stratification
Number of Arms:	2	**Number of Participants to Be Enrolled:**	Approximately *30*

STUDY TREATMENT

The investigational medicinal product (IMP) for this study is balovaptan and placebo.

One tablet of study drug (10 mg of balovaptan or placebo) should be taken orally QD at home at the same time each day, preferably in the morning, with or without food. The tablet should be swallowed whole with something to drink.

Participants who need to take their study drug at a time of day outside of their usual routine may do so (e.g., participant typically takes their study drug in the morning, but due to an unforeseen scheduling conflict cannot take their medication until the afternoon), but only one dose may be taken each day. If a dose is missed, the participant should make a note to report this missed dose to the site at their next contact. A missed dose of study treatment must not be made up the next day.

The first dose of the study drug will be administered on Day 1 after all pre-dose assessments have been conducted. At subsequent visits at Weeks 2 and 12 (except for the Week 6 visit), the study drug will be administered after all protocol-mandated study assessments have been completed.

Modification of the balovaptan or placebo dose is not permitted.

DURATION OF PARTICIPATION

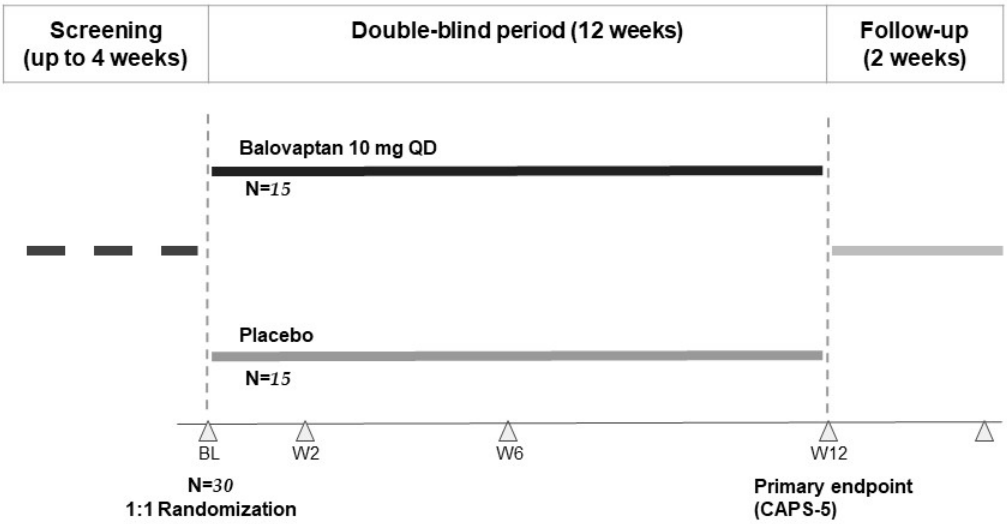
The total duration of study participation for each individual is expected to be approximately 18 weeks.

COMMITTEES

Independent Committees:	Not applicable
Other Committees:	Internal Monitoring Committee

1.2 STUDY SCHEMA

Figure 1 Study Schema



BL = baseline; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Version 5; PTSD = post-traumatic stress disorder; QD = once a day; W = week.

1.3 SCHEDULE OF ACTIVITIES

Table 1 Schedule of Activities

	Screening	Pre-Rand. Visit	Blinded Treatment Period						Safety Follow-Up [a]	Early Discont. [b, c]
Week			0	2	4 [d]	6	9 [d]	12	14	
Study Day(s)	–28 to –1	–7 to –1	1	14	28	42	*63*	84	98	
Visit window (days)				±3	±3	±3	±3	±3	–3/+7	
Informed consent [e]	x									
Medical history, demographics, and baseline conditions [f]	x									
Resting-state EEG [g]		x [h]		x		x		x		x [i]
Urinalysis [j]	x								x	x
Urinalysis for substance abuse [k]	x		x			x		x	x	x
Serology (HIV, and hepatitis B and C) [l]	x									
Coagulation [m]	x							x		x
Pregnancy test [n]	x		x			x		x		x
Weight and height (height to be measured at screening only)	x							x		x
Vital signs [o]	x		x	x		x		x	x	x
PK blood sample [p]				x		x		x		x
Clinical genotyping sample [q]			x							
Blood sample for WGS [r]			x							
RBR blood sample (optional) [s]				x						

Table 1 Schedule of Activities (cont.)

	Screening	Pre-Rand. Visit	Blinded Treatment Period						Safety Follow-Up [a]	Early Discont. [b, c]
Week			0	2	4 [d]	6	9 [d]	12	14	
Study Day(s)	–28 to –1	–7 to –1	1	14	28	42	63	84	98	
Visit window (days)				±3	±3	±3	±3	±3	–3/+7	
Complete physical examination [t]	x		x					x	x	x
Limited physical examination [t]						x				
Neurologic evaluation (upper and lower limbs)	x		x			x		x	x	x
Clinical signs and symptoms of infection [u]					x	x	x	x		
12-Lead ECG [v]	x		x	x				x	x	x
Hematology [w]	x		x			x		x	x	x
Full serum chemistry [x]	x		x			x		x	x	x
Quantitative immunoglobulins (IgA, IgG, IgM, and IgE)			x					x		x
PCL-5	x		x	x		x		x		x
SCID-5	x									
LEC-5	x									
CAPS-5 (administered by central rater)		x [h]				x		x		x
CGI-S			x			x		x		x
CGI-C						x		x		x
PGI-S			x			x		x		x
PGI-C						x		x		x

Table 1 Schedule of Activities (cont.)

	Screening	Pre-Rand. Visit	Blinded Treatment Period						Safety Follow-Up [a]	Early Discont. [b, c]
Week			0	2	4 [d]	6	9 [d]	12	14	
Study Day(s)	–28 to –1	–7 to –1	1	14	28	42	63	84	98	
Visit window (days)				±3	±3	±3	±3	±3	–3/+7	
Beck Anxiety Inventory			x			x		x		
Pittsburgh Sleep Quality Index			x			x		x		
PHQ-9			x			x		x		x
C-SSRS [y]	x	x	x	x	x	x	x	x	x	x
SDS			x			x		x		
CPFQ			x			x		x		
Computerized cognitive battery		x [h]		x		x		x		x
Wearable heart rate, step count, and sleep monitoring device (e.g., OURA™ Ring)		x [z]	x	x	x	x	x	x		x
Previous and concomitant medications [aa]	x		x	x	x	x	x	x	x	x
Adverse events [bb]	x	x	x	x	x	x	x	x	x	x
Study drug dispensation [cc]			x			x				
Study drug accountability				x	x	x	x	x		x

Table 1 Schedule of Activities (cont.)

CAPS-5=Clinician-Administered PTSD Scale for Diagnostic and Statistical Manual of Mental Disorders, Version 5; CGI-C=Clinician Global Impression of Change; CGI-S=Clinician-Global Impression of Severity; CPK=creatine phosphokinase; CK-MB=creatine kinase-MB; CPFQ=Cognitive and Physical Functioning Questionnaire; C-SSRS=Columbia-Suicide Severity Rating Scale; cTnI=cardiac troponin; DSM-5=Diagnostic and Statistical Manual of Mental Disorders, Version 5; eCRF=electronic Case Report Form; EEG=electroencephalogram; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HDL=high-density lipoprotein; hs-cTnT=high–sensitivity-cardiac troponin T; LDH=lactate dehydrogenase; LDL=low-density lipoprotein; LEC-5=Life Events Checklist for DSM-5; PCL-5=PTSD Checklist for DSM-5; PCP=phencyclidine; PGI-C=Patient Global Impression of Change; PGI-S=Patient Global Impression of Severity; PHQ-9=Patient Health Questionnaire-9; PK=pharmacokinetic; PTSD=post-traumatic stress disorder; QTc=corrected QT interval; Pre-Rand=randomization; SCID-5=Structured-Clinical Interview for DSM-5; SDS=Sheehan Disability Scale; RBR=Research Biosample Repository; UV=unscheduled visit; ULN=upper limit of normal; WGS=whole genome sequencing.

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

The visit window is ±3 days, and all assessments should be completed within the visit window. *Following any visit that may occur outside of allowable visit window,* participants should return to the initial planned schedule *(*per randomization *as Day 1)* for *all* subsequent visits. For participants who terminate early, assessments listed under the early discontinuation visit should be completed. For safety follow up, the visit window is −3/+7 days and all safety assessments should be completed within the visit window.

Unscheduled visits may be performed if clinically indicated. The following assessments should be performed at a minimum: concomitant medications, adverse events, and vital signs. Additional safety assessments may be performed as clinically indicated, per investigator discretion.

[a] A safety follow-up visit must occur for all participants at 2 weeks following their last study treatment dose.

[b] To be conducted if a participant discontinues from the study or study-drug treatment prematurely.

[c] All participants who withdraw or discontinue from the study treatment early will be asked to return as soon as possible (and within 2 weeks after the last dose of study drug) for an early discontinuation visit, unless the withdrawal occurs within 2 weeks of the Week 12 visit.

[d] Participants will be called by the site personnel to monitor safety and tolerability when not attending the clinic. *In the event that the participant cannot be reached, at least 3 documented attempts to contact the participant for these visits must occur.*

[e] Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.

[f] Medical history includes clinically significant diseases, surgeries, reproductive status, smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the participant within 24 weeks prior to the screening visit as well as details of psychosocial or non-pharmacological interventions used during the previous 24 weeks. Demographic data will include age, sex, and self-reported race/ethnicity. Participants will also be asked about their residential setting, school, or employment status, level of education, participation in educational or day programs, and any non-medical hospitalizations.

[g] EEG: Two runs each of resting eyes open and eyes closed.

Table 1 Schedule of Activities (cont.)

[h] These assessments should be completed no more than 7 days prior to the baseline visit and will be considered the baseline measure.

[i] EEG to be conducted if a participant discontinues study treatment before Week 6.

[j] Urinalysis will be performed at the site by dipstick for blood, protein, glucose, ketones, specific gravity, and pH. Microscopic examination performed at the central laboratory if blood and/or protein results are positive or strongly positive. If there is an explanation for the positive dipstick results (e.g., menses), it should be recorded and there is no need to perform microscopy and culture.

[k] Urine samples will be analyzed for the presence of drugs such as: alcohol, cannabinoids, opiates, cocaine, barbiturates, methadone, and PCP. Results will be used to verify participant eligibility pertaining to drugs of abuse. Inconclusive results may be repeated once during the screening period. Investigators should use their best clinical judgment in cases where results may be erroneous (e.g., permitted use of opiates or ingestion of food or food supplements).

[l] Viral serology includes HIV (specific tests for HIV-1 antibody, HIV-1 and -2 antibodies, and HIV-2 antibody), HBsAg, HBcAb, and HCV antibody.

[m] Coagulation assessments include INR, aPTT, and PT.

[n] Females of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening and must have a urine pregnancy test performed at the site prior to each dose administration at the specified visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents.

[o] Vital signs include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the participant is in a seated position, and body temperature. Vital sign assessments should be performed just prior to study drug administration. All vital signs should be recorded on the eCRF. *Three consecutive blood pressure readings will be recorded at intervals of at least 1 minute. The average of the three blood pressure readings will be recorded on the eCRF.*

[p] PK samples should be obtained just prior to study drug administration, if possible. At Week 6, two PK samples will be taken (pre- and post-dose). Following the pre-dose sample, at the start of the study visit, the participant will receive study drug. A post-dose sample can be taken at any time between 3 hours after study drug administration and the end of the study visit. Accurate recording of the time of study drug administration and sample collection is critical.

[q] Can be collected on any study visit if not collected at baseline visit.

[r] Not applicable for a site that has not been granted approval for WGS.

[s] Not applicable for a site that has not been granted approval for RBR sampling. Perform only for participants at participating sites who have provided written informed consent to participate.

[t] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Complete physical examinations will not include pelvic, rectal, or breast examinations. Record abnormalities observed at screening on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. Limited, symptom-directed physical examinations should be performed as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

Table 1 Schedule of Activities (cont.)

[u] Site personnel will check for any emergence of clinical signs and symptoms of infection according to semi-structured questionnaire (Appendix 9). This will occur either by telephone call or in person *site* visits at Weeks 4, 6, 9, and 12.

[v] Twelve-lead ECGs are to be performed after the participant has been in a supine position for 5 minutes. ECGs for each participant should be obtained from the same machine whenever possible and performed prior to any blood draws. ECGs obtained at baseline will be in triplicate. All others will be single recordings. In the event of prolongation of the QTc interval, an unscheduled PK sample should be obtained.

[w] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[x] Serum chemistry includes sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, CPK, total protein, albumin, phosphorus, calcium, total and direct bilirubin, ALP, ALT, AST, uric acid, LDH, cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, including hs-cTnT. If CPK value exceeds 2×ULN at baseline, CPK, creatinine, and potassium levels should be monitored at Week 2.

[y] The C-SSRS Baseline/Screening version should be used at the first screening visit; subsequent visits should use the C-SSRS Since Last Visit version.

[z] Wearable device to be distributed and data collected 7 days prior to randomization (Day 1).

[aa] Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, approved dietary and herbal supplements, nutritional supplements, and any non medicinal interventions, such as individual psychotherapy, smoking cessation therapy, and rehabilitative therapy) used by a participant 24 weeks prior to screening until the follow-up visit.

[bb] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The investigator is not required to actively monitor participants for adverse events after the end of the adverse event reporting period (defined as 2 weeks after the final dose of study drug). However, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period if the event is believed to be related to prior study drug treatment. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[cc] Participants should be instructed to take their medication at home at the same time each day, preferably in the morning. At study visits, they should take the study drug once all assessments are completed, except for Week 6. Study drug dispensation can take place at any time during the visit. *Participants who need to take their medication at a time of day outside of their normal routine may do so, but only one dose may be taken each day. If a dose is missed for that day, the participant should make a note to report this missed dose to the site at their next telephone or site visit.*

2. INTRODUCTION

2.1 STUDY RATIONALE

The purpose of this study is to assess the efficacy and safety of balovaptan, a vasopressin 1a (V1a) receptor antagonist, in participants with post-traumatic stress disorder (PTSD). Treatment options for PTSD include trauma-focused (TF) psychological interventions, such as cognitive-behavioral therapy (CBT) and pharmacological treatments, including antidepressants (selective serotonin reuptake inhibitors [SSRIs] and serotonin and norepinephrine reuptake inhibitors [SNRIs]). The overall response rate with these interventions is limited, and there continues to be a need for treatments with better benefit–risk profiles that target the core symptoms of PTSD. Patients with PTSD suffer from a cluster of debilitating symptoms that have a profound effect on many aspects of their lives.

2.2 BACKGROUND

PTSD is a chronic impairment disorder that occurs after exposure to severe stressors (e.g., combat, natural disaster, or other traumatic events) (Miao et al. 2018). It is characterized by re-experiencing, avoidance, and hyperarousal symptoms, as well as negative alterations in cognition and arousal. These symptoms can lead to disturbances to the individual and their family, as well as significant medical, financial, and social problems.

Re-experiencing symptoms manifest as one of the following: recurrent, distressing recollections in the form of thoughts, perceptions, or dreams; feeling as if the traumatic event is happening again accompanied by illusions, hallucinations, and dissociative flashbacks; or intense psychological distress or physiological reactivity when exposed to internal or external cues reminiscent of the traumatic event(s) (American Psychiatric Association [APA] 2013; Jellestad et al. 2021). Avoidance symptoms are characterized by efforts to avoid thoughts, feelings, conversation, activities, places, or things that remind the individual of the traumatic event(s), as well as marked decrease in affect. Individuals with PTSD demonstrate negative alterations in mood and elevated levels of arousal, including problems initiating and maintaining sleep, increased irritability, hypervigilance, and hyperactive startle response, as well as difficulty concentrating. These symptoms can often lead to clinically significant distress and significant impairments in daily functioning.

A diagnosis, per Diagnostic and Statistical Manual of Mental Disorders, Version 5 (DSM-5) criteria, includes exposure to trauma and this trauma is persistently experienced through unwanted memory intrusions, nightmares, flashbacks, and emotional distress following an exposure to traumatic reminders (APA 2013). In addition, individuals avoid trauma-related stimuli and demonstrate negative alterations in cognition and mood, which may include overly negative thoughts about oneself and exaggerated blame of self or others for causing the trauma or negative affect.

According to the DSM-5, some individuals may receive a diagnosis of acute stress disorder in the first month following exposure to trauma (Bryant et al. 2016). In order to meet the criteria, an individual must present with at least nine symptoms from the categories of intrusion, negative mood, dissociation, avoidance, and arousal. These symptoms present at the beginning of the traumatic event or if these symptoms are pre-existing, then they worsen after the traumatic event. The duration of the disturbance is 3 days to 1 month following a trauma exposure. Although acute stress disorder and PTSD share similar requirements for diagnosis, there is a clear differentiation such that PTSD diagnosis requires meeting a certain number of symptoms within established clusters. This includes non–fear-based symptoms and a dissociative subtype, and the symptoms persist for longer than 1 month.

PTSD is generally associated with co-occurring psychiatric disorders and approximately 80% of patients with PTSD meet criteria for at least one other psychiatric condition (Brady 1997). The most common comorbidities are depression, alcohol and substance use disorders, anxiety disorders, physical health problems, and cognitive impairment (Kessler et al. 1995; Qureshi et al. 2011; Paccella et al. 2013). Common psychiatric comorbidities exacerbate PTSD symptoms and increase functional impairment (Ikin et al. 2010; Drapkin et al. 2011).

The National Comorbidity Survey Replication (NCS-R), which was conducted between 2001 and 2003, estimated the lifetime prevalence of PTSD among adult Americans to be 6.8% (NCS-R 2007a, 2007b). The lifetime prevalence of PTSD among men was 3.6% and among women was 9.7%. The reported prevalence of PTSD ranges from 5.4% to 16.8% among military service members and veterans, which is higher than among the general population (Miao et al. 2018). Genetic and epigenetic factors may account for up to 70% of the individual differences in PTSD development, with PTSD heritability estimated at 30%.

Most guidelines strongly recommend TF-psychological interventions as treatment options for PTSD, including CBT, cognitive-processing therapy (CPT), cognitive therapy (CT), cognitive restructuring (CR), coping skills therapy (including stress inoculation therapy), exposure-based therapies, eye movement desensitization and reprocessing (EMDR), hypnosis and hypnotherapy, and brief eclectic psychotherapy (APA 2017). Individual TF-CBT and EMDR have shown to be effective in reducing PTSD symptom severity (Bisson et al. 2013; Coventry et al. 2020). However, the quality of evidence showing superiority of TF-CBT and EMDR over waitlist and/or usual care comparison is low (Bisson et al. 2013). Furthermore, although psychological interventions have shown success in alleviating symptoms, there is no evidence for a significant improvement in affect dysregulation (Coventry et al. 2020). Additionally, psychological interventions, such as TF-CBT, EMDR, and mindfulness, do not show a maintenance of treatment effects at the 6-month follow up in veterans (Coventry et al. 2020). Various psychological interventions also show high dropout rates, with one review finding up to 54% (Schottenbauer et al. 2008) and another up to 65% (Lewis et al. 2020).

Furthermore, TF-therapies having a significantly higher dropout rate compared with non-TF therapies (Lewis et al. 2020). This could be reflective of patients' psychological preparedness to confront their trauma.

Pharmacological treatments for PTSD include antidepressants, such as SSRIs, SNRIs, and monoamine oxidase (MAO) inhibitors, sympatholytic drugs such as alpha-blockers, antipsychotics, anticonvulsants, and benzodiazepines (Coventry et al. 2020; Hoskins et al. 2015; Stein et al. 2006; Davidson et al. 2006a; Davidson et al. 2006b). The (U.S.) Food and Drug Administration (FDA) has approved two SSRIs for the treatment of PTSD: sertraline and paroxetine. These SSRIs primarily act upon the serotonin neurotransmitter system and have the strongest empirical evidence. Overall response rates with the use of SSRIs rarely exceed 60% in patients with PTSD and less than 20%–30% of patients achieve complete remission (Stein et al. 2002; Zohar et al. 2002). Other medications which are not approved for treatment of PTSD, such as fluoxetine, topiramate, risperidone, and venlafaxine, are also used in clinical practice. Maintenance of effect is also only observed through continued treatment, which suggests that the medication is addressing symptoms rather than the underlying source of the disorder (Asnis et al. 2004). Beyond SSRIs, a number of different research avenues have been explored, including prazosin and d-cycloserine but although some positive signals in small studies have been observed, these have typically not translated into larger confirmatory outcomes (de Kleine et al. 2012; Germain et al. 2012; Raskind et al. 2018). Patients with PTSD often receive treatment with multiple agents that often lack evidence of benefit, including diverse antidepressants, anxiolytics, mood stabilizers and antipsychotics (Davidson and Connor 1999; Keane et al. 2006; Miao et al. 2018).

Balovaptan is a brain penetrant, potent, and highly selective human V1a receptor antagonist that blocks the activation of the V1a G protein–coupled receptor.

In vitro, balovaptan exhibited an inhibition constant of 0.7 nM for the human V1a receptor with at least 1000-fold binding selectivity over 118 other receptors, enzymes, and ion channels, including human vasopressin 2 (V2) receptor, vasopressin 1b (V1b) receptor, and human oxytocin receptors.

Previous clinical studies of balovaptan have been conducted in healthy volunteers and participants with autism spectrum disorder (ASD) using the same dose (10 mg) as proposed for this study. In those trials, an estimated 448 subjects with ASD have received 10 mg once a day (QD) of balovaptan for at least 12 weeks, of whom approximately 326 subjects received 10 mg QD of balovaptan for at least 24 weeks. Balovaptan was found to be safe and well tolerated.

Detailed information on balovaptan is provided in the Balovaptan Investigator's Brochure.

2.3 BENEFIT–RISK ASSESSMENT

This study will assess the efficacy and safety of balovaptan in adults with moderate-to-severe PTSD. Currently, the first-line therapy for PTSD is individual TF-psychological interventions. However, these psychological interventions have not shown a significant improvement in affect dysregulation or maintenance of treatment effects at 6 month follow up in veterans (Coventry et al. 2020).

Areas in the brain that are rich in vasopressin receptors have been implicated in PTSD suggesting that arginine vasopressin (AVP) may be able to influence behavior that is relevant to PTSD (Torok et al. 2019). Nonclinical studies have shown that AVP agonists result in PTSD-like behavior in rodents (Sipos et al. 2020). In AVP-deficient Brattleboro rats, which have significant reduction of AVP signaling in the brain, demonstrated improved behavioral parameters that can be linked to PTSD symptoms. Furthermore, serum AVP concentrations have been observed to be higher in veterans with PTSD compared with those without (de Kloet et al. 2008). These findings imply that treatment with a V1a antagonist, such as balovaptan, may offer a means to alleviate symptoms of PTSD.

Across previous clinical trials of balovaptan, it has been found to be safe and well tolerated. This includes studies in healthy volunteers and in individuals with ASD (children, adolescents, and adults). No pattern of adverse events possibly characteristic for the use of balovaptan in humans has emerged to date.

The following are hypothetical or potential risks for balovaptan, based on its mechanism of action and available nonclinical data: seizure risk (animal studies), hematological toxicity (animal studies; mainly peripheral decrease in neutrophils), risk of bleeding (hypothetical relative to the mechanism of action), skeletal muscle toxicity (animal studies), cardiac toxicity (animal studies and interpreted to be stress related), blood pressure changes (hypothetical risk relative to the mechanism of action), and risk of peripheral neuropathy (animal studies) (for further details see Appendix 6). However, dedicated safety monitoring across clinical trials in healthy volunteers and in subjects with ASD have not revealed a safety signal with regard to the mechanism of action of balovaptan and animal-related potential safety risks.

The dose planned in this study is 10 mg QD, and this dose is the same as the highest dose administered in the ASD clinical trials which had a treatment duration of 12 weeks or longer. The safety monitoring planned in this study will continue to cover these hypothetical and animal-related safety considerations and is considered sufficient to ensure participant safety.

Refer to Appendix 6 for information on potential risks for balovaptan and risk mitigation measures, including guidelines for managing adverse events.

More detailed information about the known and expected benefits and risks and reasonably expected events of balovaptan may be found in the Balovaptan Investigator's Brochure.

With the data thus far, the Sponsor believes the benefit–risk profile of balovaptan for participants in this study is favorable.

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

This study will evaluate the efficacy, safety, and pharmacokinetics of $10\ mg\ QD$ balovaptan compared with placebo in participants with PTSD. Specific objectives and corresponding endpoints for the study are outlined in Table 2.

Table 2 Objectives and Corresponding Endpoints

Primary Objective	
Efficacy Objective	**Corresponding Endpoint**
• To *investigate* the efficacy of balovaptan compared with placebo	• Change from baseline at Week 12 in the CAPS-5 total symptom severity score
Secondary Objectives	
Efficacy Objectives	**Corresponding Endpoints**
• To *investigate* the efficacy of balovaptan compared with placebo • To *investigate* the efficacy of balovaptan compared with placebo in depression	• Change from baseline in symptom severity as measured by CGI-S after 12 weeks of treatment • Change from baseline at Week 12 in the PHQ-9 total score
Safety Objective	**Corresponding Endpoints**
• To *investigate* the safety of balovaptan compared with placebo	Safety will be assessed through the following: • Incidence and severity of adverse events, with severity determined according to a mild/moderate/severe grading scale • Physical and neurologic examinations, vital signs, hematology, blood chemistry, including urinalysis • ECGs and Doppler echocardiograms (the latter performed only in case of confirmed cardiac biomarker elevation) • C-SSRS
Pharmacokinetic Objectives	**Corresponding Endpoints**
• To *investigate* the plasma pharmacokinetics of balovaptan	• Concentration per timepoint for balovaptan [a] • PK parameters as appropriate

Table 2 Objectives and Corresponding Endpoints (cont.)

Exploratory Objectives	
Exploratory Biomarker Objective	**Corresponding Endpoints**
• To identify and/or *investigate* biomarkers that are predictive of response to balovaptan (i.e., predictive biomarkers) or are early signs of efficacy	• Relationship between biomarkers (e.g., EEG, genomics, digital biomarkers, computerized cognitive battery) and efficacy, safety, PK, or other biomarker endpoints (see Section 8.7)
Exploratory Efficacy Objectives	**Corresponding Endpoints**
• To *investigate* the efficacy of balovaptan compared with placebo	• Change from baseline at Week 12 on the CAPS-5 symptom cluster scores • Proportion of participants with no symptoms, very mild, mild, moderate, severe, very severe in the PGI-S at each scheduled visit • Proportion of participants with no change, improvement or worsening in the CGI-C and PGI-C at Weeks 6 and 12 • Change from baseline at Week 6 on the CAPS-5 total symptom severity score
• To *investigate the* efficacy of balovaptan compared with placebo in PTSD symptoms, anxiety, sleep, functioning, and cognition	• Change from baseline at Weeks 6 and 12 on the following: – PCL-5 total score – BAI total score – PSQI total and domain scores – CPFQ total score and domain scores – SDS global score – Computerized cognitive battery

BAI=Beck Anxiety Inventory; CAPS-5=Clinician-Administered PTSD Scale for DSM-5; CGI-C=Clinician-Global Impression of Change; CGI-S=Clinician-Global Impression of Severity; CPFQ=Cognitive and Physical Functioning Questionnaire; C-SSRS=Columbia-Suicide Severity Rating Scale; DSM-5=Diagnostic and Statistical Manual of Mental Disorders, Version 5; EEG=electroencephalogram; M2=Metabolite 2; M3=Metabolite 3; PCL-5=PTSD Checklist for DSM 5; PGI-C=Patient-Global Impression of Change; PGI-S=Patient-Global Impression of Severity; PHQ-9=Patient Health Questionnaire-9; PK=pharmacokinetic; PSQI=Pittsburgh Sleep Quality Index; PTSD=Post-traumatic stress disorder; SDS=Sheehan Disability Scale.

[a] Concentration of M2 and M3 may be measured if indicated (e.g., safety concern).

The clinical question of interest is to assess the study treatment effect of *10 mg QD* balovaptan compared with placebo in terms of the change from baseline at Week 12 in the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) irrespective of adherence to randomized treatment.

4. STUDY DESIGN

4.1 OVERALL DESIGN

Study BN43546 is a Phase II, randomized, double-blind, placebo-controlled, two-arm, parallel-group, multicenter study to evaluate the efficacy and safety of 10 mg of oral balovaptan QD in adults with PTSD. The study will comprise a 28-day screening period, 12-week blinded treatment period, and a 2-week follow-up period. A study schema is provided in Section 1.2 (see Figure 1).

Participants providing informed consent will undergo screening up to 4 weeks prior to the first double-blind study drug (balovaptan or placebo) administration. Eligible participants will be randomized in a 1:1 ratio in a blinded fashion to either 10 mg of balovaptan or matching oral placebo QD. The primary efficacy endpoint is the change from baseline at Week 12 in the CAPS-5.

For participants completing the full study, the approximate length of the study will be 18 weeks or approximately 4 months (screening [up to 4 weeks], blinded treatment [12 weeks] and a safety follow-up visit 2 weeks after a participant's Week 12 visit or 2 weeks following last study treatment dose).

Participants will be recruited from sites within the United States. It is estimated that it will take approximately 9 months to reach full enrollment. Participants who prematurely discontinue from study treatment or from the study will not be replaced.

Randomization will be stratified by sex (male vs. female), type of trauma (veteran vs. civilian), and concurrent medication use (no concurrent antidepressant treatment vs. antidepressant treatment [SSRI or SNRI]; see Section 5.1). The main analysis of the primary and secondary efficacy endpoints will occur once the final data from all visits of the follow-up period have been collected and cleaned and the database is locked.

An Internal Monitoring Committee (IMC), consisting of a selected subset of internal Roche representatives who are not in direct contact with the sites, will review relevant safety data on a regular basis or on an ad-hoc basis, if deemed necessary, as described in the IMC Charter. The IMC Charter provides further details about the roles and responsibility of the members, defining the timing of meetings and communication of meeting's discussion points.

Secondary and exploratory endpoints will examine core and associated symptoms of PTSD, impact on health-related quality of life, as well as the ability to identify predictive or prognostic biomarkers. Safety will be examined via adverse events, clinical laboratory values, ECGs, physical and neurologic examinations, and safety outcome assessments such as suicidality.

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened one additional time (Section 5.4). Re-screening will not be allowed if a participant does not meet the disease-specific inclusion criteria (e.g., PTSD diagnosis as per DSM-5 and Structured-Clinical Interview for DSM-5 [SCID-5], PTSD Checklist for DSM-5 [PCL-5] score). The investigator will record reasons for screen failure in the screening log.

4.1.1 Screening Period

Consenting participants will enter a screening period of up to 28 days in length to be evaluated for eligibility. Procedures at screening are listed in the schedule of activities in Section 1.3 (see Table 1). Participants must meet all of the eligibility criteria in order to qualify for the study (see the inclusion and exclusion criteria [see Sections 5.1 and 5.2, respectively]).

To enter the double-blind period, there must be:

- No significant new or worsening psychiatric or medical illness since screening that in the opinion of the Investigator would interfere with the participant's ability to participate in the study.
- No change in medications or psychotherapy since screening except as allowed in the Concomitant Medication section (see Section 6.8.1)

4.1.2 Blinded Treatment Period

The study will enroll approximately 30 participants with moderate-to-severe PTSD (as measured by PCL-5). All participants will undergo 12 weeks of double-blind treatment consisting of four in-clinic visits.

At the baseline visit (Day 1), participants will undergo a series of assessments outlined in the schedule of activities (see Section 1.3). Breaks should be allowed between tests when necessary. Study drug (balovaptan or placebo) must be administered only after all protocol-mandated assessments are completed.

As a rule, the test sequence for all assessments should remain the same for a given participant as established at screening and baseline. At all visits, patient-reported outcome (PRO) assessments should be completed prior to any other assessments or procedures. All assessments must be performed before administration of study drug. If Columbia-Suicide Severity Rating Scale (C-SSRS) assessments at pre-randomization or Study Day 1 reveal score/category of 4 or greater, treatment must not be started and the participant should be discontinued from the study and referred to psychiatrist.

Interim telephone calls will occur at Weeks 4 and 9. Participants will be called by site personnel to monitor safety and tolerability when not attending the clinic. Assessments will include adverse event $collection$, concomitant medication review, and dose accountability.

4.1.3 Follow-Up Period

A safety follow-up visit will take place 2 weeks after the participant's Week 12 visit or 2 weeks after last dose to assess whether any adverse events have occurred following the end of treatment.

A study schema is provided in Section 1.2 (see Figure 1). A schedule of activities is provided in Section 1.3 (see Table 1).

4.2 RATIONALE FOR STUDY DESIGN

4.2.1 Rationale for Study Population

A key component of PTSD vulnerability, development and treatment seems to involve the hypothalamic-pituitary adrenocortical (HPA) axis (Yehuda, 2002). Arginine vasopressin (AVP) is an important co-stimulator of the HPA axis, modulating glucocorticoid release synergistically with corticotrophin-releasing hormone (CRH) (Engelmann et al. 2004; Rotzinger et al. 2010). In PTSD, three main brain areas have been shown to be implicated: the prefrontal cortex (PFC), the hippocampus, and the basolateral amygdala (Torok et al. 2019). These brain areas are not rich in AVP-producing cells but contain vasopressin receptors at high density. This suggests that AVP is able to influence behavior that is also relevant to PTSD by either directly innervating these areas as a neurotransmitter or released in remote areas such as the hypothalamus and traveling via the extracellular space as a neuromodulator.

In mouse models, the V1a receptor is highly expressed in the bed nucleus of the stria terminalis, a region of the amygdala implicated in stress response (Bielsky et al. 2004). V1a receptor knockout and inhibition have anxiolytic effects in mice while elevating levels of vasopressin has an anxiogenic effect.

A study of veterans with PTSD and veterans, without PTSD who witnessed or experienced traumatic events, found that serum AVP levels were higher in veterans with PTSD than other cohorts (de Kloet et al. 2008). No difference in AVP levels were found between veterans without PTSD and non-military healthy controls. A strong correlation was found between avoidance symptoms as determined by using the Clinical-Administered PTSD Scale (CAPS) and AVP serum concentrations in patients with PTSD.

These findings may imply that treatment with AVP antagonists might offer a way to alleviate symptoms in patients with PTSD.

Study BN43546 will include both males and females. The lifetime prevalence of PTSD among adult Americans has been reported to be 6.8%, with females being affected approximately twice as much as males (NCS-R 2007a, 2007b). Furthermore, the reported prevalence among military service members and veterans is higher than among the general population (Miao et al. 2018). To investigate potential differences in these populations, the study will include veterans and civilians.

To limit the impact of diagnostic heterogeneity, eligible participants must meet DSM-5 criteria for PTSD, which will be confirmed using the PCL-5 and the Structured-Clinical Interview for DSM-5 (SCID-5) (APA 2013). The PCL-5 is a 20-item, self-reported measure that assesses 20 DSM-5 symptoms of PTSD (Weathers et al. 2013c; Blevins et al. 2015). The SCID-5 is a semi-structured interview guide for making the major DSM-5 diagnoses (First 2014). It is administered by a clinician or trained mental health professional who is familiar with the DSM-5 classification and diagnostic criteria.

For pharmacological interventions of PTSD, SSRIs (sertraline, paroxetine, and fluoxetine) and SNRI (venlafaxine XR) are recommended as monotherapy (APA 2017). Participants in this study will include individuals who are on a stable dose of an antidepressant treatment and have not reached full therapeutic effect or those who are not taking any antidepressants because of intolerance or treatment failure at baseline. This will be assessed by the treating physician.

4.2.2 Rationale for Use of Placebo

Two SSRIs (sertraline and paroxetine) have been approved by the FDA for the treatment of PTSD. Overall response rates with SSRIs rarely exceed 60% in patients with PTSD and less than 20%–30% of patients achieve complete remission (Stein et al. 2002; Zohar et al. 2002).

Vasopressin signaling is involved in the body's stress response, and has been implicated in affective illnesses, including PTSD. Plasma levels of vasopressin have been noted to be increased in PTSD (de Kloet et al. 2008). Balovaptan is an antagonist at the V1a receptor, and thus may ameliorate symptoms related to elevated stress-related and vasopressin-mediated signaling.

This study will only enroll individuals who are either on a stable dose of a single antidepressant for management of PTSD or have demonstrated prior lack of tolerability or lack of efficacy (see Section 5.1). Given the limited pharmacotherapies available for the treatment of PTSD and limitations in therapeutic effect, a placebo-controlled trial is acceptable, provided that appropriate participant consent and safeguards are instituted to minimize the risk of serious or irreversible harm resulting from exposure to placebo.

4.2.3 Rationale for Biomarker Assessments

In a Phase I study of healthy volunteers (Study BP29412), 10 mg of balovaptan was found to elicit a decrease in power envelope connectivity within the α power band of a resting-state electroencephalogram (EEG) taken with eyes closed (1111327 [available on request]). The predominant source of this change in connectivity was localized to the vicinity of the left anterior insula and the left intraparietal cortex. Retrospective analyses of open-label study data indicated that broadly similar patterns of α-band power envelope connectivity change may predict clinical improvement following a change in pharmacological treatment among patients with a PTSD diagnosis. Changes in α-band connectivity have also been implicated in subsequent clinical improvement in patients

with a PTSD diagnosis following the administration of repetitive-transcranial magnetic stimulation (rTMS), and the topography of these effects could be consistent with the insular and parietal sources described above (Zandvakili et al. 2019). Thus, pharmacodynamic EEG activity elicited by balovaptan bears some similarity, both in frequency and in spatial topography, with EEG changes associated with clinical improvement in patients with PTSD receiving rTMS.

However, PTSD is a heterogeneous disorder, hence participants in this study may not all respond similarly to treatment with balovaptan. Therefore, an objective of this study is to define which patients with PTSD may be most likely to benefit from balovaptan using one or more biomarkers acquired prior to treatment and to relate the strength of any response to balovaptan with change in clinical measures. In addition to EEG, biosamples will be collected for identifying variants in the arginine vasopressin receptor 1A *(AVPR1A)* gene that may be associated with response to balovaptan. For this purpose, a mandatory predose whole blood sample will be obtained for DNA extraction from every participant on Day 1.

Additionally, digital biomarkers will be derived from a wearable device (e.g., OURA™ Ring). The following wearable sensor data will be recorded: heart rate, movement, and sleep. These measures will be recorded to enable the derivation of exploratory biomarkers related to autonomic function and arousal, movement kinematics and behavior, and sleep. Finally, established cognitive assessments will be performed and completed as a battery by the participant, and cognitive data obtained (Qureshi et al. 2011). On the basis of these data, cognitive biomarkers may be derived from different levels of cognitive functioning as well as exploring the relationship of these biomarkers to outcomes.

4.2.4 Rationale for Use of Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)

The Clinician-Administered PTSD Scale (CAPS) is a validated and widely used structured diagnostic interview, considered as the gold standard to assess symptoms associated with PTSD (Weathers et al. 2001). It has been used in multiple studies on PTSD as either a primary diagnostic or outcome measure.

The CAPS has been revised to correspond with PTSD criteria in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM–5; APA 2013). A description of the scale is provided in Section 8.1.

4.3 JUSTIFICATION FOR DOSE AND SCHEDULE

Balovaptan is a brain penetrant, potent, and highly selective human V1a receptor antagonist that blocks the activation of the V1a G protein–coupled receptor. In vitro, balovaptan exhibited an inhibition constant of 0.7 nM for the human V1a receptor with at least 1000-fold binding selectivity over 118 other receptors, enzymes, and ion channels, including human V2, V1b, and human oxytocin receptors (1042558 [available on

request]). Furthermore, the predicted brain occupancy of the V1a receptor reaches near maximal saturation (average of approximately 89% at trough) with the 10 mg dose of balovaptan. This predicted receptor occupancy was calculated according to a model which used an ex-vivo functional assay that measured the inhibition of V1a mediated and vasopressin induced platelet aggregation in human whole blood, and based on trough concentrations observed in Study BP28420 ("VANILLA") (1056966 [available on request] and 1106698 [available on request]).

Across previous clinical studies of balovaptan in healthy volunteers and in individuals with ASD (children, adolescents, and adults), a dose of 10 mg QD for at least 12 weeks has been found to be well-tolerated and without an emerging adverse event pattern considered to be related to balovaptan. Potential risks for balovaptan based on its mechanism of action and nonclinical data have not been confirmed in humans. The dose selected for this study, 10 mg QD, is the same as the highest dose administered in the ASD clinical trials. Together with the exclusion criteria and the safety monitoring scheduled for this study, balovaptan is expected to be well-tolerated by participants to be enrolled in this trial. Please see Appendix 6 for more details.

See the Balovaptan Investigator's Brochure for details about nonclinical and clinical studies.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study, including the last visit shown in the schedule of activities (see Section 1.3).

The end of this study is defined as the date of the last visit of the last participant in the study or the date at which the last data point required for statistical analysis or safety follow-up is received from the last participant, whichever occurs later. It is anticipated that it may take approximately 9 months to recruit all participants for the study; hence, the total length of the study is estimated to be approximately 13 months.

In addition, the Sponsor may decide to terminate the study at any time.

4.5 DURATION OF PARTICIPATION

The total duration of study participation for each individual is expected to be approximately 18 weeks.

5. STUDY POPULATION

Approximately 30 adult participants with PTSD will be enrolled in this study.

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

5.1 INCLUSION CRITERIA

Potential participants are eligible to be included in the study only if all of the following criteria apply:

- Capable of giving signed informed consent as described in Appendix 1 (see Section A1–3), which includes compliance with the requirements and restrictions listed in the Informed Consent Form and in this protocol and able to comply with the study protocol
- Age ≥18 and ≤60 years at the time of signing Informed Consent Form
- Current diagnosis of PTSD as per DSM-5 criteria and confirmed by the SCID-5 conducted during screening
- Moderate-to-severe PTSD, as assessed by a score of ≥33 on the PCL-5 completed during screening
- The index trauma event must have occurred in adulthood, i.e., when the participant was ≥18 years old
- The index trauma event must have occurred at least 6 months prior to screening and no more than 10 years prior to screening
- Participants who, at baseline, are:
  - Either taking a stable dose of a single antidepressant (SSRI or SNRI) for management of PTSD and have been on that medication for ≥6 weeks at that stable dosage and demonstrating residual symptoms of PTSD

    or
  - Prior demonstrated lack of tolerability or lack of efficacy (treatment failure, defined as trial of at least two antidepressant medications (SSRI or SNRI) with lack of efficacy for management of PTSD) and not taking an antidepressant medication at baseline for ≥6 weeks
- Treatment with permitted medications and/or non-pharmacological interventions should be at a stable dose/regiment for 6 weeks prior to screening, with the intent that such treatments remain stable throughout the study, with no expected changes before the Week 12 visit
- Fluent in English
- For *female participants* of childbearing potential: agree to remain abstinent (refrain from heterosexual intercourse) or use contraception method, as defined below:

  Female participants must remain abstinent or use contraceptive methods with a failure rate of <1% per year during the treatment period and for at least 14 days after the final dose of study drug.

  A *female participant* is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator

(e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.
If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- Note: No specific contraception methods for males are required. The Sponsor does not require male contraception because of the minimal seminal dose transmitted via sexual intercourse (Banholzer et al. 2012).

5.2 EXCLUSION CRITERIA

Potential participants are excluded from the study if any of the following criteria apply:

- Ongoing exposure to traumatic events within 3 months of screening
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 14 days after the final dose of study drug
- Concurrent use of any of the prohibited medications and food products listed in Section 6.8.3
- Any clinically significant psychiatric and/or neurological conditions, which may interfere with the assessment of safety or efficacy endpoints. This includes:
  - Any contraindications to EEG (e.g., requiring high concentration oxygen)
  - Significant risk for suicidal behavior, as assessed by the investigator, or a score of 4 or 5 on the C-SSRS in the past 6 months or category 6 or greater on the C-SSRS in the past 12 months (for C-SSRS categories and score see Section 8.2.7)
  - Diagnosis of schizophrenia, bipolar disorder, other psychotic disorder, or cognitive disorder, as defined by DSM-5
  - Epilepsy or seizure disorder considered not well controlled within the past 6 months or changes in anticonvulsive therapy within the last 6 months
  - Clinical diagnosis of peripheral neuropathy or signs and symptoms indicative of peripheral neuropathy
  - Substance use disorders (including alcohol or substance abuse or dependence disorder) during the last 12 months, as defined using the DSM-5 criteria
  - Diagnosis of traumatic brain injury

- Any cardiovascular disorders such as:
  - Uncontrolled hypertension (e.g., blood pressure repeatedly >160 mmHg systolic or >95 mmHg diastolic)
  - Within the last 2 years, unstable or clinically significant cardiovascular disease (e.g., myocardial infarction, angina pectoris, or New York Heart Association Class II or higher cardiac failure)
  - Confirmed (e.g., on two consecutive measurements *taken approximately 30 minutes apart during screening; the second measurement is only taken if it is necessary to confirm initial ECG abnormality*) clinically significant abnormality on ECG at screening, including, but not limited to, a QT interval corrected through the use of Fridericia's formula (QTcF) of ≥450 ms *in male participants and ≥470 ms in female participants*, absence of dominating sinus rhythm, or second- or third-degree atrioventricular block
  - Confirmed elevation above upper limit of normal (ULN) of high-sensitivity cardiac troponin T (hs-cTnT)
  - Unexplained syncopal episode within the last 12 months
- Participants who meet any of the following criteria related to other organ systems will be excluded from the study:
  - Positive serology results for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis C virus (HCV) antibody, or HIV-1 or HIV-2

    All participants must have a negative HBsAg result and negative hepatitis C antibody screening tests prior to enrollment. If total HBcAb is positive at screening, hepatitis B virus (HBV) DNA measured by polymerase chain reaction must be negative to be eligible.
  - Moderate or severe hepatic impairment defined as Child-Pugh class B (7–9 points) and class C (10–15 points), respectively (see Appendix 8)
  - Moderate or severe renal impairment defined as estimated glomerular filtration rate (eGFR) based on serum creatinine value of: <60 mL/min/1.73m^2
  - Evidence of current or past gastrointestinal (GI) disease that could potentially limit the absorption of study drug or pose unacceptable risks in the opinion of the investigator (e.g., GI bleeding, active stomach ulcer)
  - History of coagulopathies, bleeding disorders, blood dyscrasias, hematological malignancies, myelosuppression (including iatrogenic)
  - Concomitant disease or condition that could interfere with, or treatment of which might interfere with, the conduct of the study, or what would, in the opinion of the investigator, poses an unacceptable risk to the participant in this study
  - Confirmed clinically significant abnormality in parameters of hematology (e.g., a neutrophil count of <1500/μL; in case of assumed "benign ethnic neutropenia," a count of <1300/μL constitutes exclusion)
  - Confirmed clinically significant abnormality in parameters of clinical chemistry, coagulation, or urinalysis

- Medical history of malignancy, if not considered cured

- Participants who meet any of the following exclusion criteria will be excluded from the study:
  - Participants who have received treatment with investigational therapy within 8 weeks prior to randomization
  - Known hypersensitivity to balovaptan, its components, or any of the excipients used in the formulation
  - Any other condition and/or situation that the Investigator believes may interfere with the safety of the participant, study conduct, or interpretation of study data (safety or efficacy endpoints)

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and Dietary Restrictions

This study has the following meal and dietary restrictions:

- Refrain from consumption of grapefruit or grapefruit juice, grapefruit hybrids from 2 weeks before the start of study treatment until after the final dose.

5.3.2 Alcohol, Tobacco, and Cannabis

This study has the following alcohol, tobacco, and cannabis restrictions:

- Alcohol consumption is permitted as per Centers for Disease Control (CDC) and Prevention guidelines (2 drinks or less in a day for males and 1 drink or less in a day for females; one alcoholic drink equivalent is defined as containing 14 grams [0.6 fl oz] of pure alcohol) (U.S. Department of Agriculture and U.S. Department of Health and Human Services 2020).

  Participants will abstain from alcohol for 24 hours prior to study visits.

- Nicotine *and tobacco use is permitted, including the use of* nicotine patches*, cigarettes (traditional or electronic/vaping), and chewing tobacco;* the type and amount used should be recorded in the electronic Case Report Form (eCRF).
- Occasional cannabis use is permitted and should not exceed 2 times per week. Participants will abstain from cannabis use for 24 hours prior to study visits.

5.3.3 Activity

This study has no activity restrictions.

5.3.4 Contraception Requirements

During the study, female participants must use contraception or take other precautions as described in Section 5.1.

5.4 SCREEN FAILURES

Individuals who do not meet the criteria for participation in this study (screen failure), unrelated to symptom severity, may qualify for 1 re-screening opportunity (for a total of

2 screenings per individual) at the investigator's discretion. Re-screening will not be allowed if a participant does not meet the disease-specific inclusion criteria (e.g., PTSD diagnosis as per DSM-5 and SCID-5, PCL-5 score). Individuals must re-sign the consent form prior to re-screening. The investigator will record reasons for screen failure in the screening log (see Section 8).

6. STUDY TREATMENT(S) AND CONCOMITANT THERAPY

Study treatment is defined as any investigational treatment, marketed product, placebo, or medical device intended to be administered to a study participant according to the study protocol.

The investigational medicinal products (IMPs) for this study are balovaptan and placebo.

6.1 STUDY TREATMENTS ADMINISTERED

Table 3 provides a description of assigned study treatments for this study.

Table 3 Study Treatment Description

	Balovaptan	Placebo
Use	Experimental	Placebo comparator
Type of medicinal product	IMP	IMP
Drug form	Tablet	Tablet
Unit dose strength	10 mg/tablet	Not applicable
Formulation	Refer to Balovaptan Investigator's Brochure.	Refer to Balovaptan Investigator's Brochure.
Packaging	50 tablets per one high-density polyethylene bottle	50 tablets per one high-density polyethylene bottle
Labeling	Per local requirements	
Route of administration	Oral	Oral
Source	Sponsor	Sponsor

IMP = investigational medicinal product.

Guidelines for treatment interruption or discontinuation for participants who experience adverse events are provided in Appendix 6 (see Sections A6–2.1 and A6–2.2).

The total daily doses will be administered as one tablet containing either 10 mg balovaptan or placebo.

One tablet of study drug (balovaptan or placebo) should be taken orally QD at home at the same time each day, preferably in the morning, with or without food. The tablet should be swallowed whole with something to drink.

Participants who need to take their study drug at a time of day outside of their usual routine may do so (e.g., participant typically takes their study drug in the morning, but due to an unforeseen scheduling conflict cannot take their medication until the afternoon), but only one dose may be taken each day. If a dose is missed, the participant should make a note to report this missed dose to the site at their next contact. A missed dose of study treatment must not be made up the next day.

The first dose of the study drug will be administered on Day 1 after all pre-dose assessments have been conducted. At subsequent visits (except for the Week 6 visit), the study drug will be administered after all protocol-mandated study assessments have been completed.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel e.g., pharmacist) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each participant, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that participants are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor using an interactive voice or web-based response system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs 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 staff.

Only participants enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before

any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and/or the Balovaptan Investigator's Brochure for information on IMP preparation, storage, handling, and accountability.

6.3 TREATMENT ASSIGNMENT AND BLINDING

6.3.1 Treatment Assignment

This is a randomized, double-blind study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a participant, the study site will obtain the participant's identification number and treatment assignment from an IxRS.

Participants will be randomly assigned to one of two treatment arms: balovaptan *10 mg QD* or placebo. Randomization will occur in a 1:1 ratio through use of a permuted-block randomization method. To ensure a balanced assignment to each treatment arm, the randomization will be stratified by sex (male vs. female), type of trauma (veteran vs. civilian), and concurrent medication use (no concurrent antidepressant treatment vs. antidepressant treatment [SSRI or SNRI]) (see Section 4.1 for details).

6.3.2 Blinding

Study site personnel and participants will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to participant treatment assignments to fulfill their job roles during a clinical trial. *For example, some individuals from the Sponsor may have access to unblinded data as needed for ongoing analysis, including EEG, clinical, cognitive, genetic, and digital biomarker data. The core study team with direct site contact will remain blinded throughout the conduct of the study.*

While PK samples must be collected from participants assigned to the placebo arm to maintain the blinding of treatment assignment, PK results for such participants are generally not needed for the safe conduct or proper interpretation of the study data. Laboratories responsible for performing study drug PK assays will be unblinded to participant treatment assignments to identify appropriate samples for analysis. PK samples from participants assigned to the placebo arm will not be analyzed for study drug PK concentration except by request (e.g., to evaluate a possible error in dosing).

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which participant management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The treatment code should not be broken except in emergency

situations. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code. However, the investigator should inform the Medical Monitor that the treatment code has been broken.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly. Unblinding may be permitted if an investigator is deciding whether a participant should withdraw from the study and initiate treatment with a proven therapy. However, unblinding will not be permitted if an investigator is deciding whether a participant should withdraw from the study and initiate treatment with an unproven therapy.

The investigator should document and provide an explanation for any non-emergency unblinding. If the Medical Monitor agrees to participant unblinding, the investigator will be able to break the treatment code by contacting the IxRS.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 8.3.4) that are considered by the investigator or Sponsor to be related to an IMP (defined in Section 6). The participant may continue to receive treatment, and the investigator, participant, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to participant treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

6.4 STUDY TREATMENT COMPLIANCE

When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic as well as the time of administration of the preceding dose (at home) will be recorded in the source documents and recorded on the Study Drug Administration eCRF. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

When participants self-administer study treatment at home, compliance with study treatment will be assessed. Compliance regarding administration of study drug at home will be monitored by the maintenance of adequate drug dispensing logs and return records.

Study drug accountability will be performed at every site visit to monitor dose adherence.

Interim telephone calls will occur at Weeks 4 and 9. Participants will be called by the site personnel to monitor safety and tolerability when not attending the clinic. Assessments will include adverse event, concomitant medication review, and dose accountability (querying adherence, missed doses, etc).

Details on treatment administration (e.g., dose and timing) should be noted in the source documents and on the Study Drug Administration eCRF. Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Appendix 3 and Section 6.7.

6.5 DOSE MODIFICATION

Modification of the balovaptan or placebo dose is not permitted.

6.6 CONTINUED ACCESS TO STUDY TREATMENT AFTER THE END OF THE STUDY

Currently, the Sponsor does not have any plans to provide balovaptan or any other study treatments to participants who have completed the study. The Sponsor may evaluate whether to continue providing balovaptan in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

6.7 TREATMENT OF OVERDOSE

An overdose is the administration of a drug in a quantity that is higher than the assigned dose. There is no known antidote for treating an overdose with balovaptan. Cases of overdose, along with any associated adverse events, should be reported as described in Appendix 3.

In the event of an overdose, the investigator should take the following steps:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any adverse event or serious adverse event, and laboratory abnormalities.
3. Obtain a plasma sample for PK analysis within 7 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).

Decisions regarding dose interruptions will be made by the investigator in consultation with the Medical Monitor on the basis of clinical evaluation of the participant.

6.8 CONCOMITANT THERAPY

Any medication and/or vaccine, including over-the-counter or prescription medicines, vitamins, and/or herbal supplements used by a participant in addition to protocol–mandated treatment from 12 weeks prior to initiation of study treatment to the follow-up visit must be recorded on the Concomitant Medications eCRF along with the following information:

- Reason for use
- Dates of administration, including start and end dates

- Dosage information, including dose and frequency

Based on hypothetical on-target considerations, results from Good Laboratory Practice (GLP) toxicology animal studies and clinical trial experience, there is no indication of immune-suppressant effects of balovaptan. The existing safety monitoring and management guidelines, as well as the risk minimization measures outlined in the clinical protocol, are considered appropriate to support vaccinations including COVID-19 vaccines concomitant to the treatment with balovaptan.

The Medical Monitor *may* be *consulted* if there are any questions *related to* concomitant or prior therapy.

6.8.1 Permitted Therapy

In general, investigators may manage a participant's care (including preexisting conditions) as clinically indicated and per local standard practice, with the exception of prohibited therapies defined in Section 6.8.3 and taking into account cautionary therapies defined in Section 6.8.2.

It is also common for individuals with PTSD to be engaged in a variety of non-pharmacological interventions, including individual and group based behavioral and/or cognitive psychotherapies. Stable (6 weeks prior to screening) non-pharmacological intervention is permitted. The frequency of sessions cannot exceed more than twice monthly. Neither initiation of new psychotherapy nor a change to the frequency of existing psychotherapy is permitted during the course of the study.

Use of the following concomitant therapies is permitted as described below:

- SSRIs (sertraline, paroxetine, and fluoxetine) or SNRI (venlafaxine XR): stable dose (see Section 5.1)
- Non-narcotic analgesics (i.e., non-steroidal anti-inflammatory drugs [NSAIDs], acetaminophen/paracetamol)
- Prescribed opioids: no more than 2 times per week but not for 24 hours before study visits
- Trazadone: PRN up to 3 times per week
- Sedating antihistamines (e.g., alimemazine, chlorphenamine, diphenhydramine, clemastine, cyproheptadine, hydroxyzine, ketotifen, or promethazine): allowed up to 3 times per week but not for 24 hours before study visit
- Benzodiazepines: up to 3 times per week but not for 24 hours before study visits
- Other anxiolytics (buspirone, gabapentin, hydroxyzine, propranolol, atenolol, guanfacine, clonidine, pregabalin, prazosin)
- Muscle relaxants: up to 3 times per week but not for 24 hours before study visit
- Sedatives/hypnotics: allowed up to 3 times per week but not for 24 hours before study visit

- Stimulants: up to 3 times per week but not for 24 hours before study visit
- Melatonin
- Anti-epileptic drugs used for treatment of epilepsy given at stable dosage for at least 6 months prior to screening
- Drugs with known risk of neutropenia per Warnings and Precaution section of U.S. Prescribing Information while not requiring tight controls as mandated for clozapine, are allowed as long as the following criteria are met:
  - No hematological side effects have been noted with such drugs prior to study enrollment.
  - In this case hematological controls as often as every 2 weeks during study treatment should be considered by the investigator.

6.8.2 Cautionary Therapy

6.8.2.1 Medications Given with Precaution due to Effects Related to Cytochrome P450 Enzymes

Balovaptan is metabolized by cytochrome P450 3A4 (CYP3A4) and medications that are strong or moderate inhibitors or inducers of this enzyme will affect the PK of balovaptan. Therefore, the CYP3A4 inducers and inhibitors included in Appendix 10 should be avoided. If use of one of these medications is *deemed* necessary *by the investigator*, the Medical Monitor *should be consulted regarding benefits and risks* prior to concomitant administration with balovaptan.

Moderate inhibitors of CYP3A4 (e.g., erythromycin, ciprofloxacin, diltiazem) may be allowed for a treatment duration of no more than approximately 10 days (e.g., in the context of an adverse event).

These lists of medications are not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

6.8.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, herbal therapies may be used during the study at the discretion of the investigator.

6.8.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below and must be stopped 2 weeks prior to screening to ensure washout of medication:

- Moderate or strong inhibitors of CYP3A4 (e.g., ketoconazole, clarithromycin, erythromycin, ciprofloxacin, diltiazem, and grapefruit juice)

- Moderate or strong inducers of CYP3A4 (e.g., carbamazepine, phenytoin, St. John's wort)
- Quinidine
- All other clinically relevant substrates of P-gp: An interaction cannot be ruled out and caution is advised in particular for those medications that have a narrow therapeutic window (e.g., loperamide or paliperidone) or chronic adrenocorticoid or glucocorticoid use, in particular prednisolone. However, when balovaptan is administered 5 or more hours prior to such a P-gp substrate, the risk of PK interaction is predicted to be small.
- Oxytocin
- DDAVP®(desmopressin)
- Bumetanide
- Agents inhibiting vasopressin receptors (e.g., tolvaptan, conivaptan)
- Tricyclic antidepressants: TCAs, MAO inhibitors, or mirtazapine
- Agents that have been associated with significant and/or irreversible hematological toxicity and therefore require frequent hematologic monitoring (e.g., clozapine)
- Use of any concomitant medication known to potentially cause peripheral neuropathy per the Warnings and Precautions section of the U.S. Prescribing Information.
- Antipsychotic medications or mood stabilizers

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

An excessive rate of withdrawals (either because of participant discontinuing study drug or withdrawal from the study) can render the study non-interpretable. Therefore, unnecessary withdrawal of participants should be avoided and all efforts should be taken to motivate participants to comply with all the study specific procedures and to be followed until the end of the 12-week treatment period.

Before permanently discontinuing study drug (either initiated by the participant or the investigator), an interruption should be considered (see Appendix 6, Section A6–2.2 for further details). Participants, who temporarily discontinue study drug for any reason, should restart as soon as medically justified in the opinion of the investigator.

The investigator should show due diligence and explore all possible options to reach a participant who fails to return to a visit. The site must document all attempts to try to contact the participant in the source documents.

7.1 DISCONTINUATION OF STUDY TREATMENT

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study treatment. If study treatment is definitively discontinued, the

participant will remain in the study for additional assessments. Refer to the schedule of activities (see Section 1.3) for data to be collected at the time of discontinuation of study treatment and for any further follow-up evaluations that need to be completed.

Participants must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the participant
- Pregnancy
- Inability of participant to continue to comply with study requirements
- Suicidal ideation score of 4 or 5 or category 6 or greater on the C-SSRS
- Specific events that are described in Sections 7.1.1, 7.1.2, 7.1.3, and 7.1.4

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

All participants who withdraw or discontinue from the study treatment early will be asked to return as soon as possible (and within 2 weeks after the last dose of study drug) for an early discontinuation visit and complete the assessments as per the schedule of activities in Section 1.3 (see Table 1). Participants will also be asked to return for assessments of the primary and secondary efficacy outcomes at the end of the 12-week planned visit, regardless of their adherence to treatment. If the time between the early discontinuation visit and the 12-week planned visit is fewer than 2 weeks, then participants are exempted from the 12-week planned visit. If the time between the early discontinuation visit and the previous visit is fewer than 2 weeks, then participants are exempted from completing again all the primary and secondary assessments at the early discontinuation visit.

Refer to the schedule of activities in Section 1.3 (see Table 1) for details on follow-up assessments to be performed for participants who permanently discontinue study treatment. If a participant requests to be withdrawn from treatment or follow-up assessments, this request must be documented in the source documents and signed by the investigator.

7.1.1 Liver Chemistry Stopping Criteria

There is no preclinical or clinical evidence that balovaptan administration is associated with an increase in abnormal liver tests.

Discontinuation of study treatment is required by the investigator when a study participant meets abnormal liver tests as outlined Appendix 3 (see Section A3–7.6), or if

the investigator believes that it is in best interest of the participant when abnormal liver chemistries not meeting protocol-specified stopping rules.

Discontinuation of study treatment is also required if the participant experiences moderate or severe hepatic impairment, defined as Child-Pugh class B (7–9 points) and class C (10–15 points), respectively. Please see Appendix 8 for Child-Pugh classification.

7.1.2 QTc Stopping Criteria

There is no preclinical or clinical evidence that balovaptan administration may be associated with an increase in the corrected QT interval (QTc).

Nevertheless, treatment should be discontinued in case of the following:

- Sustained (at least two ECG measurements >30 minutes apart) QTcF that is >500 ms and/or >60 ms longer than the baseline value

Treatment with balovaptan should be discontinued in participants who develop changes in QT interval, as described in Appendix 6. ECG assessment should be conducted as outlined in Section 8.2.4.

7.1.3 Hematological Toxicity Criteria

Treatment discontinuation is suggested for participants who meet the following criterion for decreased absolute neutrophil count (ANC):

> If the ANC falls <800/μL and the low ANC is confirmed in a second sample to be obtained within about 3 working days. If the ANC is <800/μL for the second sample, the investigator should consider treatment discontinuation.

In cases of ANC related–treatment discontinuation, additional laboratory parameters should be considered by the Investigator, including fibrinogen, high-sensitivity C-reactive protein (hs-CRP), and check for anti-neutrophil cytoplasmic antibody (ANCA).

7.1.4 Cardiac Toxicity

Management guidelines and treatment discontinuation for cardiac events are provided in Table 4.

Table 4 Management Guidelines for Cardiac Events

Cardiac Biomarker Result	Actions
hs-cTnT elevated above ULN	• If increased to more than 50 pg/mL, permanently stop treatment and manage as cardiac emergency • If increased to above ULN and by more than 50% compared with baseline: – Check for cardio-vascular adverse events as soon as possible. – Perform 12-lead ECG as soon as possible. – Repeat cardiac biomarker testing, including troponin T, NT-proBN, and troponin I panel within 3 days of availability of results. – If repeat sample cannot be obtained within 3 days, treatment must be interrupted until repeat test results are available. • If increased to above ULN and by less than 50% compared with baseline: – Repeat cardiac biomarker testing, including troponin T, NT-proBNP, and troponin I panel, within 1 week of availability of results. – Perform 12-lead ECG within 1 week of availability of results. – If repeat sample cannot be obtained within 1 week, treatment must be interrupted until repeat test results are available.
Repeat blood sample	• If hs-cTnT has further increased or stays above ULN with 50% increase relative to baseline: – Permanently discontinue treatment. – Perform 12-lead ECG. – Refer participant to local cardiologist consultant and cardiologist consult should include Doppler echocardiogram, including assessment of systolic and diastolic ventricular wall function. • If hs-cTnT is above ULN but has not further increased plus hs-cTnT value is less than baseline value plus 50% of baseline value: – Interrupt study treatment. – Perform 12-lead ECG. – Refer participant to cardiologist consultant and cardiologist consult should include Doppler echocardiogram, including assessment of systolic and diastolic ventricular wall function. – Consider-restart of treatment with tight hs-cTnT monitoring with local cardiologist consult. • If hs-cTnT has returned below ULN, no further activity is needed and treatment can continue.

hs-cTnT=high-sensitivity cardiac troponin T; NT-proBNP=N-terminal prohormone of brain natriuretic peptide; ULN=upper limit of normal.

7.1.5 Peripheral Neuropathy

Signs and symptoms suggestive of peripheral neuropathy should promptly be followed up to confirm or disprove suspicion and to check for alternative explanations

other than study treatment. Follow-up activities may include electro-physiological examinations, temporary treatment hold, and a consultancy by an expert to diagnose peripheral neuropathy in humans.

Should the suspicion of peripheral neuropathy be verified and no alternative explanation known, study treatment should be discontinued permanently.

7.2 PARTICIPANT DISCONTINUATION OR WITHDRAWAL FROM THE STUDY

A participant may withdraw from the study at any time at his or her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a participant requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the schedule of activities (see Section 1.3). Refer to the schedule of activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued both from the study treatment and from the study at that time.

If a participant withdraws consent from the study, the Sponsor may retain and continue to use any data collected before withdrawal of consent. Samples collected prior to withdrawal may be analyzed, unless the participant specifically requests that the samples be destroyed (as documented in the source documents) or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

7.3 PARTICIPANTS LOST TO FOLLOW-UP

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

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

- The site 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. If the participant is unable or unwilling to comply with study visits, site personnel should assess reasons the participant is unable or unwilling to return to the clinic, and determine if there are ways to support participant participation.

- 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, three telephone calls and, if necessary, 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.
- Should the participant continue to be unreachable, he or she will be considered lost to follow-up and will be withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled individuals and for individuals who are not subsequently enrolled will be maintained at the study site.

Study procedures and their timing are summarized in the schedule of activities (see Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the schedule of activities, is essential and required for study 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 screened and to confirm eligibility or record reasons for screening failure as applicable.

Medical history and baseline conditions, including clinically significant diseases, surgeries history and baseline conditions, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse will be recorded at baseline. Any medication and/or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) used by the participant within 24 weeks prior to the screening visit will be recorded at baseline. Demographic data, including age, sex, and self-reported race/ethnicity, will also be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Participants will be closely monitored for safety throughout the study. For in-clinic visits, participants should be assessed for toxicity prior to each dose; treatment will be administered only if the clinical assessment and local laboratory test values are acceptable. Urgent safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

8.1 EFFICACY ASSESSMENTS

8.1.1 Clinical Outcome Assessments

Participant-reported outcomes (PRO), clinician-reported outcomes (ClinRO) and performance outcome (PerfO) instruments will be completed to assess the treatment benefit of balovaptan.

PRO data will be collected through use of the following instruments: Life Events Checklist for DSM-5 (LEC-5), PCL-5, Patient Health Questionnaire-9 (PHQ-9), Beck Anxiety Inventory (BAI), Pittsburgh Sleep Quality Index (PSQI), Sheehan Disability Scale (SDS), Cognitive and Physical Functioning Questionnaire (CPFQ), Patient-Global Impression of Severity (PGI-S), and Patient-Global Impression of Change (PGI-C).

ClinRO data will be collected through use of the following instruments: SCID-5, CAPS-5, Clinician-Global Impression of Severity (CGI-S), and Clinician-Global Impression of Change (CGI-C).

PCL-5 and LEC-5 are the PROs completed at screening, as well as the SCID-5 (ClinRO). The recommended order for administration is: PCL-5, SCID-5, and LEC-5. For all other visits, PROs must be completed before the ClinROs in the following order: PHQ-9, PCL-5, PSQI, BAI, CPFQ, SDS, PGI-S, PGI-C. ClinROs should be completed, starting with the CAPS-5, CGI-S, followed by the CGI-C.

Clinician-Administered PTSD scale for DSM-5 (CAPS-5) is the clinical outcome assessment that will be used to determine the primary endpoint (see Table 2 and Section 9.4.2). CGI-S and PHQ-9 are the clinical outcome assessments that will be used to determine the secondary endpoints (see Table 2 and Section 9.4.3). For any individual patient, the CGI-S/C should be completed by the same rater throughout the study.

PerfO data will be collected through the use of a computerized cognitive battery.

8.1.1.1 Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)

The CAPS-5 is a 30-item structured interview that can be used to make current (past month) diagnosis of PTSD, make lifetime diagnosis of PTSD, or assess PTSD symptoms over the past week (Weathers et al. 2013a, 2018; see Appendix 11). For this study the past week version of the CAPS-5 will be used and will be administered by central rater. Items are scored using a 5-point scale, rated from 0 (absent) to

4 (extreme/incapacitating), with a higher overall score indicating a worse outcome. In addition to assessing the 20 DSM-5 PTSD symptoms, questions asked target the onset and duration of symptoms, subjective distress, impact of symptoms on social and occupational functioning, improvement in symptoms since a previous CAPS administration, overall response validity, overall PTSD severity, and specifications for the dissociative subtype (depersonalization and derealization). Responses will be collected by means of free text to understand intensity and frequency of symptoms, which are then used to select a response on a 5-point Likert scale, ranging from 0 (absent) to 4 (extreme/incapacitating). A total score is calculated by summing severity scores for items 1–20, where a higher score corresponds to greater severity of PTSD or presence of PTSD. Symptom cluster severity scores can also be derived by summing the individual item severity scores for symptoms corresponding to a given DSM-5 cluster: Criterion B (items 1–5); Criterion C (items 6–7); Criterion D (items 8–14); and, Criterion E (items 15–20). For each symptom, standardized questions and probes are provided. Administration requires identification of an index traumatic event to serve as the basis for symptom inquiry via the Life Events Checklist for DSM-5 (LEC-5; see Section 8.1.1.4 for more detail). The LEC-5 will be administered prior to the CAPS-5 at screening only. The CAPS was designed to be administered by clinicians and clinical researchers who have a working knowledge of PTSD but can also be administered by appropriately trained paraprofessionals.

The full interview takes 45–60 minutes to administer. In this study, the past week version of the CAPS-5 will be administered remotely by a central assessor. This first CAPS-5 assessment will be administered no more than 7 days prior to the baseline and at Week 6 and Week 12.

8.1.1.2 Clinician-Global Impression of Severity (CGI-S) and Change (CGI-C)

The CGI-S and CGI-C are single items rated by the clinician (Guy 1976; see Appendix 11). The CGI-S is used to assess the overall severity of PTSD symptoms over the past 7 days, whereas the CGI-C is used to assess change in overall PTSD symptoms from baseline. Each item is rated on a 7-point scale, ranging from 1 (no symptoms/very much improved) to 7 (very severe/very much worse) for the CGI-S and CGI-C, respectively. Clinicians should make a judgment on severity and any changes from baseline based on the totality of information available to them (e.g., insights from the patient captured during the completion of other trial assessments). The assessments will take up to 5 minutes to complete in their entirety. The CGI-S will be collected at baseline, Week 6, and Week 12. The CGI-C will be collected at Week 6 and Week 12.

8.1.1.3 Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 is a 9-item PRO used to assess severity of depression over the last 2 weeks. It was developed using each of the 9 DSM-IV criteria. On the basis of these criteria, the diagnosis of depressive disorders is made (Kroenke et al. 2001; see

Appendix 11). Responses are rated based on frequency of symptoms on a 4-point Likert scale, ranging from 0 (not at all) to 3 (nearly every day). Reponses are reported using a recall of the last 2 weeks. A total PHQ-9 total score ranging from 0 to 27 can be calculated by summing the nine items, of which a higher score corresponds to more severe depression. Scores of 5, 10, 15, and 20 represent cutpoints for mild, moderate, moderately severe, and severe depression, respectively. It takes approximately 90 seconds to 3 minutes to complete. The PHQ-9 will be administered at baseline, Week 6, and Week 12.

8.1.1.4 Life Events Checklist for DSM-5 (LEC-5)

The LEC-5 standard version is a 17-item PRO designed to screen for potentially traumatic events in an individual's lifetime (Gray et al. 2004; Weathers et al. 2013b; see Appendix 11). The LEC-5 is intended to gather information about the potentially traumatic experiences a person has experienced. It assesses exposure to 16 events known to potentially result in PTSD or distress and one additional item assessing any other extraordinarily stressful event not captured in the first 16 items. Responses are reported on a 6-point nominal scale of which one or more responses can be made based on whether the event: happened to the individual personally; they witnessed it happen to someone else; they learned about it happening to a close family member or close friend; they were exposed to it as part of their job (e.g., first responders); they are not sure if it fits; it does not apply. There is no formal scoring protocol or interpretation per se, other than identifying whether a person has experienced one or more of the events listed.

The purpose of the LEC-5 generally and in this study is to inform other measures (e.g., CAPS-5) to establish exposure to a PTSD Criterion A traumatic event. It takes approximately 4–8 minutes to complete. The LEC-5 must be completed at the screening visit.

8.1.1.5 PTSD Checklist for DSM-5 (PCL-5)

The PCL-5 is a 20-item PRO used to assess the 20 DSM-5 symptoms of PTSD (Weathers et al. 2013c; Blevins et al. 2015; see Appendix 11). Reponses are reported on a 5-point Likert scale, ranging from 0 (not at all) to 4 (extremely). A recall period of one month has been validated. However, the PCL-5 manual acknowledges a recall period of less than one month may make more sense in some cases, but to be aware that the psychometric properties may differ to those published using the one-month recall (National Center for PTSD 2013). In this study, the one-month recall will be used at screening for diagnostic purposes and a one week recall version will be used thereafter for efficacy. This is to allow for more frequent PCL-5 administrations without overlapping recalls. A total severity score, ranging from 0 to 80, can be calculated by summing all items, of which a higher score corresponds to more severe symptoms. The PCL-5 can be used to determine a provisional diagnosis in two ways; either using a cutpoint score of 31 to 33, or alternatively, by treating each item rated as 2 (moderately) or higher as a symptom endorsed and then following the DSM-5 diagnostic rule, which

requires at least: 1 Criterion B item (Questions 1–5), 1 Criterion C item (Questions 6–7), 2 Criterion D items (Questions 8–14), and 2 Criterion E items (Questions 15–20). If a patient meets a provisional diagnosis using either of the methods above, then he or she needs further assessment (e.g., CAPS-5 or SCID-5) to confirm a diagnosis of PTSD. It takes approximately 5–10 minutes to complete. The PCL-5 will be administered at screening, baseline, Week 2, Week 6, and Week 12.

8.1.1.6 Structured-Clinical Interview for DSM-5 (SCID-5)

The SCID-5 is a structured diagnostic instrument for assessing DSM-5 disorders (First 2014; Appendix 11). The instrument is designed to be administered by a clinician or trained mental health professional. The SCID-5 is organized into diagnostic modules corresponding to categories of diagnoses. Most sections begin with an entry question that would allow the interviewer to skip the associated questions if not met. For all diagnoses, symptoms are coded as present, subthreshold, or absent. The SCID-5 will be used only at screening for the diagnosis of PTSD.

8.1.1.7 Beck Anxiety Inventory (BAI)

The BAI is a 21-item PRO used to assess severity of anxiety in psychiatric populations (Beck et al. 1988; see Appendix 11). BAI is a self-reported measure of clinical anxiety. BAI was designed to specifically assess the physiological and cognitive symptoms of anxiety and is independent of depression. Responses are reported using a recall of 1 week on the basis of how much an individual has been bothered by each symptom and then recorded using a 4-point Likert scale, ranging from 0 (not at all) to 3 (severely—it bothered me a lot). A total score, ranging from 0 to 63, can be calculated by summing the 21 items, for which a higher score corresponds to more severe anxiety. Scores of 0 to 21, 22 to 35, and 36 and above represent cutpoints for low, moderate, and concerning levels of anxiety. It takes approximately 2–4 minutes to complete. The BAI will be administered at baseline, Week 6, and Week 12.

8.1.1.8 Pittsburgh Sleep Quality Index (PSQI)

The PSQI is a 19-item PRO used to assess sleep quality over the past month (Buysse et al. 1989; see Appendix 11). It contains 7 domains, consisting of subjective sleep quality (1 item), sleep latency (2 items), sleep duration (1 item), habitual sleep efficiency (3 items), sleep disturbances (9 items), use of sleep medication (1 item), and daytime dysfunction (2 items). It is rated by entering numeric values or on a 4-point Likert scale with a range of response options from 0 (corresponding to better outcomes) to 3 (corresponding to worse outcomes). Reponses are reported using a recall of the past month. The PSQI can be scored as a total score ranging from 0 to 21 by summing all items or by domain (mentioned above), for which higher scores correspond to worse sleep quality. A global score of 5 represents poor sleep quality. It takes approximately 5–10 minutes to complete. The PSQI will be administered at baseline, Week 6, and Week12.

8.1.1.9 Sheehan Disability Scale (SDS)

The SDS is a 5-item PRO used to assess health-related quality of life and social functioning (Sheehan 1983, Sheehan and Sheehan 2008; see Appendix 11). It consists of 3 core items that are related to disruption at work, social life, and family life, as well as 2 optional items stating the number of days lost or underproductive due to symptoms. Using a recall period of the past week, items are rated on a 10-point numerical rating scale, ranging from 0 (unimpaired) to 10 (highly impaired). The measure can be scored either by item as a percentage or as a global score from 0 to 30, for which higher scores correspond to greater impairment. There are no referenced cutoff scores for this measure. It takes approximately 1–2 minutes to complete. The SDS will be administered at baseline, Week 6 and Week 12.

8.1.1.10 Cognitive and Physical Functioning Questionnaire (CPFQ)

CPFQ is a 7-item PRO used to assess physical and psychological functioning in mood and anxiety disorders (Fava et al. 2009; see Appendix 11). The participant is asked to report how affected he or she has been over the past month by seven of the most common complaints of depressed individuals. Responses are made using a 6-point Likert scale from 1 (greater than normal) to 6 (totally absent). Scoring can be calculated as a total score, ranging from 7 to 42 or by domain (cognitive, 4 items; physical, 3 items) by summing items and a higher score corresponds to poorer functioning. It takes approximately 60–90 seconds to complete. The CPFQ will be administered at baseline, Week 6, and Week 12.

8.1.1.11 Patient-Global Impression of Severity (PGI-S) and Change (PGI-C)

The PGI-S and PGI-C are single items rated by the participant that is used to assess the overall severity over the past 7 days or change of PTSD symptoms relative to baseline (see Appendix 11). Each item is rated on a 7-point scale, ranging from 1 (no symptoms/very much improved) to 7 (very severe/very much worse) for PGI-S and PGI-C, respectively. The assessments will each take approximately 30 seconds to complete. The PGI-S will be collected at baseline, Week 6, and Week 12. The PGI-C will be collected at Week 6 and Week 12.

8.1.1.12 Computerized Cognitive Battery

A computerized cognitive battery will be administered and completed by participants to assess domains such as psychomotor functioning (e.g., simple and choice-reaction time tasks), non-verbal receptive communication (e.g., facial-emotion recognition task), verbal memory, and executive function (including set-shifting and/or reversal learning). The data will be used mainly to derive cognitive biomarkers (see Section 8.7) and may also be used for exploratory efficacy endpoints. The assessments will take approximately 30 minutes to complete and will be administered at the pre-randomization visit, Week 2, Week 6, and Week 12.

8.2 SAFETY ASSESSMENTS

8.2.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

A brief *or limited* physical examination should be symptom-directed and will include, at a minimum, assessments of the skin, lungs, *and the* cardiovascular and neurologic systems.

Investigators should pay special attention to clinical signs related to previous serious illnesses. Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities beyond what is expected in the clinical situation should be recorded as adverse events on the Adverse Event eCRF.

8.2.2 Vital Signs

Temperature (tympanic), pulse rate, respiratory rate, and blood pressure will be assessed.

Blood pressure and pulse measurements will be assessed while the participant is in a seated position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

Vital signs (to be taken before any blood collection) will consist of one pulse and three blood pressure measurements (three consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the three blood pressure readings will be recorded on the eCRF.

Abnormalities observed at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. At subsequent visits, new or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

8.2.3 Neurological Examination

Neurologic examinations of the upper and lower limbs will be completed as per the schedule of activities in Section 1.3 (see Table 1)and conducted as per the instructions provided in in Appendix 7.

8.2.4 Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the schedule of activities (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR interval, QRS interval, QT interval, and QTcF. Refer to Appendix 6 for prolonged QTc management criteria and any additional QTc readings that may be necessary.

For the baseline ECG at which triplicate ECGs are required, three individual ECG tracings should be obtained as closely as possible in succession, approximately 1–2 minutes apart.

All ECG recordings must be performed through use of a standard high-quality, high-fidelity digital electrocardiograph machine. Lead placement should be as consistent as possible. ECG recordings must be performed after the participant has been resting in a supine position for at least 5 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre–ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG reports. Paper copies of ECG tracings will be kept as part of the participant's permanent study file at the site. Digital recordings will be stored at the site as part of the medical record and the central ECG laboratory. The following parameters will be provided as non-eCRF data: heart rate, RR interval, QRS interval, PR duration (beginning of P wave to first part of QRS complex), uncorrected QT interval, and QTcF based on machine readings of the individual ECG tracings. Any concerning morphologic waveform changes or other ECG abnormalities that lead to change in management or increased monitoring must be documented on the eCRF as an adverse event.

If at a particular postdose timepoint the mean QTcF is $>$500 ms and/or $>$60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 30 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted at the investigator's discretion. If a PK sample is not scheduled for that timepoint, one should be obtained. A decision on study drug discontinuation should be made, as described in Appendix 6 (see Section A6–2.7). The investigator should also evaluate the participant for potential concurrent risk factors (e.g., electrolyte abnormalities, concomitant medications known to prolong the QT interval, severe bradycardia).

8.2.5 Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical laboratory tests to be performed and to the schedule of activities (see 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 study in the Adverse Event eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days *of the final* dose of study treatment should be repeated until the values return to normal or baseline or are *considered to be stable and* no longer considered clinically significant by the investigator. If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the schedule of activities (Section 1.3).

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., serious adverse event or adverse event or dose modification), the results must be recorded on the eCRF.

Samples collected for safety laboratory tests will be destroyed no later than the time of completion of the final CSR.

8.2.6 Pregnancy Testing

The schedule for pregnancy testing for enrolled female participants is outlined in Section 1.3 and will be conducted as outlined in Appendix 2.

8.2.7 Monitoring for Suicidal Ideation and Behavior

The assessment for suicidality in clinical trials is a requirement for CNS-active molecules requested by health authorities.

The C-SSRS is a clinician-rated tool recommended by health authorities, including the FDA, to assess previous suicidality of a subject (C-SSRS Baseline/Screening version) as well as any new instances of suicidality during this study (C-SSRS Since Last Visit version to be used at subsequent visits) (Posner et al. 2009a, Posner et al. 2009a) (Appendix 11). The C-SSRS incorporates a structured interview to prompt recollection of suicidal ideation, including the intensity of the ideation, behavior, and attempts with actual/potential lethality.

The C-SSRS is made up of ten categories, all of which maintain binary responses (yes/no) to indicate a presence or absence of the behavior. The ten categories included in the C-SSRS are as follows: Category 1-Wish to be Dead; Category 2-Non-specific Active Suicidal Thoughts; Category 3-Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act; Category 4-Active Suicidal Ideation with Some Intent to Act, without Specific Plan; Category 5-Active Suicidal Ideation with Specific Plan and Intent; Category 6-Preparatory Acts or Behavior; Category 7-Aborted Attempt; Category 8-Interrupted Attempt; Category 9-Actual Attempt (non-fatal); Category 10-Completed Suicide. A yes or no binary response is also utilized in assessing self-injurious behavior without suicidal intent. The outcome of the C-SSRS is a numerical score obtained from the aforementioned categories. The maximum suicidal ideation category (1–5 on the C-SSRS) will determine the suicidal ideation score for the participant. A score of 0 represents no ideation.

Participants should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Consideration should be given to discontinuing the study drug in participants who experience signs of suicidal ideation or behavior, following a risk assessment. If the investigator concludes there is a risk of suicidality for a participant, the investigator must further evaluate the risk, which may involve local experts in the field of suicidality.

8.3 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND OTHER SAFETY REPORTING

The definitions of adverse event and serious adverse event can be found in (see Sections A3–1 and A3–2).

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 adverse event or serious adverse event and remain responsible for following up adverse events that are serious, are

considered related to the study treatment or study procedures, or caused the participant to discontinue the study treatment (see Section 7).

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. All other medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the General Medical History and Baseline Conditions eCRF, not the Adverse Event eCRF.

All adverse events will be reported from the start of treatment until 14 days after final study drug or until the last follow-up visit at the timepoints specified in the schedule of activities (see Section 1.3).

All serious adverse events will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek adverse event or serious adverse event information after conclusion of study participation. However, if the investigator learns of any serious adverse event, including a death, at any time after a participant has been discharged from the study, and he or she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about adverse event occurrences.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

After the initial adverse event or serious adverse event report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All

adverse events will be followed until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the participant is lost to follow-up (as defined in Section 7.3), or the participant withdraws consent. Further information on follow-up procedures is provided in Appendix 3.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to the Sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards or Ethics Committees (IRBs/ECs), and investigators.

For all studies except those utilizing medical devices, 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.

To determine reporting requirements for serious adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the balovaptan Investigator's Brochure.

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An investigator who receives an investigator safety report describing a serious adverse event or other specific safety information (e.g., summary or listing of serious adverse events) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5 Pregnancy

Female participants of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 14 days after the final dose of balovaptan.

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 Appendix 4.

All pregnancies reported during the study should be followed until pregnancy outcome, with follow-up information on the infant collected according to procedures outlined in Appendix 4. The Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

8.3.6 Death Events

Information on reporting deaths is provided in Appendix 3 (see Section A3–7.7)

8.3.7 Adverse Events of Special Interest

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section A3–7.6)
- Suspected transmission of an infectious agent by a study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a participant exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.

- ANC values $<800/\mu L$ and confirmed in a second sample.
- Creatine phosphokinase (CPK) values triggering a change in monitoring schedule and also when:
  - CPK values exceed $10\times$ULN for several days without trend of normalization according to CPK half-life in plasma
  - CPK increases associated with a relevant decrease in kidney function and no alternative explanation exists
  - CPK values increase again to similar values as noted before when treatment has been re-started.

- Cases of neurological abnormalities emerging from adverse event reporting or neurological examination (see Section 8.2.3) that are potentially indicative of dysfunction of peripheral nerves or otherwise represent a neurological deficit and for which no other explanation is apparent (see Safety Plan: Management of Identified and Potential Risks in Appendix 6, Section A6–2.9 for further details on when a measurement of the nerve conduction velocity (NCV) may be needed).

8.3.8 Medical Monitors and Emergency Medical Contacts

To ensure the safety of study participants, *access to the Medical Monitors is available 24 hours per day, 7 days per week. Details will be provided separately.* An Emergency Medical Call Center will be available 24 hours per day, 7 days per week, in case the above-listed contacts cannot be reached. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

8.4 PHARMACOKINETICS

Blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of balovaptan using a specific and validated liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) assay as specified in the schedule of activities in Section 1.3 (see Table 1). Concentration of metabolite 2 (M2) and metabolite 3 (M3) may be measured if indicated (e.g., safety concern).

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the pharmacokinetics of balovaptan. Samples collected for analyses of balovaptan plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Genetic analyses will not be performed on these plasma samples unless consent for this was included in the Informed Consent Form. Participant confidentiality will be maintained. At visits during which blood samples for the determination of multiple aspects of balovaptan will be taken, one sample of sufficient volume can be used.

PK samples will be destroyed no later than 5 years after the final CSR has been completed to allow for assay development and validation (if needed).

Information on unblinding of personnel responsible for performing PK assays is provided in Section 6.3.

8.5 PHARMACODYNAMICS

Refer to Section 8.7 for information on pharmacodynamic biomarkers.

8.6 GENETICS

Refer to Section 8.7 and Appendix 5 for information on genetic biomarkers.

8.7 BIOMARKER ASSESSMENTS

The following biomarker assessments will be collected, as applicable, from participants at all sites:

- EEG assessments. Resting-state EEG will be acquired at 1000 Hz from 64 locations following the extended 10–20 system electrode montage. This assessment will follow the recommendations of the International Pharmaco-EEG Society (Jobert et al. 2012) in 4-minute blocks as follows: eyes closed (recording eyes closed [REC] 1), eyes open (recording eyes open [REO] 1), eyes closed (REC2), and eyes open (REO2), amounting to a total of 16 minutes, while participants sit relaxed looking at a fixating cross during eyes-open conditions. Raw, unfiltered EEG data along with impedances (targeting $<$15 kOhm for each channel in each run) will be recorded. Resting state data will be processed offline to assess electrical brain activity including, but not limited to power at frequency bands and connectivity.
- Computerized cognitive assessments. A battery of cognitive assessments will be administered, using an electronic display and with manual responses controlled by participants using their left and/or right hands on a mouse, keyboard, or tablet as appropriate for the task. The neurocognitive assessments to be administered will include assessments of psychomotor functioning (simple and choice-reaction time tasks), non-verbal receptive communication, verbal memory, and executive function.
- Digital biomarkers. These will be derived from a wearable device (e.g., OURA™ Ring). The following wearable sensor data will be recorded: heart rate, movement, and sleep. These measures will be recorded to enable the derivation of exploratory biomarkers related to autonomic function and arousal, movement kinematics and behavior, and sleep. The wearable will be worn starting during screening about 1 week prior to randomization and worn throughout the study. Staff will instruct the participant on how to wear and care for the wearable, and on the importance of sleep hygiene.

The following biomarker samples will be collected, as applicable, from participants at all sites:

- Blood samples for exploratory research on biomarkers and biomarker assay development

Biomarker samples collected at participating sites and biomarker samples requiring separate consent are described in Section 8.11.

Exploratory biomarker research may include, but will not be limited to, analysis of biomarkers relevant to balovaptan (e.g., AVPR1A gene), PTSD and related disorders, and drug safety. Research may involve extraction of DNA, cell-free DNA, or RNA; analysis of mutations, single nucleotide polymorphisms, and other genomic variants; and

genomic profiling through use of next-generation sequencing (NGS) of a comprehensive panel of genes. Genomic research will be aimed at exploring inherited characteristics. NGS methods may include whole genome sequencing (WGS) or whole exome sequencing (WES) of blood samples, but only at participating sites (see Section 8.11.1).

Biomarker samples will be collected according to the schedule outlined in Section 1.3 (see Table 1). Biomarker samples will be sent to one or several central laboratories or to the Sponsor or a designee. Instructions for the collection and handling of biomarker samples, including sampling procedures, storage conditions, and shipment instructions, are provided in the laboratory manual.

Unless the participant gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 8.11), biomarker samples will be destroyed no later than 5 years after the final CSR has been completed.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

8.8 IMMUNOGENICITY ASSESSMENTS

Immunogenicity assessments will not be performed in this study.

8.9 HEALTH ECONOMICS AND MEDICAL RESOURCE UTILIZATION

Health economics and medical resource utilization assessments will not be performed in this study.

8.10 CLINICAL OUTCOME ASSESSMENTS

8.10.1 Data Collection Methods for Clinical Outcome Assessments

For the description of the clinical outcome assessment used in the study see Section 8.1.1.

PRO instruments will be self-administered at the clinic at specified timepoints during the study (see the schedule of activities in Section 1.3). At the clinic, instruments will be administered before the participant receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study drug.

PRO instruments will be completed through use of an electronic device provided by the Sponsor. The device will be pre-programmed to enable the appropriate instruments to be administered in the correct order at each specified timepoint. The electronic device and instructions for completing the instruments electronically will be provided by the site

staff. The data will be transmitted to a centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel.

During clinic visits, PRO instruments should be administered as outlined below:

- Participants' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for participants to complete the instruments, estimated to be approximately 15–30 minutes at baseline, Week 6, and Week 12.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Participants should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions, but may read questions verbatim upon request.
- Participants should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

ClinRO instruments will be completed at the clinic at specified timepoints during the study (see schedule of activities in Section 1.3). ClinRO instruments will be administered prior to the administration of study drug. The instruments will be completed through use of an electronic device provided by the Sponsor. Clinicians must complete the official version of each ClinRO instrument, as provided by the Sponsor. Instruments must not be copied from the protocol. The data will be transmitted to a centralized database maintained by the electronic device vendor.

8.10.2 Description of Clinical Outcome Assessment Instruments

For the description of the clinical outcome assessment used in the study see Section 8.1.1.

8.11 ADDITIONAL ASSESSMENTS AND PROCEDURES REQUIRING SEPARATE CONSENT OR PERFORMED ONLY AT PARTICIPATING SITES

8.11.1 Blood Samples for Whole Genome Sequencing or Whole Exome Sequencing (Participants at Participating Sites)

At participating sites, blood samples will be collected for DNA extraction to enable WGS or WES to identify variants (inherited characteristics) that are predictive of response to study treatment, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety.

Research will be aimed at exploring inherited characteristics.

The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS or WES is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS or WES, this section of the protocol (Section 8.11.1) will not be applicable at that site.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Blood samples collected for WGS or WES are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Data generated from blood samples collected for WGS or WES will be analyzed in aggregate rather than on an individual basis. Thus, there will be no identification and reporting of incidental findings to investigators or participants.

If permitted by local law, a participant may request access to uninterpreted WGS or WES data derived from analysis of his or her blood sample. If a participant wishes to access these data, the investigator must inform the Sponsor, using the following email address: global.return-genomics-results@roche.com. The Sponsor will provide available data to the investigator in the form of a raw genomic sequencing data file, but will not provide any interpretation of the data. The investigator should not include the data file in the participant’s medical record. Samples may be stored and analyzed in the future, and some samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.

The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Appendix 1).

8.11.2 Samples for Research Biosample Repository (Participants Providing Separate Consent at Participating Sites)

8.11.2.1 Overview of the Research Biosample Repository

The RBR is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from participants who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

8.11.2.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 8.11) will not be applicable at that site.

8.11.2.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to balovaptan, PTSD, or drug safety:

- Leftover PK samples (see Section 8.4)
- Leftover blood for DNA sample collected at baseline (Day 1)
- Additional whole-blood sample for RBR at the timepoints specified in the schedule of activities in Section 1.3 (see Table 1).

The above samples may be sent to one or more laboratories for analysis including, but not limited to, the analysis of germline or somatic variants via WGS, WES, or other analysis methods. Genomics is increasingly informing researcher's understanding of

disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or that may be predictive of which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

8.11.2.4 Confidentiality

RBR samples and associated data will be labeled with a unique participant identification number.

Participant medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

8.11.2.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to choose not to provide optional RBR samples and may

withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a participant's agreement to provide optional RBR samples. Participants who choose not to provide optional RBR samples will not provide a separate signature. The investigator should document whether or not the participant has given consent to provide optional RBR samples and (if applicable) the date(s) of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

8.11.2.6 Withdrawal from the Research Biosample Repository

Participants who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a participant wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the participant's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the Sample Informed Consent/Withdrawal eCRF. If a participant wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and participant number to the following email address:

global.rcr-withdrawal@roche.com

A participant's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a participant's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

8.11.2.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to an individual's participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

9. STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

No formal statistical hypotheses will be tested for this study. All analyses will be conducted using descriptive statistics.

9.2 SAMPLE SIZE DETERMINATION

Approximately *30* participants will be randomly assigned to study treatment *(15 in balovaptan arm and 15 in placebo arm) to perform the final analysis with reduced scope.*

9.3 ANALYSIS SETS

The following populations are defined:

Participant Analysis Set	Description
Intent to treat	All participants randomly assigned to study drug. Participants will be analyzed according to the treatment to which they were assigned.
Safety evaluable	All participants randomly assigned to study drug and who receive at least one dose of study drug. Participants will be analyzed according to the treatment they actually receive.
PK evaluable	The PK-evaluable population will include all participants who receive at least one dose of balovaptan and have sufficient evaluable concentrations to determine the overall exposure to balovaptan. Participants may be excluded from the PK-evaluable population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete. Excluded cases will be documented together with the reason for exclusion. All decisions about exclusions from the analysis will be made prior to database lock.

PK = pharmacokinetic.

9.4 STATISTICAL ANALYSES

The intent-to-treat (ITT) analysis set, as defined in 9.3, will be used for efficacy analyses. The safety analysis set, as defined in 9.3, will be used for safety analyses.

Final database lock to enable the analysis of the primary and secondary endpoints will occur once all patients have either completed their follow-up assessment or withdrawn from the study early, and all data required for analysis have been cleaned and verified.

9.4.1 General Considerations

For all endpoints, baseline will be defined as the last assessment made up to and including the day of first study drug intake.

In general, descriptive statistics will be used to summarize continuous endpoints and counts and percentages will be used to summarize categorical endpoints.

Missing values will not be replaced.

9.4.2 Primary Endpoint

The primary endpoint is the change in CAPS-5 total symptom severity score from baseline at Week 12, as defined in Section 3 (see Table 2). The change from baseline in CAPS-5 total symptom severity score at Week 12 will be calculated as the score at Week 12 minus the score at baseline. A negative change from baseline in CAPS-5 total symptom severity score indicates improvement.

Every effort will be made to minimize missing data. Participants who discontinue early from study treatment will be asked to return for collection of safety and limited efficacy data (i.e., the primary and secondary efficacy endpoints) at the scheduled visits.

9.4.3 Secondary Endpoints

The secondary endpoints are the changes from baseline at Week 12 in the CGI-S and PHQ-9, as defined in Section 3 (see Table 2).

9.4.3.1 Clinician-Global Impression of Severity (CGI-S)

The change from baseline in CGI-S will be calculated as the CGI-S score at Week 12 minus the CGI-S score at baseline. A negative change from baseline in CGI-S indicates improvement.

The count and percentages for each value of CGI-S changes will be evaluated.

9.4.3.2 Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 is a 9-question instrument to assess presence and severity of depression (see Section 8.1.1.3 for details). The total sum of responses score ranges from 0 to 27 and will be summarized using descriptive statistics at each assessment timepoint for absolute values as well as change from baseline. Additionally, the score will be categorized as shown in Table 5, and a shift table will be provided to examine changes in depression severity categories from baseline to worst post-baseline depression severity.

Table 5 Patient Health Questionnaire-9 (PHQ-9) Score and Corresponding Categories

PHQ-9 Score	Depression Severity
0–4	None-minimal
5–9	Mild
10–14	Moderate
15–19	Moderately severe
20–27	Severe

PHQ-9=Patient Health Questionnaire-9

9.4.4 Exploratory Endpoints

Exploratory endpoints as defined in Section 3, Table 2, will be analyzed descriptively by treatment arm. Descriptive statistics (mean, standard deviation, median, and range) will be presented for continuous variables and counts and percentages will be presented for categorical variables.

The relationship between biomarkers (see Section 8.7) and efficacy, safety, PK, or other biomarker endpoints *may* be explored to identify biomarkers that are predictive of response to balovaptan or are early signs of efficacy.

9.4.5 Safety Analyses

Safety will be assessed through summaries of exposure to study treatment, adverse events, physical and neurologic examinations, urine drug screens, changes in laboratory test results, changes in vital signs, ECGs and Doppler echocardiograms (where applicable), and C-SSRS.

Study treatment exposure (such as treatment duration and treatment compliance) will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms, and adverse event severity will be graded according to mild, moderate, or severe scale (see Adverse Events Severity Grading Scale; Appendix 3, Table 1). All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum post-baseline severity grade. Changes in vital signs and ECGs will be summarized.

9.4.6 Other Analyses

9.4.6.1 Summaries of Conduct of Study

Enrollment, study treatment administration, and discontinuation from the study will be summarized by treatment arm. The reasons for study treatment discontinuation will also be tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm.

9.4.6.2 Summaries of Treatment Group Comparability

Demographics and baseline characteristics (including age, sex, type of trauma [veteran*/armed forces service-related* or civilian], concurrent antidepressant use, time since triggering event, and time since PTSD diagnosis) will be summarized by treatment arm. Baseline data are the last data obtained prior to initiation of study treatment. Descriptive statistics (mean, standard deviation, median, and range) will be presented for continuous variables and counts and percentages will be presented for categorical variables.

9.4.6.3 Pharmacokinetic Analyses

Individual and mean plasma concentrations of balovaptan at each sampling timepoint will be presented by listings and descriptive summary statistics, including means, medians, geometric means, ranges, standard deviations, and coefficients of variation. If warranted by the observed data, empirical Bayes estimates for individual balovaptan PK parameters and exposure may be derived using a previously developed population PK model (1101622 [available upon request]). Concentration of M2 and M3 may be measured if indicated (e.g., safety concern) and presented in listings and descriptive summary statistics.

Graphical exploration of the relationship between balovaptan exposure and outcome measures and biomarkers as well as safety parameters may be performed. If indicated by such exploration, more formal analyses of PK to pharmacodynamic (PD), safety or efficacy measures of interest may be undertaken.

Results of population PK or PK/PD model–based analyses may be reported in a separate study summary.

9.5 INTERIM ANALYSES

There are no planned interim analyses for this study.

9.6 INTERNAL MONITORING COMMITTEE

Refer to Section 4.1 for information on the IMC for this study.

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Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

TABLE OF CONTENTS

A1–1 REGULATORY AND ETHICAL CONSIDERATIONS

This study 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 International Council for Harmonisation (ICH) Guideline for Good Clinical Practice
- Applicable laws and regulations

The protocol, Informed Consent Form, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board or Ethics Committee (IRB/EC) by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any substantial amendments to the protocol will require IRB/EC and health authority approval (as locally required) before implementation of changes, with the exception of administrative changes or changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
- Notifying the IRB/EC of serious adverse events or other significant safety findings, as required by IRB/EC procedures
- Providing oversight of the conduct of the study at the site and ensuring adherence to requirements of 21 CFR (U.S. sites only), the ICH Guideline for Good Clinical Practice, the IRB/EC, *Clinical Trials Directive (2001/20/EC) or Clinical Trials* Regulation 536/2014 (E*EA* sites only), and all other applicable local regulations

A1–2 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations 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 study and for 1 year after completion of the study (see definition of end of study in Section 4.4).

A1–3 INFORMED CONSENT PROCESS

The investigator or authorized designee will explain the nature of the study to the participant or his or her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50 (U.S. sites only), the ICH Guideline for Good Clinical Practice, and the IRB/EC.

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

If the Informed Consent Form is revised (through an amendment or an addendum) to communicate information that might affect a participant's willingness to continue in the study, the participant or the participant's legally authorized representative must re-consent by signing the most current version of the Informed Consent Form or the addendum, in accordance with applicable laws and IRB/EC policy.

A copy of each Informed Consent Form must be provided to the participant or the participant's legally authorized representative.

Participants who are re-screened are required to sign a new Informed Consent Form.

The Informed Consent Form will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

A1–4 DATA PROTECTION

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; the participant's name or any information that would make the participant identifiable will not be transferred.

Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to participants, who will be required to give consent for their data to be used as described in the Informed Consent Form.

Participants must be informed that their medical records may be examined by auditors or other authorized individuals representing the Sponsor or Sponsor collaborators and licensees, by appropriate IRB/EC members, and by inspectors from health authorities.

A1–5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring. The Sponsor has contracted IQVIA, who will be delegated responsibility for various aspects of this clinical trial.

Approximately *12* sites located in the United States will participate to enroll approximately *30* participants. Enrollment will occur through an interactive voice or web-based response system.

Central facilities will be used for certain assessments throughout the study (e.g., specified laboratory tests, biomarker and pharmacokinetic analyses), as specified in Section 8 and Appendix 2.

A1–6 DISSEMINATION OF CLINICAL STUDY DATA

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and*/or* other summar*ies of clinical study results may be available in health authority databases for public access, as required by local regulation, and* will be provided upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

A1–7 DATA QUALITY ASSURANCE

All participant data relating to the study will be recorded on printed or electronic Case Report Form (CRFs) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

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

Monitoring details describing strategy (e.g., 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 non-compliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided prior to study initiation, in the various functional monitoring plans (including, but not limited to, Quality Tolerance Limit Management Plan and Trial Monitoring Plan).

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Study monitors will perform ongoing monitoring activities as specified in the Trial Monitoring Plan to confirm that data entered on the CRF 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 study is being conducted in accordance with the currently approved protocol and any other study agreements, the ICH Guideline for Good Clinical Practice, and all applicable regulatory requirements.

Records and documents pertaining to the conduct of this study, including signed Informed Consent Forms, must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. 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.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

A1–8 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 on the CRF or entered in the electronic Case Report Form (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 study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the Trial Monitoring Plan.

A1–9 STUDY AND SITE CLOSURE

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

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

Reasons for the early closure of a study 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/EC or local health authorities, the Sponsor's procedures, or the ICH Guideline for Good Clinical Practice
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly

inform the participants and should ensure appropriate participant therapy and/or follow-up.

A1–10 PUBLICATION POLICY

The results of this study 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 study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of results of multicenter studies 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.

A1–11 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on participant safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

Appendix 2
Clinical Safety Laboratory Tests

The tests detailed in Table A2-1 will be performed by the central laboratory.

Local laboratory results are only required in the event that the central laboratory results are not available in time for study treatment administration and/or response evaluation. If a local sample is required, it is important that a sample for central analysis be obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or a response evaluation, the results together with the normal range of the parameters measured must be entered on the electronic Case Report Form.

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

Additional tests may be performed at any time during the study if determined to be necessary by the investigator or if required by local regulations.

Table A2-1 Protocol-Required Safety Laboratory Assessments

Central Laboratory Tests
• Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells) • Chemistry panel (serum): bicarbonate, sodium, potassium, chloride, glucose, BUN or urea, creatinine, CPK, total protein, albumin, phosphorus, calcium, total and direct bilirubin, ALP, ALT, AST, uric acid, and LDH If CPK value exceeds 2× ULN at baseline, creatinine and potassium levels should be monitored at Week 2 • Lipids: total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides • Cardiac biomarkers: hs-cTnT (troponin T) • Coagulation: INR, aPTT, and PT • HIV serology: HIV-1 antibody, HIV-1/2 antibody, and HIV-2 antibody • HBV serology: HBsAg and total HBcAb for all individuals; HBV DNA for individuals with negative HBsAg tests and a positive total HBcAb test • HCV serology: HCV antibody for all individuals • Lipids: cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides • Quantitative immunoglobulins: IgA, IgG, IgM, and IgE • Pregnancy test All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. • Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, and blood). Microscopic examination performed at the central laboratory if blood and/or protein results are positive or strongly positive. If there is an explanation for the positive dipstick results (e.g., menses), it should be recorded and there is no need to perform microscopy and culture.

HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HDL=high-density lipoprotein; hs-cTnT=high-sensitivity cardiac troponin T; LDL=low-density lipoprotein.

Investigators must document their review of each laboratory safety report.

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

TABLE OF CONTENTS

A3–1 DEFINITION OF ADVERSE EVENT

Adverse Event Definition

An adverse event is any untoward medical occurrence in a patient or clinical study participant temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the Adverse Event Definition

The following events meet the definition of adverse event:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, or are considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study treatment administration, even though it may have been present before the start of the study
- Signs, symptoms, or clinical sequelae of a suspected drug–drug interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study treatment or a concomitant medication
- Overdose per se will not be reported as an adverse event or serious adverse event unless it is an intentional overdose taken with possible suicidal or self-harming intent. Such overdoses should be reported regardless of sequelae.
- Lack of efficacy will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Definition of Adverse Event

The following events do not meet the definition of adverse event:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition

- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy)
- The condition that leads to the procedure is the adverse event.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of a preexisting disease or condition present or detected at the start of the study that do not worsen

A3–2 DEFINITION OF SERIOUS ADVERSE EVENT

If an event is not an adverse event per the definition in Section A3–1, it cannot be a serious adverse event even if serious conditions are met (e.g., hospitalization for signs or symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

- Results in death
- 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 that hypothetically might have caused death if it were more severe.

- 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 adverse events. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious.

  Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an adverse event.

- Results in persistent disability or 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 (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or birth defect
- Other situations:

  Medical or scientific judgment should be exercised in deciding whether serious adverse event 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 or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE]; see Section A3–2); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the electronic Case Report Form (eCRF).

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event) (see Section A3–5 for reporting instructions).

A3–3 RECORDING AND FOLLOW-UP OF ADVERSE EVENTS AND/OR SERIOUS ADVERSE EVENTS

A3–3.1 ADVERSE EVENT AND SERIOUS ADVERSE EVENT RECORDING

When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant adverse event or serious adverse event information on the eCRF.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. 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.

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs or symptoms) will be documented as the adverse event or serious adverse event.

A3–3.2 ASSESSMENT OF SEVERITY

The investigator will make an assessment of the severity of each adverse event and serious adverse event during the study and assign it to one of the categories in Table A3-1.

Table A3-1 Adverse Event Severity Grading Scale

Severity	Description
Mild	An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities
Moderate	An event that causes sufficient discomfort and interferes with normal everyday activities
Severe	An event that prevents normal everyday activities An adverse event that is assessed as severe should not be confused with a serious adverse event. Severe is a category utilized for rating the severity of an event, and both adverse events and serious adverse events can be assessed as severe. An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of a serious adverse event, NOT when it is rated as severe.

A3–3.3 ASSESSMENT OF CAUSALITY

The investigator is obligated to assess the relationship between study treatment and each occurrence of each adverse event or serious adverse event.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.

The investigator will also consult the Investigator's Brochure and/or prescribing information (for marketed products) in his or her assessment.

For each adverse event or serious adverse event, the investigator **must** document in the medical notes that he or she has reviewed the adverse event or serious adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data to the Sponsor.

The investigator may change his or her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

A3–3.4 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A3–3.4.1 Investigator 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 to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded in the originally completed CRF.

New or updated information should be recorded on the originally completed Adverse Event eCRF. For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

During the adverse event reporting period (defined in Section 8.3.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification.

A3–3.4.2 Sponsor Follow-Up

For serious adverse events and adverse events of special interest, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

A3–4 REPORTING OF SERIOUS ADVERSE EVENTS

A3–4.1 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA AN ELECTRONIC COLLECTION TOOL

The primary mechanism for reporting a serious adverse event to the Sponsor will be the electronic data collection tool, as described in Section A3–5.

If the electronic system is unavailable, the site will use the paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5, to report the event within 24 hours.

The site will enter the serious adverse event data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken off line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new serious adverse event from a study participant or receives updated data on a previously reported serious adverse event after the electronic data collection tool has been taken off line, the site can report this information on a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5.

A3–4.2 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA PAPER CRF

Under certain circumstances, serious adverse events may be reported to the Sponsor through use of a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5.

A3–5 REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS AND ADVERSE EVENTS OF SPECIAL INTEREST

A3–5.1 EVENTS THAT OCCUR PRIOR TO STUDY TREATMENT INITIATION

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., biopsy, discontinuation of medications) should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators.

A3–5.2 EVENTS THAT OCCUR AFTER STUDY TREATMENT INITIATION

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 14 days after the final dose of study treatment. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after the investigator becomes aware of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur more than 14 days after the final dose of study treatment are provided in Section A3–6.

A3–6 REPORTING ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 14 days after the final dose of study treatment), if the event is believed to be related to prior exposure to study treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special Situations Form, using the fax number or email address provided to investigators.

A3–7 PROCEDURES FOR RECORDING ADVERSE EVENTS

When an adverse event occurs, it is the responsibility of the investigator to review all documentation related to the event (e.g., hospital progress notes, laboratory reports, and diagnostics reports). The investigator will then record all relevant adverse event information on the Adverse Event eCRF. It is not acceptable for the investigator to send photocopies of the participant's medical records to the Medical Monitor in lieu of completion of the eCRF. Investigators should use correct medical terminology and concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations. Only one adverse event term should be recorded in the event field of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. 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.

A3–7.1 DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

A3–7.2 ADVERSE EVENTS THAT ARE SECONDARY TO OTHER EVENTS

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

A3–7.3 PERSISTENT OF RECURRENT ADVERSE EVENTS

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware that the event became serious; see Section A3–5 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between participant evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

A3–7.4 ABNORMAL LABORATORY VALUES

Not every abnormal laboratory value qualifies as an adverse event. A laboratory value abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A laboratory value abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event. Please see Section 8.3.7 for details on adverse events of special interest and associated reporting requirements.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × upper limit of normal (ULN) associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A3–7.3 for details on recording persistent adverse events).

A3–7.5 ABNORMAL VITAL SIGN VALUES

Not every abnormal vital sign value qualifies as an adverse event. A vital sign abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A

vital sign abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (e.g., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A3–7.3 for details on recording persistent adverse events).

A3–7.6 ABNORMAL LIVER FUNCTION TESTS

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$upper limit of normal (ULN) in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section A3–7.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either as a serious adverse event or an adverse event of special interest (see Section A3–5).

A3–7.7 DEATHS

All deaths that occur during the protocol-specified adverse event reporting period (see Section 8.3.1), regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section A3–5).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

A3–7.8 PREEXISTING MEDICAL CONDITIONS

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

A3–7.9 LACK OF EFFICACY OR WORSENING OF POST-TRAUMATIC STRESS DISORDER (PTSD)

Medical occurrences or symptoms of deterioration that are anticipated as part of post-traumatic stress disorder (PTSD) should not be recorded as adverse events. However, deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study should be recorded as an adverse event. When recording an unanticipated worsening of PTSD on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of post-traumatic stress disorder").

A3–7.10 HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section A3–2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The participant was hospitalized for an elective procedure that was planned prior to the study, was scheduled during the study despite the fact that the condition had not worsened, or was scheduled during the study when treatment became necessary because of the expected normal progression of the condition
  - The participant has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of participant requirement for outpatient care outside of normal outpatient clinic operating hours

A3–7.11 CASES OF OVERDOSE, MEDICATION ERROR, DRUG ABUSE, OR DRUG MISUSE

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse} (hereafter collectively referred to as "special situations") are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm}
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the participant, drug misuse could involve the drug being administered to someone other than the participant.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills

seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5). For balovaptan or matching placebo, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with balovaptan / matching placebo, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter balovaptan and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter balovaptan and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter balovaptan and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.

- Intercepted medication error: Enter balovaptan and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter balovaptan and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter balovaptan and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter balovaptan and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter balovaptan and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the participant: Enter balovaptan and "participant supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

A3–7.12 PARTICIPANT-REPORTED OUTCOME DATA

Adverse event reports will not be derived from (participant-reported outcome) PRO data by the Sponsor. Sites are not expected to review the PRO data for adverse events.

Appendix 4
Contraceptive and Barrier Guidance

TABLE OF CONTENTS

A4–1 PREGNANCIES IN FEMALE PARTICIPANTS

Female participants of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 14 days after the final dose of balovaptan. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the pregnancy), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event electronic Case Report Form (eCRF). The investigator should discontinue study treatment and counsel the participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly or birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

A4–2 ABORTIONS

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A4–3 ABNORMAL PREGNANCY OUTCOMES

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomaly, birth defect, ectopic pregnancy) in a female participant exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5).

Appendix 5
Genetics: Use and Analysis of DNA

Genetic variation may impact a participant's response to study treatment and susceptibility to, and severity and progression of, disease. Variable response to study treatment may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and the Institutional Review Board or Ethics Committee allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to balovaptan in post-traumatic stress disorder (PTSD) and related diseases. They may also be used to develop tests or assays, including diagnostic tests related to balovaptan and PTSD. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).

DNA samples will be analyzed for genetic variation that may be associated with disease trajectory, diagnosis, or treatment response. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to balovaptan or study treatments of this class to understand PTSD or related conditions.

The results of genetic analyses may be reported in the Clinical Study Report or in a separate study 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 balovaptan or PTSD continues but no longer than 15 years or other period as per local requirements.

Appendix 6
Safety Plan: Management of Identified and Potential Risks

TABLE OF CONTENTS

Balovaptan is not approved for clinical use in any country for any indication. However, clinical trials in healthy volunteers and participants with autism spectrum disorder (ASD) have not revealed adverse drug reactions considered causally related to the administration of balovaptan. The safety plan for participants in this study is based on potential safety risks related to toxicities observed in animals and hypothetical risks related to the mechanism of action of balovaptan. Please refer to the Balovaptan Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of study participants and minimize hypothetical risks. Eligibility criteria have been designed to exclude individuals at higher risk for toxicities. Participants will undergo comprehensive safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided in the following section.

A6–1 POTENTIAL RISKS ASSOCIATED WITH BALOVAPTAN

A6–1.1 POTENTIAL SEIZURE RISK BASED ON DATA FROM ANIMAL STUDIES

In-life convulsion and epileptiform abnormalities were observed in dogs. At no-observed-adverse-effect level (NOAEL) the balovaptan maximum concentration (C_{max}) based safety margin for electroencephalogram (EEG) effects is approximately 36-fold to the C_{max} for a 10 mg oral dose at steady state.

No convulsions have been noted in rats.

Mechanistically, the blockade of the vasopressin 1a (V1a) receptor may rather not possess pro-convulsive effects given that seizure threshold lowering effects of low-dose vasopressin were reversed by the V1a receptor SR49059 in the pentylenetetrazole paradigm in mice (Javadian et al. 2016).

In clinical trials, EEG recordings from healthy volunteers in Study BP29412, receiving the 50-mg once a day (QD) treatment regimen for 6 days, did not reveal treatment-emergent epileptiform abnormalities.

In clinical trials involving participants with ASD, two adverse events of seizure and one adverse event of abnormal EEG were reported in 2 children and 1 adult. With seizures being a known co-morbidity in ASD, 2 of the subjects were receiving ongoing anti-epileptic treatment and were thought to have subtherapeutic levels of anti-epileptic medication. Please refer to the Balovaptan Investigator's Brochure for further details.

In conclusion, the risk of balovaptan to lower the seizure threshold is considered minimal. Participants with a history of seizures who are well controlled within the

previous 6 months to screening and have not had any changes in anti-convulsive therapy, may be enrolled in this study.

A6–1.2 POTENTIAL RISK OF NEUTROPENIA BASED ON DATA FROM ANIMAL STUDIES

In 13-week toxicology studies in dogs, balovaptan-related hematologic changes were observed starting approximately 4 weeks after the first dose. Analysis of hematologic results in peripheral blood demonstrated a decrease in RBCs, WBCs, platelets, and neutrophils, with the most pronounced changes observed in peripheral neutrophils. The bone marrow of affected dogs, however, did not show hypocellularity but rather normocellularity to hypercellularity. The hematologic abnormalities were reversible after drug discontinuation.

The area under the concentration–time curve (AUC) at the NOAEL for the observed hematological toxicity in the dog provides a margin relative to a 10-mg QD dose in human adults of about 21-fold for the parent molecule, about 4.5-fold for the metabolite 3 (M3), and of about 3.5-fold for the metabolite 2 (M2). M2 is not a major metabolite in dogs and is not considered relevant for this effect.

No hematotoxicity was observed in toxicology studies in rats.

Across clinical trials, 1 subject (Study WP40734) developed a decrease in absolute neutrophil count (ANC) (from approximately 1300/μL at pre-treatment to 500–700/μL) at a dose of 10 mg balovaptan QD for 2 weeks that rapidly recovered after conclusion of the 2-week treatment period. There were no signs of infection and no adverse event relief actions were undertaken, however, the subject was withdrawn from the trial. *Six pediatric participants taking 10 mg or an equivalent dose based on predicted exposure (Study BP30153) experienced events of neutropenia (4 events in 4 participants) and neutrophil count decreased (2 events in 2 participants), of which 4 were moderate and 2 were mild. One participant had neutropenia that was ongoing at the end of the study, however, this was in the context of acute lymphocytic leukemia and Epstein Barr virus infection and was not considered to be associated with balovaptan. One participant recovered despite continuing balovaptan and the remaining 4 recovered after dose interruption or withdrawal. All events occurred after 20 weeks of study therapy and the majority were temporally associated with an infection. Neutropenia is relatively frequent in children, and an association with virus infection is recognized (Callejas Caballero et al. 2021). When the events reported in the other dose groups are considered, a difference in frequency was not seen with comparison to the placebo group (10 mg balovaptan equivalent dose [eq] 2 participants [1.7%], 4 mg balovaptan eq 2 participants [1.2%], placebo 2 participants [1.9%], open-label extension 10 mg balovaptan eq 4 participants [2.0%]).*

There were no events of neutropenia or leukopenia in adult patients with ASD taking 10 mg in Study BP30153.

Please refer to the Balovaptan Investigator's Brochure for further details.

Overall, the available clinical safety database does not suggest a causal neutropenia risk due to balovaptan administration. However, participants receiving concomitant treatment with clozapine will be excluded due to relatively high risk of agranulocytosis. Patients with clinically significant hematologic abnormalities or history of blood dyscrasias, hematologic malignancies, or myelosuppression (including iatrogenic) will be excluded from the study. Safety surveillance in Study BN43546 includes hematological monitoring and check for clinical signs and symptoms of infection.

A6–1.3 POTENTIAL RISK OF SKELETAL MUSCLE TOXICITY

Skeletal muscle degeneration associated with increases in creatine phosphokinase (CPK) was noted after treatment with a high dose of balovaptan in male rats. After treatment completion, these effects promptly reversed. The mechanism of balovaptan effects on skeletal muscle in rats is unclear. In vitro experiments indicate that M3 may play a major role. This is consistent with this finding only being observed in male rats that have higher M3 exposures than female rats. No mitochondrial toxicity or cytotoxicity due to cell-cycle inhibition was demonstrated. Based on AUC values measured at NOAEL, the margins relative to anticipated AUC after 10 mg QD balovaptan in adult humans are approximately 8-fold with regard to parent and approximately 10-fold with regard to M3.

In the literature, the involvement of the V1a receptor to regain muscle integrity after tumor necrosis factor-α exposure has been suggested based on *V1a* receptor gene delivery experiments in mice (Costa et al. 2014). No skeletal muscle effects of balovaptan have been observed in dogs.

In humans, a severe adverse event of rhabdomyolysis was reported in a patient with ASD treated with 1.5 mg QD balovaptan, and occasional CPK elevations were noted in clinical trials. Nevertheless, the totality of clinical data available to date (including analysis of CPK values and musculoskeletal adverse events) does not indicate a safety alert for skeletal muscle toxicity due to balovaptan. This conclusion is based on the observations that CPK elevations were also measured in placebo-treated subjects with ASD and that treatment-emergent CPK elevations decreased when treatment was continued. CPK levels will be monitored during the study drug treatment period and with a defined CPK-related adverse event of special interest.

Please refer to the Balovaptan Investigator's Brochure for additional details.

Overall, the risk of skeletal muscle toxicity for this study is considered minimal given the safety margin relative to NOAEL noted in rats, the absence of skeletal muscle toxicity in dogs, and the clinical trial experience not indicating skeletal muscle toxicity.

In addition to adverse event monitoring, CPK levels will be used to monitor for possible occurrences of skeletal muscle toxicity.

A6–1.4 POTENTIAL RISK OF CARDIAC TOXICITY

In rats dosed from post-natal day (PND) 14 (juvenile to adult), an increase in heart weight was observed at the highest dose tested. The increase in heart weight was considered non-adverse based on the lack of associated creatine phosphokinase (CPK) changes or a histopathological correlate. In the 26-week Good Laboratory Practice (GLP) toxicology study in adult rats, an increased incidence of spontaneous cardiomyopathy changes was observed, but these changes were considered to be non-adverse exacerbations due to stress. Cardiac pathologies were not observed when balovaptan was administered to dogs in GLP toxicology studies.

Intense exploration of interference with cardiac ion channels for balovaptan and its M3 and M2, did not reveal a pre-clinical safety alert for QTc prolongation.

In clinical trials, treatment with balovaptan (10 mg QD) for more than 12 weeks did not produce a cardiac toxicity alert based on clinical adverse event reporting and monitoring with cardiac biomarkers (troponin and N-terminal prohormone of brain natriuretic peptide [NT-proBNP]). Results from a thorough QT study are available (Study WP40734) and confirmed absence of corrected QT interval (QTc) prolonging effects after administration of balovaptan at 10 mg and 50 mg QD dosing regimens.

The risk of cardiac toxicity in Study BN43546 is considered minimal because of the lack of cardiac toxicity in dogs, the delayed onset of cardiac effects in rats (which were considered stress-related rather than direct cardiac effects, and in particular the absence of a safety alert from dedicated cardiac monitoring in clinical trials.

Safety monitoring in Study BN43546 will include *ECG,* adverse event monitoring and assessment of high-sensitivity cardiac troponin T (hs-cTnT) in conjunction with a follow-up plan if elevated hs-cTnT levels are measured.

A6–1.5 POTENTIAL RISK OF PERIPHERAL NEUROPATHY

In the 26-week toxicity study in rats and in two subsequent supplementary 26-week toxicology studies in adult and juvenile rats, test article–related microscopic effects were observed in multiple peripheral nerves (degeneration of the perineurium with edema and cellular infiltrates). The onset of peripheral nerve histopathology effects was seen as early as 13 weeks of treatment, and further progression noted after 26 weeks of

treatment. Changes in peripheral nerve histology were found to be associated with and preceded by electrophysiological abnormalities (i.e., a reduction in nerve conduction velocity (NCV) noted at Week 6, no relevant changes to amplitude in line with dominating pathology of perineurium and myelin sheath rather than axonal loss). The electrophysiogical abnormalities were recorded for sensory and mixed nerves and not for motoric nerves. The histopathologic changes did not fully recover within the 13-week recovery period included in the 26-week GLP toxicology study while the electrophysiological changes did. Of note, across sexes, the emergence of peripheral nerve toxicities does not correlate with parent plasma levels but with the plasma levels of M3. It is unproven whether the peripheral nerve effects seen in rats are caused by the parent or M3 moiety; however, the incidence of the effects are better correlated with M3 levels than with the parent. The M2 is not considered to be the causative agent because of low plasma levels. The margins between the plasma levels at the NOAEL and those after 10-mg QD dose in humans are about 10-fold with regard to parent and about 20-fold *lower* with regard to M3 *for the 10 mg QD balovaptan dose*. In addition to the effects on peripheral nerves, perivascular inflammation in certain regions of the brain was observed in rats; however, the respective safety margins are about 2-fold higher.

No such neurohistopathologies were seen in dogs.

In clinical trials, neurological monitoring (including quantitative vibration testing) did not reveal a signal of treatment-emergent peripheral neuropathy or other neurologic abnormalities. In 1 subject with ASD whose sense of vibration was lost during treatment with 10 mg QD balovaptan, subsequent nerve conduction examinations showed a severe peripheral neuropathy dominated by a decrease in electrostimulus provoked amplitude and a mildly decreased NCV. This signature contrasts with the findings from electrophysiological monitoring of peripheral nerve in rats that showed a slowing in NCV and a maintained amplitude in line with perineurial myelin sheath damage rather than axonal loss histopathologically. Post hoc, this subject reported occasional tingling in the feet that was indicative of preexisting peripheral neuropathy; however, no specific cause for peripheral neuropathy could be identified.

The risk of study treatment linked peripheral neuropathy for participants in this study is considered to be minimal because of the safety margins relative to the NOAEL in rats, no neurohistopathologies have been noted in dogs, and the results from neurological monitoring in clinical trials have not generated a signal for balovaptan caused peripheral neuropathy.

This study excludes participants with signs and symptoms of peripheral neuropathy. Neurologic examinations focusing on the lower limbs (longer nerves being more susceptible to neuropathy) will be completed during the study (see the schedule of

activities in Section 1.3, Table 1). The neurological examination must be conducted as outlined in Appendix 7.

Please refer to the Balovaptan Investigator's Brochure for additional details.

A6–1.6 *POTENTIAL* RISK OF BLEEDING

Theoretically, due to expression of V1a receptors on platelets, antagonism could impact platelet aggregation. Neither animal studies nor clinical studies *of* balovaptan *up to 50 mg for 2 weeks* have shown a bleeding risk.

Selective serotonin reuptake inhibitors (SSRIs) have been shown to possess a bleeding risk, even though fairly small (Dalton et al. 2006; Serebruany 2006). In the ASD clinical trials 156 subjects were receiving concomitant SSRI medications. No bleeding risk events were reported.

Patients with a history of coagulopathies or other bleeding disorders or current clinically relevant bleeding event will be excluded from the study.

Treatment with study drug should be stopped about 1 week prior to surgeries and invasive procedures anticipated to be associated with major blood losses or bleedings in sensitive organs (e.g., eye, brain, and spinal cord).

A6–1.7 *POTENTIAL* RISK OF BLOOD PRESSURE CHANGES

Given the vasoconstrictive effects on systemic resistance blood vessels of vasopressin mediated through the V1a receptor, blockade of this receptor by balovaptan may lead to reductions in blood pressure. However, in a cardiovascular safety pharmacology study conducted in telemetered dogs, an increase in blood pressure was observed with an approximately 19-fold margin between the NOAEL C_{max} for the dog (1917 ng/mL) and the predicted highest average C_{max} for participants in Study BN43546 (103 ng/mL). The physiology behind the blood pressure increase seen in dogs is unknown.

Ambulatory blood pressure monitoring of healthy volunteers was included in clinical Study WP40734 (a thorough QT study), which evaluated both a 10 mg QD and a 50 mg QD treatment regimen *over 2 weeks*. No significant blood pressure changes emerged; in particular, no decrease in blood pressure measurements was observed.

The absence of a decrease in blood pressure may be explained by blood concentrations of vasopressin being too low to meaningfully activate the V1a receptor and/or by the multifactorial blood pressure regulation system in the sense that blockade of the V1a receptor is compensated by alternative regulator pathways.

Nevertheless, participants should be instructed to avoid rapid movements when moving from supine to sitting to standing position. Blood pressure will be monitored at regular intervals during the treatment period.

A6–2 MANAGEMENT OF PARTICIPANTS WHO EXPERIENCE ADVERSE EVENTS

A6–2.1 DOSE MODIFICATIONS

No dose modifications will be allowed in this study.

A6–2.2 TREATMENT INTERRUPTION

Balovaptan may be withheld in participants who experience toxicity considered to be related to study drug. If balovaptan *has been* withheld for >10 days because of toxicity, the participant should be discontinued from study drug, unless resumption of treatment is approved *by the* investigator *following consultation* with the Medical Monitor. Balovaptan may be withheld for reasons other than toxicity (e.g., surgical procedures) *at the investigator's discretion following consultation* with *the* Medical Monitor. The investigator *may consult* the Medical Monitor *to* determine the acceptable length of treatment interruption.

A6–2.3 MANAGEMENT OF SEIZURES

While the risk of seizure/convulsive events due to balovaptan is considered minimal, local treatment guidelines should be followed to manage such events should they occur.

Participants experiencing an adverse event of convulsion should be seen by the relevant physician immediately and as soon as possible, they should be referred to a clinical expert in the area of epilepsy to define diagnostic steps. These may include 24-hour dedicated video EEG monitoring. Collection of blood and urine samples is recommended to measure, as applicable, levels of balovaptan, any anti-eplieptic drugs, drugs of abuse, glucose, and electrolytes (sodium, potassium, chloride, magnesium). If possible, a blood sample for prolactin should be taken within 1 hour since seizure onset. Psychogenic non-epileptic seizures are reported to occur in patients with PTSD (Popkirov et al. 2019; Perez et al. 2016). Vital signs should be monitored and a 12-lead ECG recorded as soon as possible.

Depending on the nature and severity of the convulsive event, it may not result in permanent study treatment discontinuation.

Adverse events of seizure/convulsion should be discussed with the Medical Monitor as soon as possible.

A6–2.4 MANAGEMENT OF NEUTROPENIA

As outlined above, the risk of relevant neutropenia due to balovaptan is considered low.

In case of emergent neutropenia, treatment discontinuation is suggested for participants who meet the following criterion for decreased ANC:

- If the ANC falls <800/μL and the low ANC is confirmed in a second sample to be obtained within about 3 days, the investigator should consider treatment discontinuation. In cases of ANC-related treatment discontinuation, additional laboratory parameters should be considered by the investigator, including fibrinogen, high-sensitivity C-reactive protein (hs-CRP), and an assessment for anti–neutrophil cytoplasmic antibody (ANCA).
- Follow-up management of participants who experience fever and/or infection in the context of reduced ANC should be discussed with the Medical Monitor and the participant may be referred to a specialist to decide on next steps.

ANC values below 800/μL (confirmed), should be reported as an adverse event of special interest (see Appendix 3, Section A3–5).

A6–2.5 MANAGEMENT OF BLEEDING

While the risk of bleeding events due to balovaptan is considered low, should such an event occur, a review of concomitant medications should be undertaken especially those that have known bleeding risks. Based on the clinical significance of the bleeding, treatment with study drug should be interrupted and may be permanently discontinued if no alternative causative factors of the bleeding adverse event can be identified and removed.

Blood samples to assess coagulation parameters (INR, PT, aPTT) as well as balovaptan blood levels should be taken.

A6–2.6 MANAGEMENT OF SKELETAL MUSCLE TOXICITY

Elevated CPK levels at screening and baseline are not exclusions as long as serum creatinine and potassium values do not exceed the upper limit of normal (ULN). In instances where CPK is increased more than 2×ULN at screening, additional CPK, creatinine, and potassium samples should also be obtained at Week 2 of treatment. Samples from screening, baseline, Week 2, and Week 6 can then indicate whether an elevated CPK level observed at screening is part of a fluctuation because of physical exercise, for example, or is indicative of inherently elevated CPK levels in an individual participants. Participants are advised to abstain from intense physical exercise and to report musculoskeletal adverse events to the Investigator promptly.

In the event of reports matching the related adverse events of special interest definition (see Section 8.3.7), participants should be evaluated for use of any concomitant medication as well as occurrence of any recent accidents or physical exercise. In the event that CPK values exceed 10×ULN, confirmatory samples should be obtained within 3–5 days, depending on the actual CPK value and circumstances, for example, whether or not a possible alternative explanation like an accident or sports is present. Serum creatinine and serum potassium levels should be measured at the same time. An ECG recording may provide information about QRS complex changes and arrhythmias potentially related to changes in potassium.

Hydration status should be assessed and intake of fluids is advised. The need for hospitalization and intravenous administration of fluids, respectively, should be considered, depending on the CPK increase and a participant's hydration status. The investigator may decide to temporarily withdraw treatment if no alternative explanation exists and CPK values do not show a trend for normalization according to the half-life of CPK in plasma. Treatment may be re-started once CPK values have shown a clear trend toward normalization and if CPK increases were not associated with relevant kidney dysfunction. CPK levels should be monitored until they are below 2×ULN or in the range of screening and baseline values.

CPK laboratory abnormality as per Section 8.3.7 must be reported as an adverse event of special interest.

CPK values will be assessed at baseline, at Week 6 and Week 12 (see the schedule of activities in Section 1.3 [see Table 1]) as well as at the post-treatment follow-up visit.

A6–2.7 MANAGEMENT OF CARDIAC ADVERSE EVENTS

Increases in the Corrected QT Interval (QTc) Interval

There is no preclinical or clinical evidence that balovaptan administration may be associated with an increase in the QTc interval. Nevertheless, treatment should be discontinued in case of the following:

- Sustained (at least two ECG measurements >30 minutes apart) QT interval corrected through use of Fridericia's formula (QTcF) that is >500 ms and >60 ms longer than the baseline value. In this instance, serum electrolytes, in particular, potassium, and magnesium, as well as use of any concomitant medications should be analyzed as a potential cause of the increase in the QTc interval.

Management of participants with sustained QTc prolongation should include close monitoring, with ECGs repeated until two successive ECGs show resolution of the findings, correction of any electrolyte abnormalities, and possible discontinuation of other concomitant medications that are known to prolong the QTc interval. Consultation with a

cardiologist or an electrophysiologist is recommended to help in the management of such participants.

Signs and Symptoms of Cardiac Toxicity

As outlined above, the risk of cardiac toxicity to participants in this study is considered minimal.

An algorithm relative to results from cardiac troponin T (cTnT) monitoring is provided in Section 7.1.4, Table 5

In all cases of cardio-vascular adverse even reportings and where no clear non-cardiac alternative explanation is identified, a consultation with a cardiologist should be considered with urgency driven by the clinical adverse event and further diagnostics may include, but are not limited to, 24-hour ECG recordings and echocardiographic examinations.

Control of vital signs and by ECG monitoring should be considered relative to clinical adverse event presentation.

Blood samples for cardiac biomarker monitoring (hs-cTnT, troponin I, NT-proBNP) and to measure blood levels of balovaptan together with the information of the time interval since last intake of study medication should be obtained as soon as possible.

A check of all concomitant medications should be performed and documented. In addition, a urine drug screen should be performed.

For further details see Section 7.1.4.

A6–2.8 MANAGEMENT OF BLOOD PRESSURE CHANGES

To date, pre-clinical and clinical profiling for any balovaptan associated blood pressure changes have not issued an alert.

Abnormal blood pressure values together with pulse heart rate should first be verified by repeat measurement ensuring technical conduct.

Circumstances should be carefully evaluated; for example, rapid blood pressure decrease due to rapid body erection, dehydration situations, blood sample draw, or a blood pressure increase caused by hypertension. It is advised to check for concomitant medications and conduct a urine drug screen.

Vital sign monitoring should be supplemented by ECG monitoring.

Participants should be reminded to avoid situations of rapid fluid shift from the upper to the lower part of the body. In context of blood pressure increases, ambulatory blood pressure monitoring (ABPM) may be considered.

In case of persistent blood pressure changes, participants should be seen by a clinical expert in the field of blood pressure regulation.

Depending on the magnitude and clinical relevance of the blood pressure observed, treatment with study drug may be interrupted or even permanently withdrawn. In such situations, blood samples to measure balovaptan levels in blood should be considered.

A6–2.9 MANAGEMENT OF NEUROLOGICAL TOXICITY/PERIPHERAL NEUROPATHY

This study excludes patients with signs and symptoms of peripheral neuropathy. Neurologic examinations (see Appendix 7) will be performed as per the schedule of activities (Section 1.3, Table 1).

Adverse events of neurological abnormalities should be discussed with the Medical Monitor as soon as possible.

Cases of neurological abnormalities emerging from adverse event reporting or neurological examination that are potentially indicative of dysfunction of peripheral nerves or otherwise represent a neurological deficit and for which no other explanation is apparent should be reported as an adverse event of special interest (see Section 8.3.7). For such cases, the investigator is encouraged to seek advice from and have the participant seen by an expert in the field of peripheral neuropathy (neurologist). Furthermore, a NCV exam may be recommended as a follow-up for these adverse events. The investigator must inform the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the data) of all out of range NCV data.

To define pathological values from the NCV examinations, the range of normal values of the investigating electrophysiological laboratory will be used. Repeat measurements may be indicated to describe the NCV over a prolonged period of time, allowing interpretation of the case.

Verified symptoms indicative of peripheral neuropathy should be considered to trigger permanent treatment discontinuation of the participant. Participants are asked to report any signs and symptoms indicative of peripheral neuropathy (e.g., burning, pain, numbness, tingling, impaired motoric skills) to the investigator as soon as possible.

It is also recommended to take blood samples to measure blood levels of balovaptan. Also, biomarkers indicative for alternative causes of emerging neuropathy should be evaluated with neurologist.

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Appendix 7
Structured Brief Interview and Examination for Peripheral Neuropathy

As part of the general neurologic examination, a dedicated neurologic assessment of the lower limbs must be conducted as follows:

Equipment needed:

- Cotton swab or Q-tip®
- Disposable neurological pin
- Tendon hammer
- Metal tuning fork

Ask the study participant:

"Do you have any new numbness, pain, tingling or unusual sensations anywhere on your body, e.g., in your arms, hands, feet, legs, lower back, or buttocks?"

- If yes, ask about the onset, distribution, quality, intensity, and frequency and document on the electronic Case Report Form (eCRF).

"Do you have new weakness in your arms, hands, legs or feet or any changes in how you are walking?"

- If yes, document new symptoms on the eCRF.

Guided examination of the upper limbs: Document any new abnormalities on the eCRF.

Item 1: Sensation

For each location indicated below and on the diagram (see Figure 1), ask the participant to close his or her eyes. Use the top of the sternum as the reference point. Ask the participant if the sensation feels the same, decreased, or increased.

- Distal fifth digit dorsal (n ulnaris); part of dermatome C8 assessed
- Distal third digit dorsal (n medianus): part of dermatome C7 assessed
- Latero-distal thumb (n radialis); part of dermatome C6 assessed

Light Touch

- Touch the Q-tip/cotton swab to each indicated location on each hand.

Pinprick

- Touch the disposable neurologic pin to each indicated location on each hand.

Cold

- Touch the metal tuning fork to each indicated location- on each hand.

Vibration

- Hit the tuning fork and ask the participant if he or she can feel buzzing when it is placed on the sternum.
- Then, hit the tuning fork again and place it on the indicated locations and ask the participant whether he or she can sense the vibration.

Item 2: Power

For each arm, check the power of the participant to perform the following maneuvers against resistance:

- elbow flexion and extension
- thumb abduction

Instructions for elbow flexion:

Myotomes assessed: C5/6 (musculocutaneous and radial nerve) and Muscles assessed: biceps brachii, coracobrachialis, and brachialis

- Ask the patient to flex their elbow: "Put your hands up like a boxer."
- Apply resistance by pulling the forearm whilst stabilizing the shoulder joint: "Don't let me pull your arm away from you."

Instructions for elbow extension:

Myotome assessed: C7 (radial nerve) and muscles assessed: triceps brachii

- With the patient's elbows still in the flexed position, apply resistance by pushing the forearm towards the patient whilst stabilizing the shoulder joint: "Don't let me push your arm towards you."

Instructions for thumb abduction:

Myotome assessed: T1 (median nerve) and muscle assessed: abductor pollicis brevis

- Ask the patient to turn their hand over so their palm is facing upwards and to position their thumb over the midline of the palm. Advise them to keep it in this position whilst you apply downward resistance with your own thumb: "Point your thumbs to the ceiling and don't let me push them down."

Note any new onset weakness (i.e., power less than full strength with maximum effort against resistance).

- Each movement is to be rated as per the scale proposed by the Medical Research Council by the Royal College of Physicians and Surgeons:

0: no muscle function
1: muscle activation without movement
2: move with gravity
3: move (“just”) against gravity
4: good / against resistance, but not normal muscle power
5: normal strength

Guided physical examination of the lower limbs: Document any new abnormalities on the eCRF.

Expose both of the study participant’s legs from the upper thighs downward.

Item 1: Gait

- Observe the study participant’s natural gait.
- Ask the study participant to walk on his or her tiptoes and then on the back of the heels. This will elicit any compensated weakness or dystonia.
- Ask the study participant to walk heel-to-toe in a straight line. This will bring out any uncoordination due to sensory or motor neuropathy or cerebellar signs.

Item 2: Tone and Deep Tendon Reflexes

- Ask the study participant to lie on the examination couch and to relax his or her legs.
- Observe any new signs of deformity, fasciculation, wasting, or atrophic skin changes.
- Asking the participant to remain relaxed, gently roll each leg in laterally and medially. Then support each knee in dorsiflexion with your palm. Gently lift each leg and allow it to fall naturally.
- Put each leg into dorsiflexion at the knee. Use the tendon hammer to tap the patellar tendon to elicit the patellar reflex. Then place the legs flat with the knee and ankle dorsiflexed. Tap the Achilles tendon to elicit the ankle reflex.
- Finally with the leg relaxed, take the plantar surface of each foot in turn and sharply dorsiflex the ankle to check for clonus (sustained clonus of >5 beats is abnormal).
- Grade the reflex response as: No (“0”), little (“+”), moderate (“++”), or strong (“+++”) reaction (patellar and ankle reflexes)
- Check for emerging clonus when plantar surface of foot is dorsiflexed sharply (plantar reflex).
  - Note: sustained clonus of >5 beats is abnorma

Note any abnormalities of tone, hyporeflexia, hyperreflexia, or sustained clonus.

Item 3: Power

For each leg, check the power of the participant to perform the following maneuvers against resistance:

- Hip flexion and extension
- Knee flexion and extension
- Ankle dorsiflexion and plantar flexion

Note any new onset weakness (i.e., power less than full strength with maximum effort against resistance).

- Each movement is to be rated as per the scale proposed by the Medical Research Council by the Royal College of Physicians and Surgeons:

0: no muscle function
1: muscle activation without movement
2: move with gravity
3: move (“just”) against gravity
4: good / against resistance, but not normal muscle power
5: normal strength

Item 4: Sensation

For each dermatome indicated on the diagram (see Figure 2: S1, S2, L2, L4, and L5), ask the participant to close his or her eyes. Use the top of the sternum as the reference point. Ask the participant if the sensation feels the same, decreased, or increased.

Light Touch

- Touch the Q-tip/cotton swab to the sternum and then each indicated dermatome (S1, S2, L2, L4, and L5) on each leg.

Pinprick

- Touch the disposable neurologic pin to the sternum and then each indicated dermatome (S1, S2, L2, L4, and L5) on each leg.

Cold

- Touch the metal tuning fork to the sternum and then each indicated dermatome (S1, S2, L2, L4, and L5)

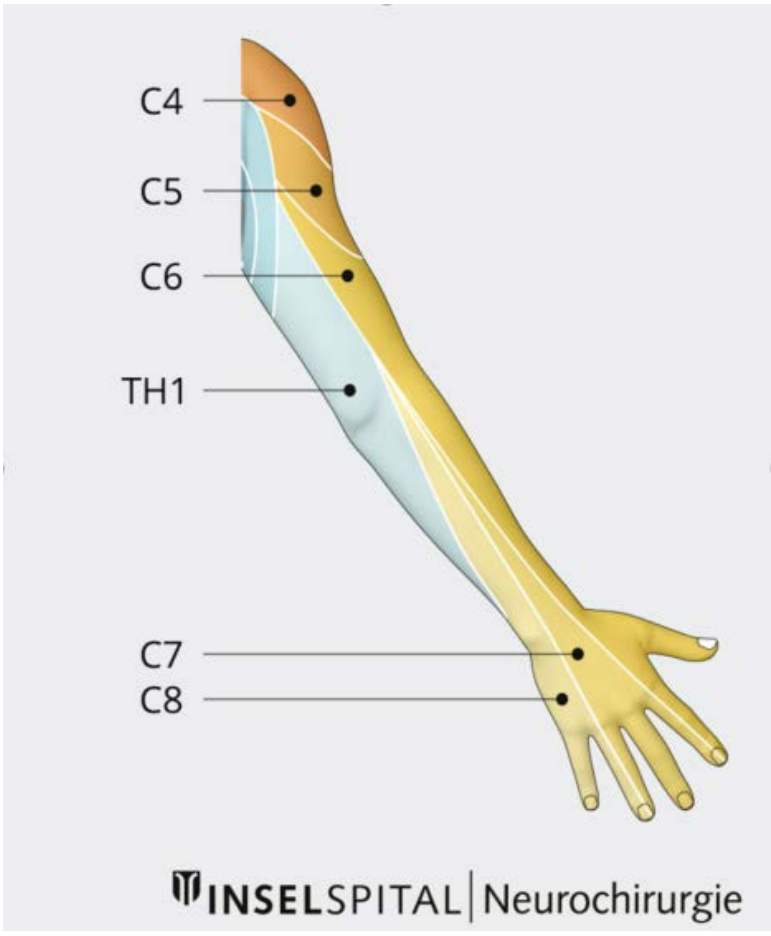
Vibration

- Hit the tuning fork and ask the participant if he or she can feel buzzing when it is placed on the sternum.
- Then, hit the tuning fork again and place it on the dorsum of the interphalangeal joint of the hallux (left/right) and ask the participant whether he can sense the vibration.
- Repeat this on the medial malleolus of each ankle.

Joint Position Sense

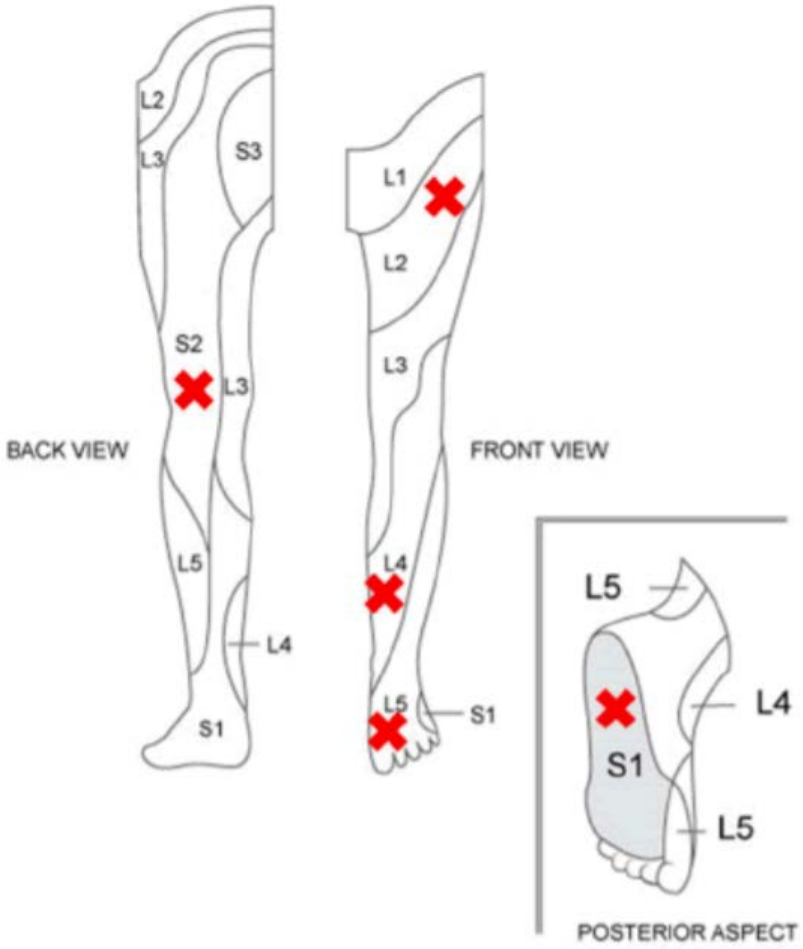
- Ask the participant to keep his or her eyes closed. Hold the big toe at its base. Use your hand to move the toe up or down. Ask the participant to tell you in which direction you are moving the toe. Repeat on the other foot.

Figure 1: Dermatomes of the Upper Limb



Adapted from https://neurochirurgie.insel.ch/erkrankungen-spezialgebiete/wirbelsaeule/bandscheibenvorfall/zervikaler-bandscheibenvorfall

Figure 2: Dermatomes of the Lower Limb



Appendix 8
Child–Pugh Classification

Hepatic impairment will be classified according to the Child-Pugh system (Table A8-1), and the parameters to determine Child-Pugh classification for each participant will be collected at Screening.

Table A8-1 Child–Pugh Classification of Hepatic Function

	Points Scored for Observed Findings		
	1	2	3
Hepatic encephalopathy grade [a]	0	1 or 2 [b]	3 or 4 [b]
Ascites [c]	Absent	Slight	Moderate
Serum bilirubin, mg/dL (μmol/L)	< 2 (< 34)	2 to 3 (34 to 50)	> 3 (> 50)
Serum albumin, g/dL (g/L)	> 3.5 (> 35)	2.8 to 3.5 (28 to 35)	< 2.8 (< 28)
International normalized ratio	< 1.7	1.7 to 2.3	> 2.8

Note: Chronic hepatic impairment is classified into Child-Pugh class A to C, employing the added score of the 5 parameters described above.

Severe impairment (Child-Pugh class C): 10 to 15 points

Moderate impairment (Child-Pugh class B): 7 to 9 points

[a] In this study (BN43546), hepatic encephalopathy will be graded according to the following criteria:

Grade 0: normal consciousness, personality, neurological examination, or normal electroencephalogram.

Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, or 5 cycles per second (cps) waves.

Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, or slow triphasic waves.

Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, or slower waves.

Grade 4: unarousable coma, no personality/behavior, decerebrate, or slow 2 to 3 cps delta activity.

[b] Subjects with hepatic encephalopathy Grade 2 or above will not be enrolled into the study.

[c] Subjects with evidence of severe ascites will not be enrolled into the study. Ascites will be graded according to the following criteria:

Absent: no ascites is detectable by manual examination or by ultrasound investigation (if performed).

Slight: ascites palpitation doubtful, but ascites measurable by ultrasound investigation (if performed).

Moderate: ascites detectable by palpitations and by ultrasound investigation (if performed).

Severe: necessity of paracentesis; does not respond to treatment.

Appendix 9
Questionnaire to Evaluate for Signs and Symptoms Indicative of Infections

The following questionnaire will be used to evaluate signs and symptoms indicative of infection in participants either by telephone interview or in-person between site personnel and the participant at Weeks 4, 6, 9, and 12.

The objective of the questionnaire is to assess fever, infections of pharynx and the respiratory system, and skin given that these are the most prevalent sites of infections in context of agranulocytosis and to provide guidance using a semi-structured interview format.

- Study staff: Introduce yourself and explain the purpose of the interview.

Check for Infections

- "Did you have any episodes of feeling like you were having a "fever" (e.g., fatigue, shivering, "feeling hot")?
- "Did you experience a runny nose, sore throat, or cough since we talked last time?"
- "Did you experience any infections of your skin or in your mouth?"
- "Did you suffer from diarrhea?"
- If yes to any of the above:
  - "Can you describe in more detail the symptoms, when they started, and how long they lasted?"
  - "Did you measure your body temperature at the time of the symptoms and can you remember the date when done?"
  - "Did you visit a health care provider?"
  - "Have the symptoms resolved or are they improving?"
  - "Did you take any medicines (over the counter or prescription)?"

Appendix 10
Examples of Cytochrome P450 3A4 Inducers and Inhibitors

Strong CYP3A4 Inducers	
Apalutamide	Mitotane
Avasimibe	Phenobarbital
Carbamazepine	Phenytoin
Enzalutamide	Rifapentine
Ivosidenib	Rifampin
Lumacaftor	St. John's Wort extract
Moderate CYP3A4 Inducers	
Asunaprevir	Lesinurad
Beclabuvir	Lorlatinib
Bosentan	Modafinil
Cenobamate	Nafcillin
Dabrafenib	Rifabutin
Daclatasvir	Semagacestat
Efavirenz	Talviraline
Elagolix	Telotristat ethyl
Etravirine	Thioridazine
Lersivirine	
Strong CYP3A4 Inhibitors	
Boceprevir	Nefazodone
Ceritinib	Nelfinavir
Clarithromycin	Posaconazole
Cobicistat	Ribociclib
Conivaptan	Ritonavir
Danoprevir	Saquinavir
Elvitegravir	Telaprevir
Idelalisib	Telithromycin
Indinavir	Tipranavir
Itraconazole	Troleandomycin
Ketoconazole	Tucatinib
Lopinavir	VIEKIRA PAK (dasabuvir, ombitasvir, paritaprevir, ritonavir)
Mibefradil	Voriconazole
Mifepristone	

Appendix 10: Examples of Cytochrome P450 3A4 Inducers and Inhibitors

Moderate CYP3A4 Inhibitors	
Amprenavir	Fluconazole
Aprepitant	Grapefruit juice
Atazanavir	Imatinib
Casopitant	Isavuconazole
Cimetidine	Istradefylline
Ciprofloxacin	Lefamulin
Crizotinib	Letermovir
Cyclosporine	Magnolia vine (*Schisandra sphenanthera*)
Darunavir	Netupitant
Diltiazem	Nilotinib
Dronedarone	Ravuconazole
Duvelisib	Tofisopam
Erythromycin	Verapamil
Faldaprevir	Voxelotor
Fedratinib	

CYP3A4 = cytochrome P450 3A4.
Sourced from https://www.druginteractionsolutions.org/.

REFERENCES

Drug Interaction Solutions, University of Washington School of Pharmacy [resource on the internet]. 2020. Available from: https://www.druginteractionsolutions.org/.

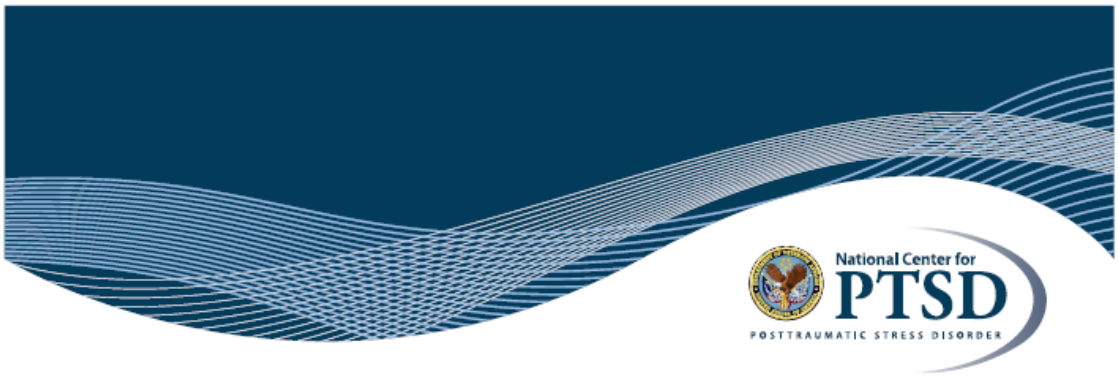
Appendix 11
Clinical Outcome Assessment Instruments

All assessments (except Structured-Clinical Interview for DSM-5 [SCID-5]) will be completed through use of an electronic device. Please note, the assessments shown in this appendix may not be exactly the same as they appear on the electronic device.

TABLE OF CONTENT

A11–1 CLINICIAN-ADMINISTERED PTSD SCALE FOR DSM-5 (CAPS-5)

(Sample; Not to Be Used to Enter Subject Data)



Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5)

Past Week Version

Version date: 16 April 2018

Reference: Weathers, F. W., Blake, D. D., Schnurr, P. P., Kaloupek, D. G., Marx, B. P., & Keane, T. M. (2015). *The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) – Past Week* [Measurement instrument]. Available from https://www.ptsd.va.gov/

URL: https://www.ptsd.va.gov/professional/assessment/adult-int/caps.asp

Note: This is a fillable form. You may complete it electronically.

Name: _____

Interviewer: _____

Study: _____

ID#: _____

Date: _____

CAPS-5 Past Week

The CAPS-5 Past Week instrument assesses PTSD symptoms which have occurred in the past week. This version is best used for determining whether PTSD symptoms have changed over time (e.g., in a treatment study in which you are interested in comparing a participant's PTSD symptoms at baseline versus mid-treatment). It should NOT be used to establish PTSD diagnostic status.

Instructions:

Standard administration and scoring of the CAPS-5 are essential for producing reliable and valid scores and diagnostic decisions. The CAPS-5 should be administered only by qualified interviewers who have formal training in structured clinical interviewing and differential diagnosis, a thorough understanding of the conceptual basis of PTSD and its various symptoms, and detailed knowledge of the features and conventions of the CAPS-5 itself.

Administration

1. Criterion A should already have been evaluated in a prior administration of the PAST MONTH version of the CAPS-5. Thus, for most applications of the PAST WEEK version, Criterion A does not need to be re-evaluated. However, if Criterion A has not been established, to identify an index traumatic event to serve as the basis for symptom inquiry, administer the Life Events Checklist and Criterion A inquiry provided on p. 4 , or use some other structured, evidence-based method. The index event may involve either a single incident (e.g., "the accident") or multiple, closely related incidents (e.g., "the worst parts of your combat experiences").
2. Read prompts verbatim, one at a time, and in the order presented, EXCEPT:
   a. Use the respondent's own words for labeling the index event or describing specific symptoms.
   b. Rephrase standard prompts to acknowledge previously reported information, but return to verbatim phrasing as soon as possible. For example, inquiry for item 20 might begin: "You already mentioned having problem sleeping. What kinds of problems?"
   c. If you don't have sufficient information after exhausting all standard prompts, follow up ad lib. In this situation, repeating the initial prompt often helps refocus the respondent.
   d. As needed, ask for specific examples or direct the respondent to elaborate even when such prompts are not provided explicitly.
3. In general, DO NOT suggest responses. If a respondent has pronounced difficulty understanding a prompt it may be necessary to offer a brief example to clarify and illustrate. However, this should be done rarely and only after the respondent has been given ample opportunity to answer spontaneously.
4. DO NOT read rating scale anchors to the respondent. They are intended only for you, the interviewer, because appropriate use requires clinical judgment and a thorough understanding of CAPS-5 scoring conventions.
5. Move through the interview as efficiently as possible to minimize respondent burden. Some useful strategies:
   a. Be thoroughly familiar with the CAPS-5 so that prompts flow smoothly.
   b. Ask the fewest number of prompts needed to obtain sufficient information to support a valid rating.
   c. Minimize note-taking and write while the respondent is talking to avoid long pauses.
   d. Take charge of the interview. Be respectful but firm in keeping the respondent on task, transitioning between questions, pressing for examples, or pointing out contradictions.

CAPS-5 Past Week

The CAPS-5 Past Week instrument assesses PTSD symptoms which have occurred in the past week. This version is best used for determining whether PTSD symptoms have changed over time (e.g., in a treatment study in which you are interested in comparing a participant's PTSD symptoms at baseline versus mid-treatment). It should NOT be used to establish PTSD diagnostic status.

Instructions:

Standard administration and scoring of the CAPS-5 are essential for producing reliable and valid scores and diagnostic decisions. The CAPS-5 should be administered only by qualified interviewers who have formal training in structured clinical interviewing and differential diagnosis, a thorough understanding of the conceptual basis of PTSD and its various symptoms, and detailed knowledge of the features and conventions of the CAPS-5 itself.

Administration

1. Criterion A should already have been evaluated in a prior administration of the PAST MONTH version of the CAPS-5. Thus, for most applications of the PAST WEEK version, Criterion A does not need to be re-evaluated. However, if Criterion A has not been established, to identify an index traumatic event to serve as the basis for symptom inquiry, administer the Life Events Checklist and Criterion A inquiry provided on p. 4 , or use some other structured, evidence-based method. The index event may involve either a single incident (e.g., "the accident") or multiple, closely related incidents (e.g., "the worst parts of your combat experiences").
2. Read prompts verbatim, one at a time, and in the order presented, EXCEPT:
   a. Use the respondent's own words for labeling the index event or describing specific symptoms.
   b. Rephrase standard prompts to acknowledge previously reported information, but return to verbatim phrasing as soon as possible. For example, inquiry for item 20 might begin: "You already mentioned having problem sleeping. What kinds of problems?"
   c. If you don't have sufficient information after exhausting all standard prompts, follow up ad lib. In this situation, repeating the initial prompt often helps refocus the respondent.
   d. As needed, ask for specific examples or direct the respondent to elaborate even when such prompts are not provided explicitly.
3. In general, DO NOT suggest responses. If a respondent has pronounced difficulty understanding a prompt it may be necessary to offer a brief example to clarify and illustrate. However, this should be done rarely and only after the respondent has been given ample opportunity to answer spontaneously.
4. DO NOT read rating scale anchors to the respondent. They are intended only for you, the interviewer, because appropriate use requires clinical judgment and a thorough understanding of CAPS-5 scoring conventions.
5. Move through the interview as efficiently as possible to minimize respondent burden. Some useful strategies:
   a. Be thoroughly familiar with the CAPS-5 so that prompts flow smoothly.
   b. Ask the fewest number of prompts needed to obtain sufficient information to support a valid rating.
   c. Minimize note-taking and write while the respondent is talking to avoid long pauses.
   d. Take charge of the interview. Be respectful but firm in keeping the respondent on task, transitioning between questions, pressing for examples, or pointing out contradictions.

Scoring

1. As with previous versions of the CAPS, CAPS-5 symptom severity ratings are based on symptom frequency and intensity, except for items 8 (amnesia) and 12 (diminished interest), which are based on amount and intensity. However, CAPS-5 items are rated with a single severity score, in contrast to previous versions of the CAPS which required separate frequency and intensity scores for each item that were either summed to create a symptom severity score or combined in various scoring rules to create a dichotomous (present/absent) symptom score. Thus, on the CAPS-5 the clinician combines information about frequency and intensity before making a single severity rating. Depending on the item, frequency is rated as either the number of occurrences (how often in the past month) or percent of time (how much of the time in the past month). Intensity is rated on a four-point ordinal scale with ratings of *Minimal, Clearly Present, Pronounced*, and *Extreme*. Intensity and severity are related but distinct. Intensity refers to the strength of a typical occurrence of a symptom. Severity refers to the total symptom load over a given time period, and is a combination of intensity and frequency. This is similar to the quantity/frequency assessment approach to alcohol consumption. In general, intensity rating anchors correspond to severity scale anchors described below and should be interpreted and used in the same way, except that severity ratings require joint consideration of intensity and frequency. Thus, before taking frequency into account, an intensity rating of *Minimal* corresponds to a severity rating of *Mild / subthreshold*, Clearly Present corresponds with *Moderate / threshold*, Pronounced corresponds with *Severe / markedly elevated*, and Extreme corresponds with *Extreme / incapacitating*.

2. The five-point CAPS-5 symptom severity rating scale is used for all symptoms. Rating scale anchors should be interpreted and used as follows:

   0 Absent The respondent denied the problem or the respondent's report doesn't fit the *DSM-5* symptom criterion.

   1 Mild / subthreshold The respondent described a problem that is consistent with the symptom criterion but isn't severe enough to be considered clinically significant. The problem doesn't satisfy the *DSM-5* symptom criterion and thus doesn't count toward a PTSD diagnosis.

   2 Moderate / threshold The respondent described a clinically significant problem. The problem satisfies the *DSM-5* symptom criterion and thus counts toward a PTSD diagnosis. The problem would be a target for intervention. This rating requires a minimum frequency of *2 X month* or *some of the time (20-30%)* PLUS a minimum intensity of *Clearly Present*.

   3 Severe / markedly elevated The respondent described a problem that is well above threshold. The problem is difficult to manage and at times overwhelming, and would be a prominent target for intervention. This rating requires a minimum frequency of *2 X week* or *much of the time (50-60%)* PLUS a minimum intensity of *Pronounced*.

   4 Extreme / incapacitating The respondent described a dramatic symptom, far above threshold. The problem is pervasive, unmanageable, and overwhelming, and would be a high-priority target for intervention.

3. Use the scoring grid on the next page to determine the appropriate severity score for each CAPS-5 item. Start on the left side of the grid with the row corresponding to your intensity rating. Then follow the row that corresponds to the reported frequency to determine the severity score. For example, if your intensity rating is *Pronounced*, and the reported frequent is 2 x week, the corresponding severity score would be *Severe / markedly elevated*. However, if your intensity rating is *Pronounced*, but the reported frequency is 10%, then the corresponding severity score would be *Moderate / threshold*.

CAPS-5 Past Week Scoring Rules			
INTENSITY	*FREQUENCY (# of times or %)*		*SEVERITY*
Minimal	*1x/week or more*	*1-100%*	*1 = Mild / subthreshold*
Clearly Present		*1-19%*	*1 = Mild / subthreshold*
	1x/week or more[a]	*20-100%*	*2 = Moderate / threshold*
Pronounced	*1x/week only[a]*	*1-49%*	*2 = Moderate / threshold*
	2x/week or more[b]	*50-100%*	*3 = Severe / markedly elevated*
Extreme	*1x/week only[a]*	*1-19%*	*2 = Moderate / threshold*
	At least 2x/week but not daily/almost every day[b]	*20-79%*	*3 = Severe / markedly elevated*
	Daily/almost every day[c]	*80-100%*	*4 = Extreme / incapacitating*

[a]For D1: 1-2 important parts [b]For D1: several important parts [c]For D1: most/all important parts

4. You need to establish that a symptom not only meets the *DSM-5* criterion phenomenologically, but is also functionally related to the index traumatic event, i.e., started or got worse as a result of the event. CAPS-5 items 1-8 and 10 (reexperiencing, effortful avoidance, amnesia, and blame) are inherently linked to the event. Evaluate the remaining items for trauma-relatedness (TR) using the TR inquiry and rating scale. The three TR ratings are:

   a. ***Definite*** = the symptom can clearly be attributed to the index trauma, because (1) there is an obvious change from the pre-trauma level of functioning and/or (2) the respondent makes the attribution to the index trauma with confidence.

   b. ***Probable*** = the symptom is likely related to the index trauma, but an unequivocal connection can't be made. Situations in which this rating would be given include the following: (1) there seems to be a change from the pre-trauma level of functioning, but it isn't as clear and explicit as it would be for a *Definite*; (2) the respondent attributes a causal link between the symptom and the index trauma, but with less confidence than for a rating of *Definite*; (3) there appears to be a functional relationship between the symptom and inherently trauma-linked symptoms such as reexperiencing symptoms (e.g., numbing or withdrawal increases when reexperiencing increases).

   c. ***Unlikely*** = the symptom can be attributed to a cause other than the index trauma because (1) there is an obvious functional link with this other cause and/or (2) the respondent makes a confident attribution to this other cause and denies a link to the index trauma. Because it can be difficult to rule out a functional link between a symptom and the index trauma, a rating of *Unlikely* should be used only when the available evidence strongly points to a cause other than the index trauma. NOTE: Symptoms with a TR rating of *Unlikely* should not be counted toward a PTSD diagnosis or included in the total CAPS-5 symptom severity score.

5. **CAPS-5 total symptom severity score** is calculated by summing severity scores for items 1-20. NOTE: Severity scores for the two dissociation items (29 and 30) should NOT be included in the calculation of the total CAPS-5 severity score.

6. **CAPS-5 symptom cluster severity scores** are calculated by summing the individual item severity scores for symptoms contained in a given *DSM-5* cluster. Thus, the Criterion B (reexperiencing) severity score is the sum of the individual severity scores for items 1-5; the Criterion C (avoidance) severity score is the sum of items 6 and 7; the Criterion D (negative alterations in cognitions and mood) severity score is the sum of items 8-14; and the Criterion E (hyperarousal) severity score is the sum of items 15-20. A symptom cluster score may also be calculated for dissociation by summing items 29 and 30.

7. **PTSD diagnostic status** should be evaluated with the PAST MONTH version of the CAPS-5. This PAST WEEK version of the CAPS-5 should be used only to evaluate PTSD symptom severity over the past week.

NOTE: This is the PAST WEEK version of the CAPS-5, which should be used only to evaluate PTSD symptom severity over the past week. PTSD diagnostic status should be evaluated with the PAST MONTH version of the CAPS-5.

Criterion A:

Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways:

1. Directly experiencing the traumatic event(s).
2. Witnessing, in person, the event(s) as it occurred to others.
3. Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental.
4. Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains; police officers repeatedly exposed to details of child abuse). Note: Criterion A4 does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related.

NOTE: Criterion A should already have been evaluated in a prior administration of the PAST MONTH version of the CAPS-5. Thus, for most applications of the PAST WEEK version, Criterion A does not need to be re-evaluated.

[Administer Life Events Checklist or other structured trauma screen]

I'm going to ask you about the stressful experiences questionnaire you filled out. First I'll ask you to tell me a little bit about the event you said was the worst for you. Then I'll ask how that event may have affected you over the past week. In general I don't need a lot of information – just enough so I can understand any problems you may have had. Please let me know if you find yourself becoming upset as we go through the questions so we can slow down and talk about it. Also, let me know if you have any questions or don't understand something. Do you have any questions before we start?

The event you said was the worst was (EVENT). What I'd like for you to do is briefly describe what happened.

Index event (specify): _____

What happened? (*How old were you? How were you involved? Who else was involved? Was anyone seriously injured or killed? Was anyone's life in danger? How many times did this happen?*)

Exposure type:

____ Experienced
____ Witnessed
____ Learned about
____ Exposed to aversive details

Life threat?
(NO) (YES) (self ___ other ___)

Serious injury?
(NO) (YES) (self ___ other ___)

Sexual violence?
(NO) (YES) (self ___ other ___)

Criterion A met?
(NO) (PROBABLE) (YES)

For the rest of the interview, I want you to keep (EVENT) in mind as I ask you about different problems it may have caused you. You may have had some of these problems before, but for this interview we're going to focus just on the past week. For each problem I'll ask if you've had it in the past week, and if so, how often and how much it bothered you.

Criterion B:

Presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:

Item 1 (B1): Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s). Note: In children older than 6 years, repetitive play may occur in which themes or aspects of the traumatic event(s) are expressed.

In the past week, have you had any unwanted memories of (EVENT) while you were awake, so not counting dreams? (Rate 0=Absent if only during dreams)

How does it happen that you start remembering (EVENT)?

[If not clear:] (***Are these unwanted memories, or are you thinking about (EVENT) on purpose?***) (Rate 0=Absent unless perceived as involuntary and intrusive)

How much do these memories bother you?

Are you able to put them out of your mind and think about something else?

[If not clear:] (***Overall, how much of a problem is this for you? How so?***)

Circle: Distress = ○ *Minimal* ○ *Clearly Present* ○ *Pronounced* ○ *Extreme*

How often have you had these memories in the past week?
# of times _____

⓪ Absent
① *Mild / subthreshold*
② *Moderate / threshold*
③ *Severe / markedly elevated*
④ *Extreme / incapacitating*

Key rating dimensions = frequency / intensity of distress

Moderate = at least 1 X week / distress clearly present, some difficulty dismissing memories

Severe = at least 2 X week / pronounced distress, considerable difficulty dismissing memories

Item 2 (B2): Recurrent distressing dreams in which the content and/or affect of the dream are related to the event(s). Note: In children, there may be frightening dreams without recognizable content.

In the past week, have you had any <u>unpleasant dreams</u> about (EVENT)?

Describe a typical dream. (*What happens?*)

[If not clear:] (***Do they wake you up?***)

[If yes:] (***What do you experience when you wake up? How long does it take you to get back to sleep?***)

[If reports not returning to sleep:] (***How much sleep do you lose?***)

How much do these dreams bother you?

<u>Circle:</u> Distress = ○ *Minimal* ○ *Clearly Present* ○ *Pronounced* ○ *Extreme*

How often have you had these dreams in the past week? # of times _____

0 *Absent*
1 *Mild / subthreshold*
2 *Moderate / threshold*
3 *Severe / markedly elevated*
4 *Extreme / incapacitating*

Key rating dimensions = frequency / intensity of distress

Moderate = at least 1 X week / distress clearly present, less than 1 hour sleep loss

Severe = at least 2 X week / pronounced distress, more than 1 hour sleep loss

Item 3 (B3): Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.) Note: In children, trauma-specific reenactment may occur in play.

In the past week, have there been times when you <u>suddenly acted</u> or <u>felt</u> as if (EVENT) were <u>actually happening</u> again?

[If not clear:] (***This is different than thinking about it or dreaming about it – now I'm asking about flashbacks, when you feel like you're actually back at the time of (EVENT), actually reliving it.***)

How much does it seem as if (EVENT) were happening again? (*Are you confused about where you actually are?*)

What do you do while this is happening? (*Do other people notice your behavior? What do they say?*)

How long does it last?

<u>Circle:</u> Dissociation = ○ *Minimal* ○ *Clearly Present* ○ *Pronounced* ○ *Extreme*

How often has this happened in the past week? # of times _____

0 *Absent*
1 *Mild / subthreshold*
2 *Moderate / threshold*
3 *Severe / markedly elevated*
4 *Extreme / incapacitating*

Key rating dimensions = frequency / intensity of dissociation

Moderate = at least 1 X week / dissociative quality clearly present, may retain some awareness of surroundings but relives event in a manner clearly distinct from thoughts and memories

Severe = at least 2 X week / pronounced dissociative quality, reports vivid reliving, e.g., with images, sounds, smells

Item 4 (B4): Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

In the past week, have you gotten emotionally upset when something reminded you of (EVENT)?

What kinds of reminders make you upset?

How much do these reminders bother you?

Are you able to calm yourself down when this happens? (*How long does it take?*)

[If not clear:] (***Overall, how much of a problem is this for you? How so?***)

Circle: Distress = ○ *Minimal* ○ *Clearly Present* ○ *Pronounced* ○ *Extreme*

How often has this happened in the past week? # of times _____

(0) *Absent*
(1) *Mild / subthreshold*
(2) *Moderate / threshold*
(3) *Severe / markedly elevated*
(4) *Extreme / incapacitating*

Key rating dimensions = frequency / intensity of distress

Moderate = at least 1 X week / distress clearly present, some difficulty recovering

Severe = at least 2 X week / pronounced distress, considerable difficulty recovering

Item 5 (B5): Marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

In the past week, have you had any physical reactions when something reminded you of (EVENT)?

Can you give me some examples? (*Does your heart race or your breathing change? What about sweating or feeling really tense or shaky?*)

What kinds of reminders trigger these reactions?

How long does it take you to recover?

Circle: Physiological reactivity = ○ *Minimal* ○ *Clearly Present* ○ *Pronounced* ○ *Extreme*

How often has this happened in the past week? # of times _____

(0) *Absent*
(1) *Mild / subthreshold*
(2) *Moderate / threshold*
(3) *Severe / markedly elevated*
(4) *Extreme / incapacitating*

Key rating dimensions = frequency / intensity of physiological arousal

Moderate = at least 1 X week/ reactivity clearly present, some difficulty recovering

Severe = at least 2 X week / pronounced reactivity, sustained arousal, considerable difficulty recovering

Item 4 (B4): Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

In the past week, have you gotten <u>emotionally upset</u> when <u>something reminded you</u> of (EVENT)?

What kinds of reminders make you upset?

How much do these reminders bother you?

Are you able to calm yourself down when this happens? (*How long does it take?*)

[If not clear:] (***Overall, how much of a problem is this for you? How so?***)

<u>Circle:</u> Distress = ○ *Minimal* ○ *Clearly Present* ○ *Pronounced* ○ *Extreme*

How often has this happened in the past week? # of times _____

⓪ *Absent*
① *Mild / subthreshold*
② *Moderate / threshold*
③ *Severe / markedly elevated*
④ *Extreme / incapacitating*

Key rating dimensions = frequency / intensity of distress

Moderate = at least 1 X week / distress clearly present, some difficulty recovering

Severe = at least 2 X week / pronounced distress, considerable difficulty recovering

Item 5 (B5): Marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

In the past week, have you had any <u>physical reactions</u> when <u>something reminded you</u> of (EVENT)?

Can you give me some examples? (*Does your heart race or your breathing change? What about sweating or feeling really tense or shaky?*)

What kinds of reminders trigger these reactions?

How long does it take you to recover?

<u>Circle:</u> Physiological reactivity = ○ *Minimal* ○ *Clearly Present* ○ *Pronounced* ○ *Extreme*

How often has this happened in the past week? # of times _____

⓪ *Absent*
① *Mild / subthreshold*
② *Moderate / threshold*
③ *Severe / markedly elevated*
④ *Extreme / incapacitating*

Key rating dimensions = frequency / intensity of physiological arousal

Moderate = at least 1 X week/ reactivity clearly present, some difficulty recovering

Severe = at least 2 X week / pronounced reactivity, sustained arousal, considerable difficulty recovering

Criterion C:

Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following:

Item 6 (C1): Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).

In the past week, have you tried to avoid thoughts or feelings about (EVENT)?

What kinds of thoughts or feelings do you avoid?

How hard do you try to avoid these thoughts or feelings? (*What kinds of things do you do?*)

[If not clear:] (***Overall, how much of a problem is this for you? How would things be different if you didn't have to avoid these thoughts or feelings?***)

Circle: Avoidance = ○ *Minimal* ○ *Clearly Present* ○ *Pronounced* ○ *Extreme*

How often in the past week? # of times _____

0 *Absent*
1 *Mild / subthreshold*
2 *Moderate / threshold*
3 *Severe / markedly elevated*
4 *Extreme / incapacitating*

Key rating dimensions = frequency / intensity of avoidance

Moderate = at least 1 X week / avoidance clearly present

Severe = at least 2 X week / pronounced avoidance

Item 7 (C2): Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).

In the past week, have you tried to avoid things that remind you of (EVENT), like certain people, places, or situations?

What kinds of things do you avoid?

How much effort do you make to avoid these reminders? (*Do you have to make a plan or change your activities to avoid them?*)

[If not clear:] (***Overall, how much of a problem is this for you? How would things be different if you didn't have to avoid these reminders?***)

Circle: Avoidance = ○ *Minimal* ○ *Clearly Present* ○ *Pronounced* ○ *Extreme*

How often in the past week? # of times _____

0 *Absent*
1 *Mild / subthreshold*
2 *Moderate / threshold*
3 *Severe / markedly elevated*
4 *Extreme / incapacitating*

Key rating dimensions = frequency / intensity of avoidance

Moderate = at least 1 X week / avoidance clearly present

Severe = at least 2 X week / pronounced avoidance

Criterion D:

Negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:

Item 8 (D1): Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs).

In the past week, have you had difficulty remembering some important parts of (EVENT)? (*Do you feel there are gaps in your memory of (EVENT)?*)

What parts have you had difficulty remembering?

Do you feel you should be able to remember these things?

[If not clear:] (***Why do you think you can't? Did you have a head injury during (EVENT)? Were you knocked unconscious? Were you intoxicated from alcohol or drugs?***) (Rate 0=Absent if due to head injury or loss of consciousness or intoxication during event)

[If still not clear:] (***Is this just normal forgetting? Or do you think you may have blocked it out because it would be too painful to remember?***) (Rate 0=Absent if due only to normal forgetting)

Circle: Difficulty remembering = ○ *Minimal* ○ *Clearly Present* ○ *Pronounced* ○ *Extreme*

In the past week, how many of the important parts of (EVENT) have you had difficu y remembering? (*What parts do you still remember?*)

# of important aspects _____

Would you be able to recall these things if you tried?

(0) *Absent*

(1) *Mild / subthreshold*

(2) *Moderate / threshold*

(3) *Severe / markedly elevated*

(4) *Extreme / incapacitating*

Key rating dimensions = amount of event not recalled / intensity of inability to recall

Moderate = at least one important aspect / difficulty remembering clearly present, some recall possible with effort

Severe = several important aspects / pronounced difficulty remembering, little recall even with effort

Item 9 (D2): Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., "I am bad,""No one can be trusted,""The world is completely dangerous,""My whole nervous system is permanently ruined").

In the past week, have you had strong negative beliefs about yourself, other people, or the world?

Can you give me some examples? (*What about believing things like "I am bad," "there is something seriously wrong with me," "no one can be trusted," "the world is completely dangerous"?*)

How strong are these beliefs? (*How convinced are you that these beliefs are actually true? Can you see other ways of thinking about it?*)

Circle: Conviction = ○ *Minimal* ○ *Clearly Present* ○ *Pronounced* ○ *Extreme*

How much of the time in the past week have you felt that way, as a percentage? % of time _____

Did these beliefs start or get worse after (EVENT)? (*Do you think they're related to (EVENT)? How so?*) Circle: Trauma-relatedness = ○ *Definite* ○ *Probable* ○ *Unlikely*

0 *Absent*
1 *Mild / subthreshold*
2 *Moderate / threshold*
3 *Severe / markedly elevated*
4 *Extreme / incapacitating*

Key rating dimensions = frequency / intensity of beliefs

Moderate = some of the time (20-30%) / exaggerated negative expectations clearly present, some difficulty considering more realistic beliefs

Severe = much of the time (50-60%) / pronounced exaggerated negative expectations, considerable difficulty considering more realistic beliefs

Item 10 (D3): Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.

In the past week, have you blamed yourself for (EVENT) or what happened as a result of it? Tell me more about that. (*In what sense do you see yourself as having caused (EVENT)? Is it because of something you did? Or something you think you should have done but didn't? Is it because of something about you in general?*)

What about blaming someone else for (EVENT) or what happened as a result of it? Tell me more about that. (*In what sense do you see (OTHERS) as having caused (EVENT)? Is it because of something they did? Or something you think they should have done but didn't?*)

How much do you blame (YOURSELF OR OTHERS)?

How convinced are you that (YOU OR OTHERS) are truly to blame for what happened? (*Do other people agree with you? Can you see other ways of thinking about it?*)

(Rate 0=Absent if only blames perpetrator, i.e., someone who deliberately caused the event and intended harm)

Circle: Conviction = ○ *Minimal* ○ *Clearly Present* ○ *Pronounced* ○ *Extreme*

How much of the time in the past week have you felt that way, as a percentage? % of time _____

0 *Absent*
1 *Mild / subthreshold*
2 *Moderate / threshold*
3 *Severe / markedly elevated*
4 *Extreme / incapacitating*

Key rating dimensions = frequency / intensity of blame

Moderate = some of the time (20-30%) / distorted blame clearly present, some difficulty considering more realistic beliefs

Severe = much of the time (50-60%) / pronounced distorted blame, considerable difficulty considering more realistic beliefs

Item 11 (D4): Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame).

In the past week, have you had any strong negative feelings such as fear, horror, anger, guilt, or shame?

Can you give me some examples? (*What negative feelings do you experience?*)

How strong are these negative feelings?

How well are you able to manage them?

[If not clear:] (***Overall, how much of a problem is this for you? How so?***)

Circle: Negative emotions = ◯ *Minimal* ◯ *Clearly Present* ◯ *Pronounced* ◯ *Extreme*

How much of the time in the past week have you felt that way, as a percentage? % of time _____

Did these negative feelings start or get worse after (EVENT)? (*Do you think they're related to (EVENT)? How so?*)

Circle: Trauma-relatedness = ◯ *Definite* ◯ *Probable* ◯ *Unlikely*

0 *Absent*
1 *Mild / subthreshold*
2 *Moderate / threshold*
3 *Severe / markedly elevated*
4 *Extreme / incapacitating*

Key rating dimensions = frequency / intensity of negative emotions

Moderate = some of the time (20-30%) / negative emotions clearly present, some difficulty managing

Severe = much of the time (50-60%) / pronounced negative emotions, considerable difficulty managing

Item 12 (D5): Markedly diminished interest or participation in significant activities.

In the past week, have you been less interested in activities that you used to enjoy?

What kinds of things have you lost interest in or don't do as much as you used to? (*Anything else?*)

Why is that? (Rate 0=Absent if diminished participation is due to lack of opportunity, physical inability, or developmentally appropriate change in preferred activities)

How strong is your loss of interest? (*Would you still enjoy (ACTIVITIES) once you got started?*)

Circle: Loss of interest = ◯ *Minimal* ◯ *Clearly Present* ◯ *Pronounced* ◯ *Extreme*

Overall, in the past week, how many of your usual activities have you been less interested in, as a percentage? % of activities _____

What kinds of things do you still enjoy doing?

Did this loss of interest start or get worse after (EVENT)? (*Do you think it's related to (EVENT)? How so?*)

Circle: Trauma-relatedness = ◯ *Definite* ◯ *Probable* ◯ *Unlikely*

0 *Absent*
1 *Mild / subthreshold*
2 *Moderate / threshold*
3 *Severe / markedly elevated*
4 *Extreme / incapacitating*

Key rating dimensions = percent of activities affected / intensity of loss of interest

Moderate = some activities (20-30%) / loss of interest clearly present but still has some enjoyment of activities

Severe = many activities (50-60%) / pronounced loss of interest, little interest or participation in activities

Item 13 (D6): Feelings of detachment or estrangement from others.

In the past week, have you felt distant or cut off from other people?

Tell me more about that.

How strong are your feelings of being distant or cut off from others? (*Who do you feel closest to? How many people do you feel comfortable talking with about personal things?*)

Circle: Detachment or estrangement =
○ *Minimal* ○ *Clearly Present* ○ *Pronounced* ○ *Extreme*

How much of the time in the past week have you felt that way, as a percentage? % of time ____

Did this feeling of being distant or cut off start or get worse after (EVENT)? (*Do you think it's related to (EVENT)? How so?*)
Circle: Trauma-relatedness = ○ *Definite* ○ *Probable* ○ *Unlikely*

0 *Absent*
1 *Mild / subthreshold*
2 *Moderate / threshold*
3 *Severe / markedly elevated*
4 *Extreme / incapacitating*

Key rating dimensions = frequency / intensity of detachment or estrangement

Moderate = some of the time (20-30%) / feelings of detachment clearly present but still feels some interpersonal connection

Severe = much of the time (50-60%) / pronounced feelings of detachment or estrangement from most people, may feel close to only one or two people

Item 14 (D7): Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings).

In the past week, have there been times when you had difficulty experiencing positive feelings like love or happiness?

Tell me more about that. (*What feelings are difficult to experience?*)

How much difficulty do you have experiencing positive feelings? (*Are you still able to experience any positive feelings?*)

Circle: Reduction of positive emotions =
○ *Minimal* ○ *Clearly Present* ○ *Pronounced* ○ *Extreme*

How much of the time in the past week have you felt that way, as a percentage? % of time ____

Did this trouble experiencing positive feelings start or get worse after (EVENT)? (*Do you think it's related to (EVENT)? How so?*)
Circle: Trauma-relatedness = ○ *Definite* ○ *Probable* ○ *Unlikely*

0 *Absent*
1 *Mild / subthreshold*
2 *Moderate / threshold*
3 *Severe / markedly elevated*
4 *Extreme / incapacitating*

Key rating dimensions = frequency / intensity of reduction in positive emotions

Moderate = some of the time (20-30%) / reduction of positive emotional experience clearly present but still able to experience some positive emotions

Severe = much of the time (50-60%) / pronounced reduction of experience across range of positive emotions

Criterion E:

Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:

Item 15 (E1): Irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects.

In the past week, have there been times when you felt especially irritable or angry and showed it in your behavior?

Can you give me some examples? (*How do you show it? Do you raise your voice or yell? Throw or hit things? Push or hit other people?*)

Circle: Aggression = ○ *Minimal* ○ *Clearly Present* ○ *Pronounced* ○ *Extreme*

How often in the past week? # of times _____

Did this behavior start or get worse after (EVENT)? (*Do you think it's related to (EVENT)? How so?*) Circle: Trauma-relatedness = ○ *Definite* ○ *Probable* ○ *Unlikely*

0 *Absent*
1 *Mild / subthreshold*
2 *Moderate / threshold*
3 *Severe / markedly elevated*
4 *Extreme / incapacitating*

Key rating dimensions = frequency / intensity of aggressive behavior

Moderate = at least 1 X week / aggression clearly present, primarily verbal

Severe = at least 2 X week / pronounced aggression, at least some physical aggression

Item 16 (E2): Reckless or self-destructive behavior.

In the past week, have there been times when you were taking more risks or doing things that might have caused you harm?

Can you give me some examples?

How much of a risk do you take? (*How dangerous are these behaviors? Were you injured or harmed in some way?*)

Circle: Risk = ○ *Minimal* ○ *Clearly Present* ○ *Pronounced* ○ *Extreme*

How often have you taken these kinds of risks in the past week?
# of times _____

Did this behavior start or get worse after (EVENT)? (Do you think it's related to (EVENT)? How so?) Circle: Trauma-relatedness = ○ *Definite* ○ *Probable* ○ *Unlikely*

0 *Absent*
1 *Mild / subthreshold*
2 *Moderate / threshold*
3 *Severe / markedly elevated*
4 *Extreme / incapacitating*

Key rating dimensions = frequency / degree of risk

Moderate = at least 1 X week / risk clearly present, may have been harmed

Severe = at least 2 X week / pronounced risk, actual harm or high probability of harm

Item 17 (E3): Hypervigilance.

In the past week, have you been especially alert or watchful, even when there was no specific threat or danger? (*Have you felt as if you had to be on guard?*)

Can you give me some examples? (*What kinds of things do you do when you're alert or watchful?*)

[If not clear:] (***What causes you to react this way? Do you feel like you're in danger or threatened in some way? Do you feel that way more than most people would in the same situation?***)

Circle: Hypervigilance = ○ *Minimal* ○ *Clearly Present* ○ *Pronounced* ○ *Extreme*

How much of the time in the past week have you felt that way, as a percentage? % of time _____

Did being especially alert or watchful start or get worse after (EVENT)? (*Do you think it's related to (EVENT)? How so?*)

Circle: Trauma-relatedness = ○ *Definite* ○ *Probable* ○ *Unlikely*

0 *Absent*
1 *Mild / subthreshold*
2 *Moderate / threshold*
3 *Severe / markedly elevated*
4 *Extreme / incapacitating*

Key rating dimensions = frequency / intensity of hypervigilance

Moderate = some of the time (20-30%) / hypervigilance clearly present, e.g., watchful in public, heightened awareness of threat

Severe = much of the time (50-60%) / pronounced hypervigilance, e.g., scans environment for danger, may have safety rituals, exaggerated concern for safety of self/family/ home

Item 18 (E4): Exaggerated startle response.

In the past week, have you had any strong startle reactions?

What kinds of things made you startle?

How strong are these startle reactions? (*How strong are they compared to how most people would respond? Do you do anything other people would notice?*)

How long does it take you to recover?

Circle: Startle = ○ *Minimal* ○ *Clearly Present* ○ *Pronounced* ○ *Extreme*

How often has this happened in the past week? # of times _____

Did these startle reactions start or get worse after (EVENT)? (*Do you think it's related to (EVENT)? How so?*)

Circle: Trauma-relatedness = ○ *Definite* ○ *Probable* ○ *Unlikely*

0 *Absent*
1 *Mild / subthreshold*
2 *Moderate / threshold*
3 *Severe / markedly elevated*
4 *Extreme / incapacitating*

Key rating dimensions = frequency / intensity of startle

Moderate = at least 1 X week / startle clearly present, some difficulty recovering

Severe = at least 2 X week / pronounced startle, sustained arousal, considerable difficulty recovering

Item 19 (E5): Problems with concentration.

In the past week, have you had any problems with concentration?

Can you give me some examples?

Are you able to concentrate if you really try?

[If not clear:] ***(Overall, how much of a problem is this for you? How would things be different if you didn't have problems with concentration?)***

Circle: Problem concentrating = ○ *Minimal* ○ *Clearly Present* ○ *Pronounced* ○ *Extreme*

How much of the time in the past week have you had problems with concentration, as a percentage? % of time ____

Did these problems with concentration start or get worse after (EVENT)? *(Do you think they're related to (EVENT)? How so?)*

Circle: Trauma-relatedness = ○ *Definite* ○ *Probable* ○ *Unlikely*

⓪ *Absent*

① *Mild / subthreshold*

② *Moderate / threshold*

③ *Severe / markedly elevated*

④ *Extreme / incapacitating*

Key rating dimensions = frequency / intensity of concentration problems

Moderate = some of the time (20-30%) / problem concentrating clearly present, some difficulty but can concentrate with effort

Severe = much of the time (50-60%) / pronounced problem concentrating, considerable difficulty even with effort

Item 20 (E6): Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep).

In the past week, have you had any problems falling or staying asleep?

What kinds of problems? *(How long does it take you to fall asleep? How often do you wake up in the night? Do you wake up earlier than you want to?)*

How many total hours do you sleep each night?

How many hours do you think you should be sleeping?

Circle: Problem sleeping = ○ *Minimal* ○ *Clearly Present* ○ *Pronounced* ○ *Extreme*

How often in the past week have you had these sleep problems?
# of times ____

Did these sleep problems start or get worse after (EVENT)? *(Do you think they're related to (EVENT)? How so?)*

Circle: Trauma-relatedness = ○ *Definite* ○ *Probable* ○ *Unlikely*

⓪ *Absent*

① *Mild / subthreshold*

② *Moderate / threshold*

③ *Severe / markedly elevated*

④ *Extreme / incapacitating*

Key rating dimensions = frequency / intensity of sleep problems

Moderate = at least 1 X week / sleep disturbance clearly present, clearly longer latency or clear difficulty staying asleep, 30-90 minutes loss of sleep

Severe = at least 2 X week / pronounced sleep disturbance, considerably longer latency or marked difficulty staying asleep, 90 min to 3 hrs loss of sleep

Criterion F: -

Duration of the disturbance (Criteria B, C, D, and E) is more than 1 month.

NOTE: Items 21 and 22 are not applicable for the PAST WEEK version. They are listed here without prompts only to maintain correspondence with item numbering on the PAST MONTH version. Onset and duration of symptoms should be assessed with

Item 21: Onset of symptoms.

Item 22: Duration of symptoms.

Criterion G:

The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Item 23: Subjective distress.

Overall, in the past week, how much have you been bothered by these (PTSD SYMPTOMS) you've told me about? [Consider distress reported on earlier items]	0 *None* 1 *Mild, minimal distress* 2 *Moderate, distress clearly present but still manageable* 3 *Severe, considerable distress* 4 *Extreme, incapacitating distress*

Item 24: Impairment in social functioning.

In the past week, have these (PTSD SYMPTOMS) affected your relationships with other people? How so? [Consider impairment in social functioning reported on earlier items]	0 *No adverse impact* 1 *Mild impact, minimal impairment in social functioning* 2 *Moderate impact, definite impairment but many aspects of social functioning still intact* 3 *Severe impact, marked impairment, few aspects of social functioning still intact* 4 *Extreme impact, little or no social functioning*

Item 25: Impairment in occupational or other important area of functioning.

[If not clear:] **Are you working now?** [If yes:] **In the past week, have these (PTSD SYMPTOMS) affected your work or your ability to work? How so?** [If no:] **Why is that?** (*Do you feel that your (PTSD SYMPTOMS) are related to you not working now? How so?*) [If unable to work because of PTSD symptoms, rate at least 3=Severe. If unemployment is not due to PTSD symptoms, or if the link is not clear, base rating only on impairment in other important areas of functioning] **Have these (PTSD SYMPTOMS) affected any other important part of your life?** [As appropriate, suggest examples such as parenting, housework, schoolwork, volunteer work, etc.] **How so?**	0 *No adverse impact* 1 *Mild impact, minimal impairment in occupational/ other important functioning* 2 *Moderate impact, definite impairment but many aspects of occupational/other important functioning still intact* 3 *Severe impact, marked impairment, few aspects of occupational/other important functioning still intact* 4 *Extreme impact, little or no occupational/other important functioning*

Global Ratings

Item 26: Global validity.

Estimate the overall validity of responses. Consider factors such as compliance with the interview, mental status (e.g., problems with concentration, comprehension of items, dissociation), and evidence of efforts to exaggerate or minimize symptoms.	0 *Excellent, no reason to suspect invalid responses* 1 *Good, factors present that may adversely affect validity* 2 *Fair, factors present that definitely reduce validity* 3 *Poor, substantially reduced validity* 4 *Invalid responses, severely impaired mental status or possible deliberate "faking bad" or "faking good"*

Item 27: Global severity.

Estimate the overall severity of PTSD symptoms. Consider degree of subjective distress, degree of functional impairment, observations of behaviors in interview, and judgment regarding reporting style.	0 *No clinically significant symptoms, no distress and no functional impairment* 1 *Mild, minimal distress or functional impairment* 2 *Moderate, definite distress or functional impairment but functions satisfactorily with effort* 3 *Severe, considerable distress or functional impairment, limited functioning even with effort* 4 *Extreme, marked distress or marked impairment in two or more major areas of functioning*

Item 28: Global improvement.

Rate total overall improvement since the previous rating. Rate the degree of change, whether or not, in your judgment, it is due to treatment.	⓪ *Asymptomatic* ① *Considerable improvement* ② *Moderate improvement* ③ *Slight improvement* ④ *No improvement* ⑤ *Insufficient information*

Specify whether with dissociative symptoms: The individual's symptoms meet the criteria for posttraumatic stress disorder, and in addition, in response to the stressor, the individual experiences persistent or recurrent symptoms of either of the following:

Item 29 (1): Depersonalization: Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one's mental processes or body (e.g., feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).

In the past week, have there been times when you felt as if you were separated from yourself, like you were watching yourself from the outside or observing your thoughts and feelings as if you were another person? [If no:] (***What about feeling as if you were in a dream, even though you were awake? Feeling as if something about you wasn't real? Feeling as if time was moving more slowly?***) **Tell me more about that.** **How strong is this feeling?** (*Do you lose track of where you actually are or what's actually going on?*) **What do you do while this is happening?** (*Do other people notice your behavior? What do they say?*) **How long does it last?** Circle: Dissociation = ○ *Minimal* ○ *Clearly Present* ○ *Pronounced* ○ *Extreme* [If not clear:] (***Was this due to the effects of alcohol or drugs? What about a medical condition like seizures?***) [Rate 0=Absent if due to the effects of a substance or another medical condition] **How often has this happened in the past week?** # of times _____ **Did this feeling start or get worse after (EVENT)?** (*Do you think it's related to (EVENT)? How so?*) Circle: Trauma-relatedness = ○ *Definite* ○ *Probable* ○ *Unlikely*	⓪ *Absent* ① *Mild / subthreshold* ② *Moderate / threshold* ③ *Severe / markedly elevated* ④ *Extreme / incapacitating* ***Key rating dimensions = frequency / intensity of dissociation*** **Moderate** = at least 1 X week / dissociative quality clearly present but transient, retains some realistic sense of self and awareness of environment **Severe** = at least 2 X week / pronounced dissociative quality, marked sense of detachment and unreality

Item 30 (2): Derealization: Persistent or recurrent experiences of unreality of surroundings (e.g., the world around the individual is experienced as unreal, dreamlike, distant, or distorted).

In the past week, have there been times when things going on around you seemed unreal or very strange and unfamiliar?

[If no:] (***Do things going on around you seem like a dream or like a scene from a movie? Do they seem distant or distorted?***)

Tell me more about that.

How strong is this feeling? (*Do you lose track of where you actually are or what's actually going on?*)

What do you do while this is happening? (*Do other people notice your behavior? What do they say?*)

How long does it last?

Circle: Dissociation = ○ *Minimal* ○ *Clearly Present* ○ *Pronounced* ○ *Extreme*

[If not clear:] (***Was this due to the effects of alcohol or drugs? What about a medical condition like seizures?***) [Rate 0=Absent if due to the effects of a substance or another medical condition]

How often has this happened in the past week? # of times ____

Did this feeling start or get worse after (EVENT)? (*Do you think it's related to (EVENT)? How so?*)

Circle: Trauma-relatedness = ○ *Definite* ○ *Probable* ○ *Unlikely*

0 *Absent*

1 *Mild / subthreshold*

2 *Moderate / threshold*

3 *Severe / markedly elevated*

4 *Extreme / incapacitating*

Key rating dimensions = frequency / intensity of dissociation

Moderate = at least 1 X week / dissociative quality clearly present but transient, retains some realistic sense of environment

Severe = at least 2 X week / pronounced dissociative quality, marked sense of unreality

CAPS-5 SUMMARY SHEET

Name: _____ ID#: _____ Interviewer: _____ Study: _____ Date: _____

A. Exposure to actual or threatened death, serious injury, or sexual violence	
Criterion A met?	(0) = NO (1) = YES

B. Intrusion symptoms (need 1 for diagnosis)	**Past Week**	
Symptom	*Sev*	*Sx (Sev ≥ 2)?*
(1) B1 – Intrusive memories		(0) = NO (1) = YES
(2) B2 – Distressing dreams		(0) = NO (1) = YES
(3) B3 – Dissociative reactions		(0) = NO (1) = YES
(4) B4 – Cued psychological distress		(0) = NO (1) = YES
(5) B5 – Cued physiological reactions		(0) = NO (1) = YES
B subtotals	*B Sev* = 0	*#B Sx* = 0

C. Avoidance symptoms (need 1 for diagnosis)	**Past Week**	
Symptom	*Sev*	*Sx (Sev ≥ 2)?*
(6) C1 – Avoidance of memories, thoughts, feelings		(0) = NO (1) = YES
(7) C2 – Avoidance of external reminders		(0) = NO (1) = YES
C subtotals	*C Sev* = 0	*#C Sx* = 0

D. Cognitions and mood symptoms (need 2 for diagnosis)	**Past Week**	
Symptom	*Sev*	*Sx (Sev ≥ 2)?*
(8) D1 – Inability to recall important aspect of event		(0) = NO (1) = YES
(9) D2 – Exaggerated negative beliefs or expectations		(0) = NO (1) = YES
(10) D3 – Distorted cognitions leading to blame		(0) = NO (1) = YES
(11) D4 – Persistent negative emotional state		(0) = NO (1) = YES
(12) D5 – Diminished interest or participation in activities		(0) = NO (1) = YES
(13) D6 – Detachment or estrangement from others		(0) = NO (1) = YES
(14) D7 – Persistent inability to experience positive emotions		(0) = NO (1) = YES
D subtotals	*D Sev* = 0	*#D Sx* = 0

E. Arousal and reactivity symptoms (need 2 for diagnosis)	**Past Week**	
Symptom	*Sev*	*Sx (Sev ≥ 2)?*
(15) E1 – Irritable behavior and angry outbursts		(0) = NO (1) = YES
(16) E2 – Reckless or self-destructive behavior		(0) = NO (1) = YES
(17) E3 – Hypervigilance		(0) = NO (1) = YES
(18) E4 – Exaggerated startle response		(0) = NO (1) = YES
(19) E5 – Problems with concentration		(0) = NO (1) = YES
(20) E6 – Sleep disturbance		(0) = NO (1) = YES
E subtotals	*E Sev* = 0	*#E Sx* = 0

PTSD totals	Past Week	
Totals	*Total Sev*	*Total # Sx*
Sum of subtotals (B+C+D+E)	0	0

F. Duration of disturbance	Current
(22)	NOT APPLICABLE

G. Distress or impairment (need 1 for diagnosis)	Past Week	
Criterion	*Sev*	*Cx (Sev ≥ 2)?*
(23) Subjective distress		0 = NO 1 = YES
(24) Impairment in social functioning		0 = NO 1 = YES
(25) Impairment in occupational functioning		0 = NO 1 = YES
G subtotals	*G Sev =* 0	*#G Cx =* 0

Global ratings	Past Week
(26) Global validity	
(27) Global severity	
(28) Global improvement	

Dissociative symptoms (need 1 for subtype)	Past Week	
Symptom	*Sev*	*Sx (Sev ≥ 2)?*
(29) 1 – Depersonalization		0 = NO 1 = YES
(30) 2 – Derealization		0 = NO 1 = YES
Dissociative subtotals	*Diss Sev =* 0	*#Diss Sx =* 0

A11–2 CLINICIAN-GLOBAL IMPRESSION OF SEVERITY (CGI-S)

(Sample; Not to Be Used to Enter Subject Data)

Taking into account all aspects of the individual's PTSD symptoms, please rate how the individual's symptom severity has been during the past 7 days? Do not consider other conditions or comorbidities in your assessment.

☐ No symptoms

☐ Very mild

☐ Mild

☐ Moderate

☐ Severe

☐ Very severe

A11–3 CLINICIAN-GLOBAL IMPRESSION OF CHANGE (CGI-C)

(Sample; Not to Be Used to Enter Subject Data)

Taking into account all aspects of the individual's PTSD symptoms, how much would you rate the change in clinical status since their admission to the study? Do not consider other conditions or comorbidities in your assessment.

☐ Very much improved

☐ Much improved

☐ Minimally improved

☐ No change

☐ Minimally worse

☐ Much worse

☐ Very much worse

A11–4 PATIENT-HEALTH QUESTIONNAIRE-9 (PHQ-9)

(Sample; Not to Be Used to Enter Subject Data)

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

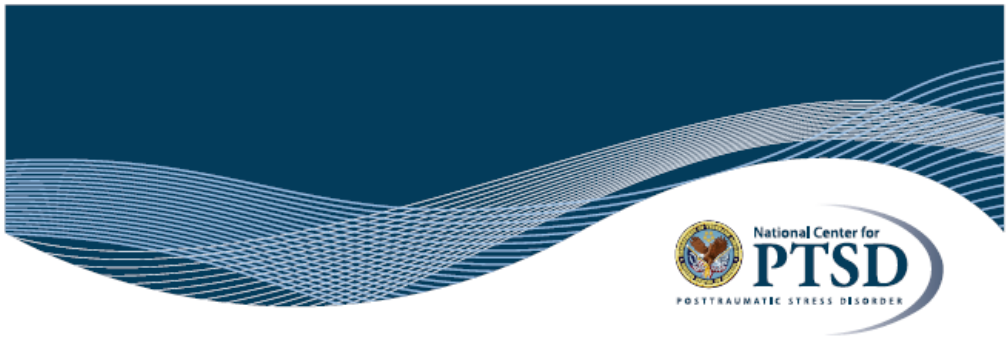
If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

A11–5 LIFE-EVENTS CHECKLIST FOR DSM-5 (LEC-5)

(Sample; Not to Be Used to Enter Subject Data)



Life Events Checklist for *DSM-5* (LEC-5)

Standard Version

Version date: 12 April 2018

Reference: Weathers, F. W., Blake, D. D., Schnurr, P. P., Kaloupek, D. G., Marx, B. P., & Keane, T. M. (2013). *The Life Events Checklist for DSM-5 (LEC-5) – Standard.* [Measurement instrument]. Available from https://www.ptsd.va.gov/

URL: https://www.ptsd.va.gov/professional/assessment/te-measures/life_events_checklist.asp

Note: This is a fillable form. You may complete it electronically.

LEC-5 Standard

Instructions: Listed below are a number of difficult or stressful things that sometimes happen to people. For each event check one or more of the boxes to the right to indicate that: (a) it happened to you personally; (b) you witnessed it happen to someone else; (c) you learned about it happening to a close family member or close friend; (d) you were exposed to it as part of your job (for example, paramedic, police, military, or other first responder); (e) you're not sure if it fits; or (f) it doesn't apply to you.

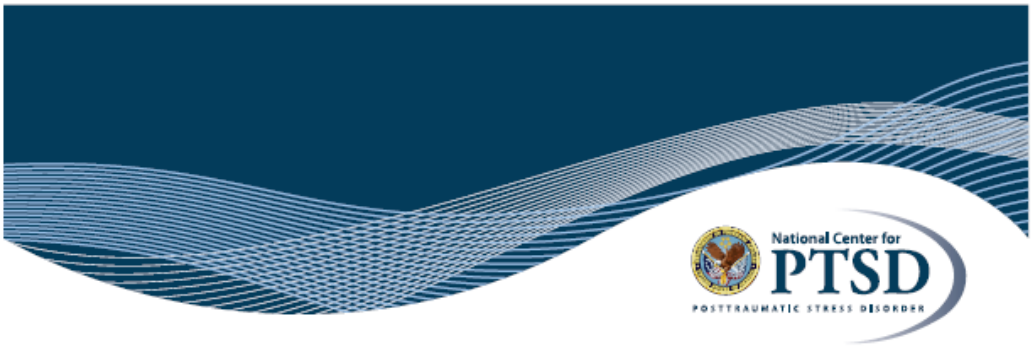
Be sure to consider your *entire life* (growing up as well as adulthood) as you go through the list of events.

Event	Happened to me	Witnessed it	Learned about it	Part of my job	Not sure	Doesn't apply
1. Natural disaster (for example, flood, hurricane, tornado, earthquake)						
2. Fire or explosion						
3. Transportation accident (for example, car accident, boat accident, train wreck, plane crash)						
4. Serious accident at work, home, or during recreational activity						
5. Exposure to toxic substance (for example, dangerous chemicals, radiation)						
6. Physical assault (for example, being attacked, hit, slapped, kicked, beaten up)						
7. Assault with a weapon (for example, being shot, stabbed, threatened with a knife, gun, bomb)						
8. Sexual assault (rape, attempted rape, made to perform any type of sexual act through force or threat of harm)						
9. Other unwanted or uncomfortable sexual experience						
10. Combat or exposure to a war-zone (in the military or as a civilian)						
11. Captivity (for example, being kidnapped, abducted, held hostage, prisoner of war)						
12. Life-threatening illness or injury						
13. Severe human suffering						
14. Sudden violent death (for example, homicide, suicide)						
15. Sudden accidental death						
16. Serious injury, harm, or death you caused to someone else						
17. Any other very stressful event or experience						

LEC-5 Standard (12 April 2018) National Center for PTSD Page 1 of 1

A11–6 PTSD CHECKLIST FOR DSM-5 (PCL-5)

(Sample; Not to Be Used to Enter Subject Data)



PTSD Checklist for *DSM-5* (PCL-5)

(Past Week Version)

Version date: 11 April 2018

Reference: Weathers, F. W., Litz, B. T., Keane, T. M., Palmieri, P. A., Marx, B. P., & Schnurr, P. P. (2013). *The PTSD Checklist for DSM-5 (PCL-5) – Standard* [Measurement instrument]. Available from https://www.ptsd.va.gov/

URL: https://www.ptsd.va.gov/professional/assessment/adult-sr/ptsd-checklist.asp

Note: This is a fillable form. You may complete it electronically.

PCL-5

Instructions: Below is a list of problems that people sometimes have in response to a very stressful experience. Please read each problem and then select one of the options to indicate how much you have been bothered by that problem in the past week. The options include not at all, a little bit, moderately, quite a bit, and extremely.

In the past week, how much were you bothered by:	Not at all	A little bit	Moderately	Quite a bit	Extremely
1. Repeated, disturbing, and unwanted memories of the stressful experience?	0	1	2	3	4
2. Repeated, disturbing dreams of the stressful experience?	0	1	2	3	4
3. Suddenly feeling or acting as if the stressful experience were actually happening again (as if you were actually back there reliving it)?	0	1	2	3	4
4. Feeling very upset when something reminded you of the stressful experience?	0	1	2	3	4
5. Having strong physical reactions when something reminded you of the stressful experience (for example, heart pounding, trouble breathing, sweating)?	0	1	2	3	4
6. Avoiding memories, thoughts, or feelings related to the stressful experience?	0	1	2	3	4
7. Avoiding external reminders of the stressful experience (for example, people, places, conversations, activities, objects, or situations)?	0	1	2	3	4
8. Trouble remembering important parts of the stressful experience?	0	1	2	3	4
9. Having strong negative beliefs about yourself, other people, or the world (for example, having thoughts such as: I am bad, there is something seriously wrong with me, no one can be trusted, the world is completely dangerous)?	0	1	2	3	4
10. Blaming yourself or someone else for the stressful experience or what happened after it?	0	1	2	3	4
11. Having strong negative feelings such as fear, horror, anger, guilt, or shame?	0	1	2	3	4
12. Loss of interest in activities that you used to enjoy?	0	1	2	3	4
13. Feeling distant or cut off from other people?	0	1	2	3	4
14. Trouble experiencing positive feelings (for example, being unable to feel happiness or have loving feelings for people close to you)?	0	1	2	3	4
15. Irritable behavior, angry outbursts, or acting aggressively?	0	1	2	3	4
16. Taking too many risks or doing things that could cause you harm?	0	1	2	3	4
17. Being "superalert" or watchful or on guard?	0	1	2	3	4
18. Feeling jumpy or easily startled?	0	1	2	3	4
19. Having difficulty concentrating?	0	1	2	3	4
20. Trouble falling or staying asleep?	0	1	2	3	4

PCL-5 (11 April 2018) National Center for PTSD Page 1 of 1

A11–7 STRUCTURED-CLINICAL INTERVIEW FOR DSM-5 (SCID-5)

(Sample; Not to Be Used to Enter Subject Data)

STRUCTURED CLINICAL INTERVIEW FOR DSM-5 DISORDERS – CLINICAL TRIALS VERSION

SCID-5-CT Modified For Roche BN43546 (PTSD)

Michael B. First, MD: Janet B. W. Williams, PhD, Rhonda Karg, PhD, and Robert L. Spitzer, MD

Subject #:_____ **Date of Interview:** ___ ___ ___
mon day year

Rater Name: _____

Rater Signature: _____

Investigator Reviewing: _____ **Date of Review:** ___ ___ ___
mon day year

Investigator Signature: _____

Web page: **http://www.scid5.org** E-mail: **scid5@columbia.edu**

INCLUDED IN STUDY:	**EXCLUDED FROM STUDY** (based on assessments included in the SCID-CT):
____ Current primary PTSD (page 11))	____ Lifetime Manic Episode (Pages 15, 16\8) ____ Lifetime Hypomanic Episode (Page 19) ____ History of Primary psychotic or psychotic depression symptoms or substance-induced psychotic symptoms (Page 24) ____ Alcohol Use Disorder in past 12 months (Page 28) ____ Substance (other than nicotine) Use Disorder in past 12 months (Page 33)

OVERVIEW

I'm going to be asking you about problems or difficulties you may have had, and I'll be making some notes as we go along. Do you have any questions before we begin?

How old are you?

Whom do you live with? (What kind of place do you live in?)

What kind of work do you do? Are you working now?

HISTORY OF CURRENT ILLNESS

What led to your coming here (this time)? (What's the major problem you've been having trouble with?)

What was going on in your life when this began?

When were you last feeling OK (your usual self)?

TREATMENT HISTORY

NOTE: The goal of this section of the overview is to determine the overall "landscape" of the person's lifetime psychopathology. Avoid going into excessive detail. For major past episodes, determine symptoms ("What was that for?"*), medications and other treatments (*"What treatment did you get for that?"*), approximate onset and offset (*"When did it start? When were you feeling better?"*).*

When was the first time you saw someone for emotional or psychiatric problems? (What was that for? What treatment(s) did you get? What medications?)

Have you ever had any treatment for drugs or alcohol?

Have you ever been hospitalized for emotional or psychiatric problems? How many times?

Age (or date)	Description (symptoms, triggering events)	Treatment
_____	_____	_____
_____	_____	_____
_____	_____	_____

Continue treatment history on next page if necessary

CURRENT MEDICAL PROBLEMS/SUBSTANCE USE

How has your physical health been? (Have you had any medical problems?)

Do you take any medications, vitamins, or other nutritional supplements (other than those you've already told me about)?

IF YES: What are you taking and at what dose?

How much have you been drinking (alcohol) in the past few months? Have you been taking any drugs in the past few months? (What about marijuana, cocaine, or other street drugs?)

TREATMENT HISTORY (CONTINUED)

Age (or date)	Description (symptoms, triggering events)	Treatment

POSTTRAUMATIC STRESS DISORDER	
I'd now like to ask about some things that may have happened to you that may have been extremely upsetting. People often find that talking about these experiences can be helpful. I'll start by asking if these experiences apply to you, and if so, I'll ask you to briefly describe what happened and how you felt at the time. For each question: if event happened within the past month, inquire if there was another event of this type.	
Have you ever been in a life-threatening situation like a major disaster or fire, in combat, or a serious car or work-related accident?	
What about being physically assaulted or abused, or threatened with physical assault?	
What about being sexually assaulted or abused, or threatened with sexual assault?	
How about seeing another person being physically or sexually assaulted or abused, or threatened with physical or sexual assault?	
Have you ever seen another person killed or dead, or badly hurt?	
How about learning that one of these things happened to someone you are close to?	
IF UNKNOWN: Have you ever been the victim of a serious crime?	
IF NO EVENTS ENDORSED: What would you say has been the most stressful or traumatic experience you have had over your life?	
IF MORE THAN ONE EVENT REPORTED: Which of (EVENTS REPORTED ABOVE) would you say has affected you the most or caused you the most problems during the past month? *Indicate event that affected respondent the most:* EVENT 1: ---------- *and continue with* PTSD criterion A	
Indicate the traumatic event applicable to each pass through the PTSD criteria; and continue with G12 EVENT 2: _____ EVENT 3: _____	

ASK AS MANY QUESTIONS **AS NEEDED** TO DETERMINE WHETHER TRAUMA MEETS CRITERION A REQUIREMENTS IF DIRECT EXPOSURE TO TRAUMA: **What happened? Were you afraid of dying or being seriously hurt? Were you seriously hurt?** IF WITNESSED TRAUMATIC EVENT HAPPENING TO OTHERS: **What happened? What did you see? How close were you to** (TRAUMATIC EVENT)**? Were you concerned about your own safety?** IF LEARNED ABOUT TRAUMATIC EVENT: **What happened? Who did it involve? (How close [emotionally] were you to them? Did it involve violence, suicide, or a bad accident?)**	A. Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways: 1. Directly experiencing the traumatic event(s). 2. Witnessing, in person, the event(s) as it occurred to others. 3. Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental. 4. Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains; police officers repeatedly exposed to details of child abuse). **Note:** Criterion A4 does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related. **If other reported traumatic events,** , record next most traumatic event, and cycle again through items to determine if full criteria are met. **If no other possibly qualifying events, EXCLUDE FROM STUDY**	— +
Now I'd like to ask a few questions about specific ways that (TRAUMATIC EVENT) **may have affected you during the past month.** **For example, during the past month,**	B. Presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:	
...have you had memories of (TRAUMATIC EVENT)**, including feelings, physical sensations, sounds, smells, or images, when you didn't expect to or want to? How often did that happen during** (MONTH)**?**	1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s).	— +
...what about repeatedly having upsetting dreams that reminded you of (TRAUMATIC EVENT)**? Tell me about that. How often did this happen during** (MONTH)**?**	2. Recurrent distressing dreams in which the content and/or effect of the dream are related to the traumatic events.	— +
...what about having found yourself acting or feeling as if you were back in the situation? (Have you had "flashbacks" of [TRAUMATIC EVENT]**?)**	3. Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.)	— +

During the past month... **...have you hsd you a strong emotional or physical reaction when something reminded you of** (TRAUMATIC EVENT)**?** **Give me some examples of the kinds of things that would have triggered this reaction. (Things like...seeing a person who resembles the person who attacked you, hearing the screech of brakes if you were in a car accident, hearing the sound of helicopters if you were in combat, any kind of physically intimacy if you were raped?)** *NOTE:* IF DENIES EMOTIONAL OR PHYSICAL REACTION TO REMINDERS, CODE "—" FOR BOTH B(4) EMOTIONAL REACTION B(5) (PHYSICAL REACTION).		
IF ACKNOWLEDGES STRONG EMOTIONAL OR PHYSICAL REACTION: **What kind of reaction have you had? Have you gotten very upset or stayed upset for a while, even after the reminder had gone away? (For how long do the symptoms last?)**	4. Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).	— +
IF ACKNOWLEDGES STRONG EMOTIONAL OR PHYSICAL REACTION: **What about having physical symptoms—like breaking out in a sweat, breathing heavily or irregularly, or feeling your heart pound or race when something reminded you of** (TRAUMATIC EVENT)**? How about feeling tense or shaky?**	5. Marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).	— +
	AT LEAST ONE OF THE ABOVE CRITERION B SXS IS RATED "+".	NO YES ↓

If other reported traumatic events, return to **criterion A** record next most traumatic event, and cycle again through items to determine if full criteria are met.

If no other possibly qualifying events, EXCLUDE FROM STUDY

During the past month,	C. Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following:	
...have you done things to avoid remembering or thinking about (TRAUMATIC EVENT), **like keeping yourself busy, distracting yourself by playing computer or video games or watching TV, or using drugs or alcohol to "numb" yourself or try to forget what happened? How long has this gone on? (Hss this happened for almost all the time during the past month?** IF NO: **How about doing things to avoid having feelings similar to those you had during** (TRAUMATIC EVENT)? **(Has this happened for almost all the time during the past month?**	1. Avoidance of, or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).	— +
...are there things, places, or people that you tried to avoid because they bring up upsetting memories, thoughts, or feelings about (TRAUMATIC EVENT)? **(Has this been for almost all the time during the past month?** IF NO: **How about avoiding certain activities, situations, or topics of conversation? (Has this happened for almost all the time during the past month?**	2. Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations), that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).	— +
	AT LEAST ONE OF THE ABOVE CRITERION C SXS IS RATED "+".	**NO** **YES**

If other reported traumatic events, return to **criterion A**, record next most traumatic event, and cycle again through items to determine if full criteria are met.

If no other possibly qualifying events, EXCLUDE FROM STUDY

During the past month...	D. Negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:	
...Have you been unable to remember some important part of what happened? (Tell me about that.) How many times has this happened? IF YES: **Did you get a head injury during** (TRAUMATIC EVENT)**? Were you drinking a lot or were taking any drugs at the time of** (TRAUMATIC EVENT)**?**	1. Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs).	— +
.....has there a change in how you thought about yourself? (Like feeling you were "bad," or permanently damaged or "broken"?) Tell me about that. How long did you feel this way about yourself? (Have you felt this way almost all of the time during the past month? IF NO: **Has there been a change in how you see other people or the way the world works? Like you couldn't trust anyone anymore? Like the world was a completely dangerous place? Tell me about that. How long have you thought this way? Have you felt this way almost all of the time during the past month?**	2. Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., "I am bad," "No one can be trusted," "The world is completely dangerous," "My whole nervous system is permanently ruined").	— +
...Have you blame dyourself for the (TRAUMATIC EVENT) **or how it affected your life? (Like thinking that** [TRAUMATIC EVENT] **was your fault or that you should have done something to prevent it? Like thinking that you should have gotten over it by now?)** IF YES: **Tell me about it. Have you thought this way about yourself almost all of the time during the past month?** IF NO: **Have you blames someone else for** (TRAUMATIC EVENT)**? Tell me about that. (What did they have to do with** [TRAUMATIC EVENT]**?) Have you thought this way almost all of the time during the past month?**	3. Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.	— +
...have you had bad feelings a lot of the time, like feeling sad, angry, afraid, guilty, ashamed, or numb? (Tell me about that.) Have you felt this way almost all of the time during the past month? IF YES: **Was this different from the way you were before** (TRAUMATIC EVENT)**?**	4. Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame).	— +

During the past month... **...have you been a lot less interested in things that you were interested in before** (TRAUMATIC EVENT), **like spending time with family or friends, reading books, watching TV, cooking, or sports? (Tell me about that.) Have you felt this way almost all of the time during the past month?** IF NO LOSS OF INTEREST: **Have you still been doing as many activities as you were before** (TRAUMATIC EVENT)**? (Have youbeen involved in fewer activities almost all of the time during the past month?**	5. Markedly diminished interest or participation in significant activities.	— +
...have you felt distant or disconnected from others or did you close yourself off from other people almost all of the time during the past month (Tell me about that.) IF YES: **Was this different from the way you were before** (TRAUMATIC EVENT)**?** **Have you felt this way almost all of the time during the past month?**	6. Feelings of detachment or estrangement from others.	— +
...have you been unable to experience good feelings, like feeling happy, joyful, satisfied, loving, or tender toward other people? (Tell me about that.) How long have you been unable to experience good feelings? (Have you been unable to experience good feelings almost all of the time during the past month? IF YES: **Was this different from the way you were before** (TRAUMATIC EVENT)**?**	7. Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings).	— +
	AT LEAST TWO OF THE ABOVE CRITERION D SXS ARE RATED "+".	NO YES ↓ **If other reported traumatic events,** return to **criterion A** record next most traumatic event, and cycle again through items to determine if full criteria are met. **If no other possibly qualifying events, EXCLUDE FROM STUDY**

During the past month...	E. Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:	
...have you lost control of your anger, so that you threatened or hurt someone or damaged something? Tell me what happened. (Was it over something little or even nothing at all?) How often has this happened during the past month? IF NO: **Since** (TRAUMATIC EVENT), **have you been more quick-tempered or had a shorter "fuse" than before? How often hss this happened during the past month?** IF YES TO EITHER: **How different was this from the way you have been before** (TRAUMATIC EVENT)**?**	1. Irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects.	— +
...have you done reckless things, like drive dangerously, or drink or use drugs without caring about the consequences? How often has this happened during the past month? IF NO: **How about hurting yourself on purpose or trying to kill yourself? (What did you do?) How often has this happened during the past month?** IF YES TO ETIHER: **How different was this from the way you were before** (TRAUMATIC EVENT)**?**	2. Reckless or self-destructive behavior.	— +
...have you noticed that you have been more watchful or on guard? (Give me some examples.) Have you felt this way almost all of the time during the past month? IF NO: **Have you been extra aware of your surroundings and your environment? Have you felt this way most of the time during the past month?** IF YES TO ETIHER: **How different was this from the way you were before** (TRAUMATIC EVENT)**?**	3. Hypervigilance.	— +
...have you been jumpy or easily startled, like by sudden noises? (Is this a change from before [TRAUMATIC EVENT]**?) Have you felt this way most of the time during the past month?**	4. Exaggerated startle response.	— +

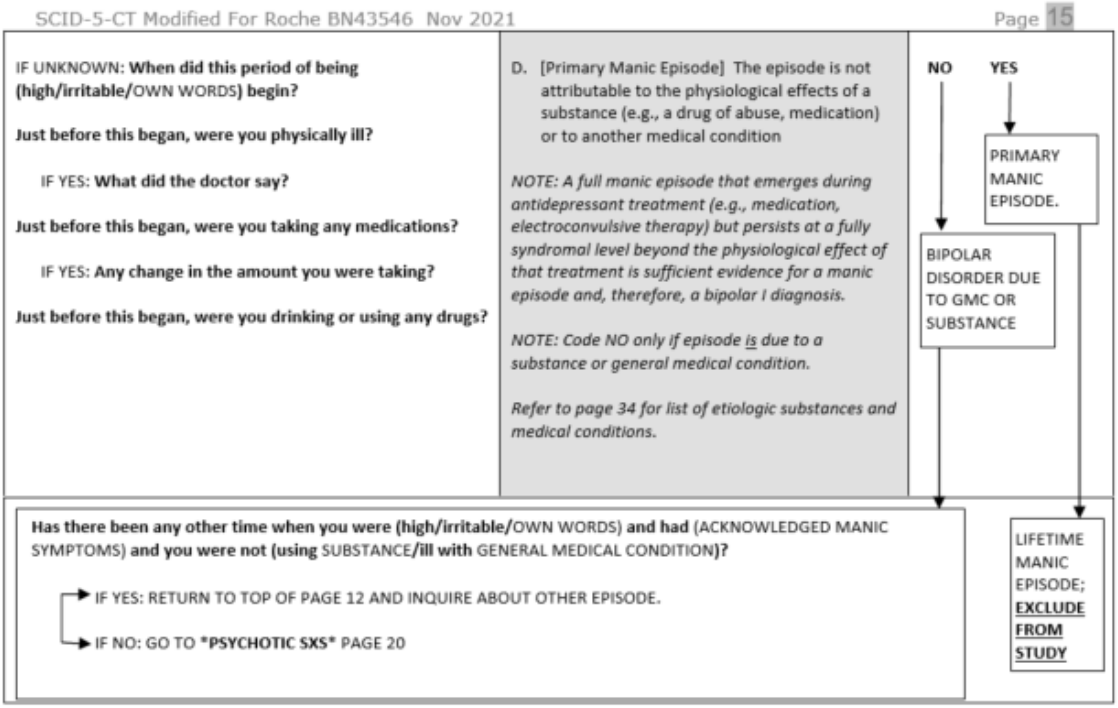
...have you had trouble concentrating? (What are some examples? (Was this a change from before [TRAUMATIC EVENT]**?) Have you felt this way most of the time during the past month?**	5. Problems with concentration.	– +
...how have you been sleeping during (MONTH SELECTED)**? (Is this a change from before** [TRAUMATIC EVENT]**?) Have you had trouble for most of the time during the past month?**	6. Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep).	– +
	AT LEAST TWO OF THE ABOVE CRITERION E SXS ARE RATED "+". **YES** **If other reported traumatic events,** return to **Criterion A** record next most traumatic event, and cycle again through items to determine if full criteria are met. **If no other possibly qualifying events, EXCLUDE FROM STUDY**	
IF UNCLEAR: **About how long did these** (PTSD SXS RATED "+") **last altogether?**	F. Duration of the disturbance [symptoms in Criteria B, C, D, and E is more than 1 month. – + **If other reported traumatic events,** return to **Criterion A** record next most traumatic event, and cycle again through items to determine if full criteria are met. **If no other possibly qualifying events, EXCLUDE FROM STUDY**	
IF UNCLEAR: **What effect has** (PTSD SXS DURING PAST MONTH) **have on your life?** ASK THE FOLLOWING QUESTIONS ONLY AS NEEDED: **How hss** (PTSD SXS) **affected your relationships or your interactions with other people? (Have** [PTSD SXS] **caused you any problems in your relationships with your family, romantic partner, or friends?)** **How have** (PTSD SXS) **affectedyour work/school? (How about your attendance at work/school? Have** [PTSD SXS] **made it more difficult to do your work/schoolwork? Have** [PTSD SXS] **affected the quality of your work/schoolwork?)** **How have** [PTSD SXS] **affected your ability to take care of things at home? What about being involved in things that were important to you, like religious activities, physical exercise, or hobbies?** **Have** (PTSD SXS) **affected any other important part of your life?** IF HAVE NOT INTERFERED WITH LIFE: **How much have you been bothered or upset by** (PTSD SXS)**?**	G. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. – + **If other reported traumatic events,** return to **Criterion A** record next most traumatic event, and cycle again through items to determine if full criteria are met. **If no other possibly qualifying events, EXCLUDE FROM STUDY**	

Have you been drinking a lot or using a lot of drugs during this past month? Tell me about that. **How much have you been (drinking/using** [DRUGS]**)? (Do you think your problems during the past month have been more due to your [drinking/**(DRUG) **use] rather than to your reaction to** [TRAUMATIC EVENT] **itself?)**	H. The disturbance is not attributable to the physiological effects of a substance (e.g., medication, alcohol) or another medical condition.	NO YES **If other reported traumatic events,** return to **Criterion A** record next most traumatic event, and cycle again through items to determine if full criteria are met. **If no other possibly qualifying events, EXCLUDE FROM STUDY**
Are these symptoms that main problem you have been having in the past month?	PTSD is the primary diagnosis	NO YES **EXCLUDE FROM STUDY** **PTSD INCLUSION CRITERION MET**

LIFETIME MANIC EPISODE	MANIC EPISODE CRITERIA	
Have you ever had a period of time when you were feeling so good, "high," excited, or "on top of the world" that other people thought you were not your normal self? IF YES: **What was it like? (Was that more than just feeling good?) '** **Did you also feel like you were "hyper" or "wired" and had an unusual amount of energy? Were you much more active than is typical for you? (Did other people comment on how much you were doing?)**		
IF NO: **Have you ever had a period of time when you were feeling irritable, angry, or short-tempered for most of the day, every day, for at least several days? (Was that different from the way you usually are?)** **What was it like?** **Did you also feel like you were "hyper" or "wired" and had an unusual amount of energy? Were you much more active than is typical for you? (Did other people comment on how much you were doing?)**	A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy lasting at least one week (or any duration if hospitalization is necessary) Check if: ___ elevated, expansive mood ___ irritable mood	– + Go To ***PSYCHOTIC SXS*** Page 20
How long did this last? (As long as 1 week?) IF LESS THAN ONE WEEK: **Did you need to go into the hospital to protect you from hurting yourself or someone else, or from doing something that could have caused serious financial or legal problems?)** **Did you feel (high/irritable/**OWN WORDS**) for most of the day, nearly every day during this time?)**	. . . lasting at least one week (or any duration if hospitalization is necessary) NOTE: IF ELEVATED MOOD LASTS LESS THAN 1 WEEK, CHECK WHETHER IRRITABLE MOOD LASTS AT LEAST 1 WEEK BEFORE SKIPPING TO ***LIFETIME HYPOMANIC EPISODE,*** PAGE 16.	– + Go To ***LIFETIME HYPOMANIC EPISODE*** Page 16
Have you had more than one time like that? (Which time was the most extreme?) IF UNCLEAR: **Have you had any times like that in the past year, since** (ONE YEAR AGO)**?**	*NOTE: If there is evidence for more than one past episode, select the one with the most impairment for your inquiry about past manic episode. If there was an episode in the past year, ask about that episode. If possible, avoid episodes that appear to be substance-induced.*	

FOR ITEMS B.1 TO B.7, FOCUS ON THE WORST PERIOD OF THE EPISODE THAT YOU ARE INQUIRING ABOUT. IF UNCLEAR: **During** (EPISODE), **when were you the most (high/irritable/**OWN WORDS)**?**	B. During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree and represent a noticeable change from usual behavior:	
During that time... **. ...how did you feel about yourself? (More self-confident than usual? Did you feel much smarter or better than everyone else? Did you feel like you had any special powers or abilities?)**	1. Inflated self-esteem or grandiosity	– +
...did you need less sleep than usual? (How much sleep did you get?) IF YES: **Did you still feel rested?**	2. Decreased need for sleep (e.g., feels rested after only three hours of sleep)	– +
...were you much more talkative than usual? (Did people have trouble stopping you or understanding you? Did people have trouble getting a word in edgewise?)	3. More talkative than usual or pressure to keep talking	– +
...did you have thoughts racing through your head? (What was that like?)	4. Flight of ideas or subjective experience that thoughts are racing	– +
...were you so easily distracted by things around you that you had trouble concentrating or staying on one track? (Give me an example of that.)	5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli) as reported or observed.	– +
. . how did you spend your time? (Work, friends, hobbies? Were you especially busy during that time?) **(Did you find yourself more enthusiastic at work or working harder at your job? Did you find yourself more engaged in school activities or studying harder?)** **(Were you more sociable during that time, such as calling on friends or going out with them more than you usually do or making a lot of new friends?)** **(Were you spending more time thinking about sex or involved in doing something sexual, by yourself or with others? Was that a big change for you?)** **Were you physically restless during this time, doing things like pacing a lot, or being unable to sit still? (How bad was it?)**	6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity).	– +

During that time **. . did you do anything that could have caused trouble for you or your family?** **(Spending money on things you didn't need or couldn't afford? How about giving away money or valuable things? Gambling with money you couldn't afford to lose?)** **(Anything sexual that was likely to get you in trouble? Driving recklessly?)** **(Did you make any risky or impulsive business investments or get involved in a business scheme that you wouldn't normally have done?)**	7. Excessive involvement in activities which have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)	– +
	AT LEAST THREE "B" SXS ARE CODED "+" (FOUR IF MOOD ONLY IRRITABLE)	**NO** **YES**
IF NOT ALREADY ASKED: **Has there been any other time when you were (high/irritable**/OWN WORDS**) and had even more of the symptoms that I just asked you about?** → IF YES: RETURN TO TOP OF PAGE 12 AND INQUIRE ABOUT WORST EPISODE. → IF NO: GO TO ***PSYCHOTIC SXS*** PAGE 20		Continue with CRITERION C, next item.
IF UNKNOWN: **What effect did these** (MANIC SXS) **have on your life?** IF UNKNOWN: **Did you need to go into the hospital to protect you from hurting yourself or someone else, or from doing something that could have caused serious financial or legal problems?** ASK THE FOLLOWING QUESTIONS AS NEEDED: **How did** (MANIC SXS) **affect your relationships or your interactions with other people? (Did [**MANIC SXS**] cause you any problems in your relationships with your family, romantic partner or friends?)** **How did** (MANIC SXS) **affect your work/school? (How about your attendance at work or school? Did** (MANIC SXS) **make it more difficult to do your work/schoolwork)?** **How did** (MANIC SXS) **affect your ability to take care of things at home?**	C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others or there are psychotic features.	**NO** **YES**
IF NOT ALREADY ASKED: **Has there been any other time when you were (high/irritable/**OWN WORDS**) and had** (ACKNOWLEDGED MANIC SYMPTOMS) **and you got into trouble with people or were hospitalized?** → IF YES: RETURN TO TOP OF PAGE 12 AND INQUIRE ABOUT MORE SEVERE EPISODE. → IF NO: GO TO ***LIFETIME HYPOMANIC CRITERION C,*** PAGE 18.		Continue with CRITERION D, next page.


SCID-5-CT Modified For Roche BN43546 Nov 2021
Page 15
IF UNKNOWN: When did this period of being (high/irritable/OWN WORDS) begin?
Just before this began, were you physically ill?
IF YES: What did the doctor say?
Just before this began, were you taking any medications?
IF YES: Any change in the amount you were taking?
Just before this began, were you drinking or using any drugs?
D. [Primary Manic Episode] The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, medication) or to another medical condition
NOTE: A full manic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a manic episode and, therefore, a bipolar I diagnosis.
NOTE: Code NO only if episode is due to a substance or general medical condition.
Refer to page 34 for list of etiologic substances and medical conditions.
NO
YES
PRIMARY MANIC EPISODE.
BIPOLAR DISORDER DUE TO GMC OR SUBSTANCE
Has there been any other time when you were (high/irritable/OWN WORDS) and had (ACKNOWLEDGED MANIC SYMPTOMS) and you were not (using SUBSTANCE/ill with GENERAL MEDICAL CONDITION)?
IF YES: RETURN TO TOP OF PAGE 12 AND INQUIRE ABOUT OTHER EPISODE.
IF NO: GO TO *PSYCHOTIC SXS* PAGE 20
LIFETIME MANIC EPISODE; EXCLUDE FROM STUDY

LIFETIME HYPOMANIC EPISODE	HYPOMANIC EPISODE CRITERIA	
When you were [high/irritable/OWN WORDS**], did it last for at least 4 days?) (Did it last for most of the day, nearly every day?)** **What was it like?**	A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 4 consecutive days and persistent most of the day, nearly every day.	− + ↓ Go To ***PSYCHOTIC SXS*** Page 20
Have you had more than one time like that? (Which time was the most extreme?) IF UNCLEAR: **Have you had any times like that in the past year?**	*NOTE: If there is evidence for more than one past episode, select the "worst" (most intense) one for your inquiry about past hypomanic episode. If there was an episode in the past year, ask about that episode. If possible, avoid episodes that are likely to be substance-induced.*	
	B. During the period of mood disturbance and increased energy and activity, 3 (or more) of the following symptoms (4 if the mood is only irritable)have persisted, represent a noticeable change from usual behavior, and have been present to a significant degree and represent a noticeable change from usual behavior:	
During that time... **...how did you feel about yourself?** **(More self-confident than usual? Did you feel much smarter or better than everyone else? Did you feel like you had any special powers or abilities?)**	1. Inflated self-esteem or grandiosity	− +
...did you need less sleep than usual? (How much sleep did you get?) IF YES: **Did you still feel rested?**	2. Decreased need for sleep (e.g., feels rested after only three hours of sleep)	− +
...were you much more talkative than usual? (Did people have trouble stopping you or understanding you? Did people have trouble getting a word in edgewise?)	3. More talkative than usual or pressure to keep talking	− +
...did you have thoughts racing through your head? (What was that like?)	4. Flight of ideas or subjective experience that thoughts are racing	− +
...were you so easily distracted by things around you that you had trouble concentrating or staying on one track? (Give me an example of that.)	5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)	− +

. . how did you spend your time? (Work, friends, hobbies?) (Were you especially productive or busy during that time?) **(Did you find yourself more enthusiastic at work or working harder at your job?) (Did you find yourself more engaged in school activities or studying harder?)** **(Were you more sociable during that time, such as calling on friends or going out with them more than you usually do or making a lot of new friends?)** **(Were you spending more time thinking about sex or involved in doing something sexual, by yourself or with others? (Was that a big change for you?)** **Were you physically restless during this time, doing things like pacing a lot, or being unable to sit still? (How bad was it?)**	6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation	– +
. . did you do anything that could have caused trouble for you or your family? **(Spending money on things you didn't need or couldn't afford? How about giving away money or valuable things? Gambling with money you couldn't afford to lose?)** **(Anything sexual that was likely to get you in trouble? Driving recklessly?)** **(Did you make any risky or impulsive business investments or get involved in a business scheme that you wouldn't normally have done?)**	7. Excessive involvement in activities which have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)	– +
	AT LEAST THREE "B" SXS ARE CODED "+" (FOUR IF MOOD ONLY IRRITABLE)	**NO** **YES**

IF NOT ALREADY ASKED: **Has there been any other time when you were (high/irritable/**OWN WORDS**) and had even more of the symptoms that I just asked you about?**

→ IF YES: RETURN TO **TOP OF PAGE** 16 AND INQUIRE ABOUT MOST INTENSE EPISODE.

→ IF NO: GO TO ***PSYCHOTIC SXS*** PAGE 20

Continue with CRITERION C

LIFETIME HYPOMANIC CRITERION C		
IF UNKNOWN: **Is this very different from the way you usually are? (How were you different? At work? With friends?)**	C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic	**NO** **YES**
IF NOT ALREADY ASKED: **Have there been any other times when you were (high/irritable/**OWN WORDS**) in which you were really different from the way you usually are?** → IF YES: RETURN TO TOP OF PAGE 16 AND INQUIRE ABOUT MORE SEVERE EPISODE. → IF NO: GO TO ***PSYCHOTIC SXS*** PAGE 20		Continue with CRITERION D
IF UNKNOWN: **Did other people notice the change in you? (What did they say?)**	D. The disturbance in mood and the change in functioning are observable by others DESCRIBE	**NO** **YES**
IF NOT ALREADY ASKED: **Have there been any other times when you were (high/irritable/OWN WORDS) and other people did notice the change in the way you were acting?** → IF YES: RETURN TO TOP OF PAGE 16 AND INQUIRE ABOUT MORE SEVERE EPISODE. → IF NO: GO TO ***PSYCHOTIC SXS*** PAGE 20		Continue with CRITERION E
IF UNKNOWN: **What effect did these** (HYPOMANIC SXS) **have on your life?** ASK THE FOLLOWING QUESTIONS AS NEEDED: **How did** (HYPOMANIC SXS) **affect your relationships or your interactions with other people? (Have they caused you any problems in your relationships with your family, romantic partner or friends?)** **How did** (HYPOMANIC SXS) **affect your work/school? (How about your attendance at work or school? Has it affected the quality of your work/schoolwork?)** **How did** (HYPOMANIC SXS) **affect your ability to take care of things at home?** IF UNKNOWN: **Did you need to go into the hospital to protect you from hurting yourself or someone else, or from doing something that could have caused serious financial or legal problems?**	E. The episode was not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization, and there are no psychotic features. DESCRIBE:	**NO** **YES** LIFETIME MANIC EPISODE; **EXCLUDE FROM STUDY** Continue with CRITERION F

IF UNKNOWN: **When did this period of being (high/irritable/OWN WORDS) begin?**

Just before this began, were you physically ill?

IF YES: **What did the doctor say?**

Just before this began, were you taking any medications?

IF YES: **Any change in the amount you were taking?**

Just before this began, were you drinking or using any street drugs?

F. [Primary Hypomanic Episode:] The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, medication) or to another medical condition.

NOTE: A full hypomanic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a hypomanic episode diagnosis. However, caution is indicated so that one or two symptoms (particularly increased irritability, edginess, or agitation following antidepressant use) are neither taken as sufficient for diagnosis of a hypomanic episode, nor necessarily indicative of a bipolar diathesis.

Refer to page 34 for list of etiologic substances and medical conditions.

NO **YES**

PRIMARY MOOD EPISODE

BIPOLAR DISORDER DUE TO GMC OR SUBSTANCE

IF NOT ALREADY ASKED: **Has there been any other time when you were (high/irritable**/OWN WORDS) **and had** (ACKNOWLEDGED MANIC SYMPTOMS) **and you were not (using** SUBSTANCE/**ill with** GENERAL MEDICAL CONDITION)?

→ IF YES: RETURN TO TOP OF PAGE 16 AND INQUIRE ABOUT OTHER EPISODE.

→ IF NO: GO TO ***PSYCHOTIC SXS*** PAGE 20

LIFETIME HYPOMANIC EPISODE; **EXCLUDE FROM STUDY**

PSYCHOTIC AND ASSOCIATED SYMPTOMS	PSYCHOTIC AND ASSOCIATED SYMPTOMS CRITERIA	
FOR ANY PSYCHOTIC AND ASSOCIATED SYMPTOMS THAT ARE PRESENT, DETERMINE WHETHER THE SYMPTOM IS DEFINITELY "PRIMARY" OR WHETHER THERE IS A POSSIBLE OR DEFINITE ETIOLOGIC SUBSTANCE (INCLUDING MEDICATIONS) OR GENERAL MEDICAL CONDITION (SEE PAGE 34 FOR LIST OF ETIOLOGICAL GENERAL MEDICAL CONDITIONS). RATE ITEM AS "+" ONLY IF IT IS PRIMARY. THE FOLLOWING QUESTIONS MAY BE USEFUL IF THE OVERVIEW HAS NOT ALREADY PROVIDED THE INFORMATION: **Just before** (PSYCHOTIC SXS) **began, were you using drugs? ...on any medications? ...did you drink much more than usual or stop drinking after you had been drinking a lot for a while? ...were you physically ill?** IF YES TO ANY: **Has there been a time when you had** (PSYCHOTIC SXS) **and were not** (USING DRUGS/TAKING MEDICATION/CHANGING YOUR DRINKING HABITS/ILL)?		
Now I am going to ask you about unusual experiences that people sometimes have. **Has it ever seemed like people were talking about you or taking special notice of you? (What do you think they were saying about you?)** IF YES: **Were you convinced they were talking about you or did you think it might have been your imagination?** **Did you ever have the feeling that something on the radio, TV, or in a movie was meant especially for you? (Not just that it was particularly relevant to you, but that it was specifically meant for you.)** **Did you ever have the feeling that the words in a popular song were meant to send you a special message?** **Did you ever have the feeling that what people were wearing was intended to send you a special message?** **Did you ever have the feeling that street signs or billboards had a special meaning for you?**	**Delusions of reference**, i.e. events, objects, or other people in the individual's immediate environment have a particular or unusual significance. DESCRIBE:	– +
What about anyone going out of their way to give you a hard time, or trying to hurt you? (Tell me about that.) **Have you ever had the feeling that you were being followed, spied on, manipulated, or plotted against?** **Did you ever have the feeling that you were being poisoned or that your food had been tampered with?**	**Persecutory delusion**, i.e., the individual (or his or her group) is being attacked, harassed, cheated, persecuted, or conspired against. DESCRIBE:	– +

Have you ever thought that you were especially important in some way, or that you had special powers or knowledge? (Tell me about that.) **Did you ever believe that you had a special or close relationship with a celebrity or someone else famous?**	**Grandiose delusion**, i.e., content involves exaggerated power, knowledge or importance, or a special relationship to a deity or famous person DESCRIBE:	–	+
Have you ever been convinced that something was very wrong with your physical health even though your doctor said nothing was wrong . . . like you had cancer or some other disease? (Tell me about that.) **Have you ever felt that something strange was happening to parts of your body?'**	**Somatic delusion**, i.e., content involves change or disturbance in body appearance or functioning. DESCRIBE:	–	+
Have you ever felt that you had committed a crime or done something terrible for which you should be punished? (Tell me about that.) **Have you ever felt that something you did, or should have done but did not do, caused serious harm to your parents, children, other family members, or friends? (Tell me about that.)** **What about feeling responsible for a disaster such as a fire, flood, or earthquake? (Tell me about that.)**	**Delusion of guilt**. i.e., a belief that a minor error in the past will lead to disaster, or that he or she has committed a horrible crime and should be punished severely, or that he or she is responsible for a disaster (e.g., an earthquake or fire) with which there can be no possible connection DESCRIBE:	–	+
Have you ever been convinced that your spouse or partner was being unfaithful to you? IF YES: **How did you know he/she was being unfaithful? (What clued you into this?)**	**Jealous delusion**, i.e., that one's sexual partner is unfaithful DESCRIBE:	–	+
Did you ever have a "secret admirer" who, when you tried to contact them, denied that they were in love with you? (Tell me about that.) **Were you ever romantically involved with someone famous? (Tell me about that.)**	**Erotomanic delusion,** i.e., that another person, usually of higher status, is in love with the individual. DESCRIBE	–	+

Are you a religious or spiritual person? →IF YES: **Have you ever had any religious or spiritual experiences that the other people in your religious or spiritual community have not experienced?** →IF YES: **Tell me about your experiences. (What did they think about these experiences of yours?)** →IF NO: **Have you ever felt that God, the devil, or some other spiritual being or higher power has communicated directly with you? (Tell me about that. Do others in your religious or spiritual community also have such experiences?)** →IF NO: **Have you ever felt that God, or the devil or some other spiritual being or higher power has communicated directly with you? (Tell me about that. Do others in your religious or spiritual community also have such experiences?)**	**Religious delusion,** i.e., a delusion with a religious or spiritual content. DESCRIBE:	–	+
Did you ever feel that someone or something outside yourself was controlling your thoughts or actions against your will? (Tell me about that.)	**Delusion of being controlled,** i.e., feelings, impulses, thoughts, or actions are experienced as being under the control of some external force rather than under one's own control. DESCRIBE:	–	+
Did you ever feel that certain thoughts that were not your own were put into your head? (Tell me about that.)	**Thought insertion,** i.e., that certain thoughts are not one's own, but rather are inserted into one's mind. DESCRIBE:	–	+
What about thoughts being taken out of your head? (Tell me about that.)	**Thought withdrawal,** i.e., that one's thoughts have been "removed" by some outside force. DESCRIBE:	–	+
Did you ever feel as if your thoughts were being broadcast out loud so that other people could actually hear what you were thinking? (Tell me about that.)	**Thought broadcasting,** i.e., the delusion that one's thoughts are being broadcast out loud so that others can perceive them.	–	+
Did you ever believe that someone could read your mind? (Tell me about that.)	**Other delusions** (e.g., that others can read the person's mind, a delusion that one has died several years ago) DESCRIBE:	–	+

	HALLUCINATIONS A perception-like experience with the clarity and impact of a true perception, but without the external stimulation of the relevant sensory organ. The person may or may not have insight into the nonveridical nature of the hallucination (i.e., one hallucinating person may recognize the false sensory experience, whereas another may be convinced that the experience is grounded in reality). Note: Code "-" for hallucinations that are so transient as to be without diagnostic significance. Code "-" for hypnagogic or hynopompic hallucinations occurring when falling asleep or upon awakening	
Did you ever hear things that other people couldn't, such as noises, or the voices of people whispering or talking? (Were you awake at the time?) IF YES: **What did you hear? How often did you hear it?**	**Auditory hallucinations** (i.e., involving the perception of sound, most commonly of voice) when fully awake, heard either inside or outside of one's head. DESCRIBE:	– +
Did you have visions or see things that other people couldn't see? (Tell me about that. Were you awake at the time?)	**Visual hallucinations** (i.e., a hallucination involving sight, which may consist of formed images, such as of people or of unformed images, such as flashes of light.) *Note: Distinguish from an illusion, i.e., a misperception of a real external stimulus* DESCRIBE:	– +
What about strange sensations on your skin, like feeling like something is creeping or crawling on or under your skin? How about the feeling of being touched or stroked? (Tell me about that.)	**Tactile hallucinations**, i.e., a hallucination involving the perception of being touched or of something being under one's skin. DESCRIBE	– +
What about having unusual sensations inside a part of your body, like a feeling of electricity? (Tell me about that.)	**Somatic hallucinations**, i.e., a hallucination involving the perception of physical experience localized within the body (e.g., a feeling of electricity). DESCRIBE:	– +

How about eating or drinking something that you thought tasted bad or strange even though everyone else who tasted it thought it was fine? (Tell me about that.)	**Gustatory hallucinations**, i.e., a hallucination involving the perception of taste (usually unpleasant) DESCRIBE	
What about smelling unpleasant things that other people couldn't smell, like decaying food or dead bodies? (Tell me about that.)	**Olfactory hallucinations**, i.e., a hallucination involving the perception of odor DESCRIBE:	
	ANY PSYCHOTIC ITEM CODED "+"	**NO** **YES**

EXCLUDE FROM STUDY

GO TO ***ALCOHOL USE DISORDERS***, Page 25

SUBSTANCE USE DISORDERS		
ALCOHOL USE DISORDER PAST SIX MONTHS		
What are your drinking habits like? (How much do you drink? **Have you drunk alcohol at least six times in the past 12 months, that is, since** (12 MONTHS AGO)**?**		
IF DID NOT DRINK AT LEAST SIX TIMES IN PAST 12 MONTHS, SKIP TO ***NON-ALCOHOL SUBSTANCE USE,*** PAGE 29.		
	ALCOHOL USE DISORDER CRITERIA	
I'd now like to ask you some more questions about your drinking habits since (12 MONTHS AGO)**....**	A. A problematic pattern of alcohol use, leading to clinically significant impairment or distress, as manifested by at least two of the following occurring within a 12-month period:	
During the past 12 months... **...have you found that once you started drinking you ended up drinking much more than you intended to? For example, you planned to have only one or two drinks but you ended up having many more. (Tell me about that. How often did this happen?)** IF NO: **What about drinking for a much longer period of time than you were intending to?**	1. Alcohol is often taken in larger amounts OR over a longer period than was intended.	− +
...have you wanted to stop, cut down, or control your drinking? IF YES: **How long did this desire to stop, cut down, or control your drinking last?** IF NO: **During the past two months, did you ever try to cut down, stop, or control your drinking? How successful were you? (Did you make more than one attempt to stop, cut down, or control your drinking?)**	2. There is a persistent desire OR unsuccessful efforts to cut down or control alcohol use.	− +
...have you spent a lot of time drinking, being drunk, or hung over? (How much time?)...	3. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects.	− +

During the past 12 months, since (12 MONTHS AGO)... **...have you had a strong desire or urge to drink in between those times when you were drinking? (Has there been a time when you had such strong urges to have a drink that you had trouble thinking about anything else?)** IF NO: **How about having a strong desire or urge to drink when you were around bars or around people with whom you go drinking?**	4. Craving, or a strong desire or urge to use alcohol.	–	+
...have you missed work or school or often arrived late because you were intoxicated, high, or very hung over? IF NO: **How about doing a bad job at work or school, or failing courses or getting kicked out of school because of your drinking?** IF NO: **How about getting into trouble at work or school because of your use of alcohol?** IF NO: **How about not taking care of things at home because of your drinking, like making sure there is food and clean clothes for your family and making sure your children go to school and get medical care? How about not paying your bills?** IF YES TO ANY: **How often?**	5. Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to alcohol use; alcohol-related absences, suspensions, or expulsions from school; neglect of children or household).	–	+
...has your drinking caused problems with other people, such as family members, friends, or people at work? (Have you found yourself regularly getting into arguments about what happens when you drink too much? Have you gotten into physical fights when you were drunk?) IF YES: **Did you keep on drinking anyway? (Over what period of time)?**	6. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol (e.g., arguments with spouse about consequences of intoxication, physical fights).	–	+
...have you had to give up or reduce the time you spent at work or school, with family or friends, or on things you like to do (like sports, cooking, other hobbies) because you were drinking or hungover?	7. Important social, occupational, or recreational activities given up or reduced because of alcohol use.	–	+

During the past 12 months, since (12 MONTHS AGO)... **...have you ever had a few drinks right before doing something that requires coordination and concentration like driving, boating, climbing on a ladder, or operating heavy machinery?** IF YES: **Would you say that the amount you had to drink affected your coordination or concentration so that it was more likely that you or someone else could have been hurt?** IF YES AND UNKNOWN: **How many times? (When?)**	8. Recurrent alcohol use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by alcohol use).	–	+
...has your drinking caused you any problems like making you very depressed or anxious? How about putting you in a "mental fog," making it difficult for you to sleep, or making it so you couldn't recall what happened while you were drinking? **Has your drinking caused significant physical problems or make a physical problem worse, like stomach ulcers, liver disease, or pancreatitis?** IF YES TO EITHER OF ABOVE: **Did you keep on drinking anyway?**	9. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol (e.g., continued drinking despite recognition that an ulcer was made worse by alcohol consumption).	–	+
...have you ever found that you needed to drink much more in order to get the feeling you wanted than you did when you first started drinking? IF YES: **How much more?** IF NO: **What about finding that when you drank the same amount, it had much less effect than before? (How much less?)**	10. Tolerance, as defined by either of the following: a. A need for markedly increased amounts of alcohol to achieve intoxication or desired effect. b. Markedly diminished effect with continued use of the same amount of alcohol	–	+

During the past six months, since (SIX MONTHS AGO)... **...have you ever had any withdrawal symptoms, in other words felt sick when you cut down or stopped drinking?** IF YES: **What symptoms did you have? (Sweating or a racing heart? Your hand(s) shaking? Trouble sleeping? Feeling nauseated or vomiting? Feeling agitated? Feeling anxious? How about having a seizure or seeing, feeling, or hearing things that weren't really there?)** IF NO: **Have you ever started the day with a drink, or did you often drink or take some other drug or medication to keep yourself from getting the shakes or becoming sick?**	11. Withdrawal, as manifested by either of the following: a. At least TWO of the following developing within several hours to a few days after the cessation of (or reduction in) alcohol use: -- autonomic hyperactivity (e.g., sweating or pulse rate greater than 100 bpm) -- increased hand tremor -- insomnia -- nausea or vomiting -- psychomotor agitation -- anxiety -- generalized tonic-clonic seizures -- transient visual, tactile, or auditory hallucinations or illusions b. Alcohol (or a closely related substance such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms,	– +
IF UNCLEAR: **When did** (SXS RATED "+" ABOVE) **occur? (Did they all happen within the past 12 months?)**	AT LEAST TWO ALCOHOL USE ITEMS CODED "+" AND ITEMS OCCURRED DURING THE LAST 12 MONTHS	**NO** → Continue on next page **YES** ↓

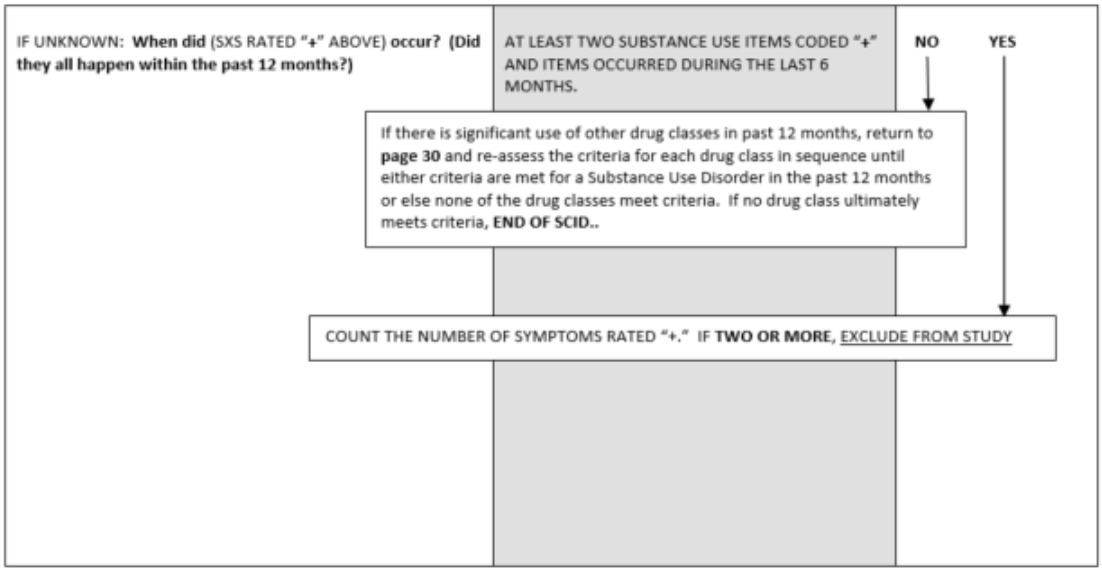
COUNT THE NUMBER OF SYMPTOMS RATED "+." IF **TWO OR MORE**, EXCLUDE FROM STUDY

NON-ALCOHOL SUBSTANCE USE DISORDER Now I'd like to ask you about your use of drugs or medicines over the past 12 months, since (12 MONTHS AGO).	
Drug Classes to Be Inquired About:	**Indicate Use Pattern Based on Questions at Bottom of the Page**
Sedatives-hypnotics-anxiolytics: In the past 12 months, Have you taken any pills to calm you down, help you relax, or help you sleep? (Drugs like Valium, Xanax, Ativan, Klonopin, Ambien, Sonata or Lunesta?)	
Cannabis: In the past 12 months, Have you used marijuana ("pot", "grass", "weed"), hashish ("hash"), THC, K2, or "spice?"	
Stimulants: In the past 12 months, Have you used any stimulants or "uppers" to give you more energy, keep you alert, lose weight, or help you focus? (Drugs like speed, methamphetamine, crystal meth, "crank," Ritalin or methylphenidate, Dexedrine, Adderall or amphetamine or prescription diet pills?) How about cocaine or "crack"?	
Opioids: In the past 12 months, Have you ever used heroin or methadone? How about prescription pain killers? (Drugs like morphine, codeine, Percocet, Percodan, Oxycontin, Tylox, or oxycodone, Vicodin, Lortab, Lorcet or hydrocodone, suboxone or buprenorphine?)	
Phencyclidine and Related Substances: In the past 12 months, Have you ever used PCP ("angel dust," "peace pill") or ketamine ("Special K," "Vitamin K	
Other Hallucinogens: In the past 12 months, have you used any drugs to "trip" or heighten your senses? (Drugs like LSD, "acid", peyote, mescaline, "mushrooms," psilocybin, Ecstasy (MDMA, "molly"), bath salts, DMT, or other hallucinogens?)	
Inhalants: In the past 12 months, have you ever used glue, paint, or correction fluid, gasoline, or other inhalants to get high?	
Other: What about other drugs, like anabolic steroids, nitrous oxide (laughing gas, "whippets"), nitrites (amyl nitrite, butyl nitrite, "poppers," "snappers"), diet pills (phentermine), or over-the-counter medicine for allergies, colds, cough, or sleep?	
IF NO ILLEGAL OR RECREATIONAL DRUGS USED AT LEAST **SIX** TIMES WITHIN THE PAST 12 MONTHS AND NEVER ABUSED ANY OVER-THE-COUNTER OR PRESCRIBED MEDICATIONS (E.G., TAKING MORE THAN PRESCRIBED OR RECOMMENDED, OR DOCTOR-SHOPPING TO GET PRESCRIPTIONS) IN PAST 12 MONTHS, **END OF SCID**.	
IF ACKNOWLEDGES USE OF A DRUG FROM ANY CLASS BELOW, FOLLOW UP WITH THE FOLLOWING QUESTIONS: During the past 12 months, when were you taking (SUBSTANCE) the most? How long did that period last? During that time, how often were you taking it? How much were you using? During the past 12 months, have you had a time when your use of (SUBSTANCE) caused problems for you? During the past 12 months, has anyone objected to your use of (SUBSTANCE)? IF ILLICIT OR RECREATIONAL DRUG: Have you used (SUBSTANCE) at least six times during the past 12 months? IF PRESCRIBED/OTC MEDICATION AND UNKNOWN: Over the past 12 months, did you get hooked or become dependent on (PRESCRIBED DRUG)? Did you ever take more of it than was prescribed or run out of your prescription early? (Did you ever have to go to more than one doctor to make sure you didn't run out?)	

NON-ALCOHOL SUBSTANCE DEPENDENCE	SUBSTANCE USE DISORDER CRITERIA	
Which drugs or medications caused you the most problems over the past 12 months, since (12 MONTHS AGO)**? Which ones did you use the most? Which were your "drugs of choice?"**		
I'd now like to ask you some more questions about your use of (SUBSTANCE USED MOST HEAVILY OR CAUSED MOST PROBLEMS) **in the past 12 months, since** (12 MONTHS AGO).	A. A problematic pattern of substance use leading to clinically significant impairment or distress, as manifested by at least two of the following occurring within a [6]-month period:	
During the past 12 months… **…have you found that once you started using** (DRUG) **you ended up using much more than you intended to? For example, you planned to have** (SMALL AMOUNT OF DRUG) but **you ended up having much more. (Tell me about that. How often did that happen?)** IF NO: **What about using** (DRUG) **for a much longer period of time than you were intending to?**	1. The substance is often taken in larger amounts OR over a longer period than was intended.	– +
…have you wanted to stop or cut down using (DRUG), **or control your use of** (DRUG)? IF YES: **How long did this desire to stop, cut down, or control your use of** (DRUG) **last?** IF NO: **During the past year, did you ever try to cut down, stop, or control your use of** (DRUG)? **How successful were you? (Did you make more than one attempt to stop, cut down, or control your use of** [DRUG]**?)**	2. There is a persistent desire OR unsuccessful efforts to cut down or control substance use.	– +
…have you spent a lot of time getting [DRUG] **or using** [DRUG] **or has it taken a lot of time for you to get over the effects of** [DRUG]? **(How much time?)**	3. A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects.	– +
…have you had a strong desire or urge to use [DRUG] **In between those times when you were using** [DRUG]**? (Has there been a time when you had such strong urges to use** [DRUG] **that you had trouble thinking about anything else?)** IF NO: **How about having a strong desire or urge to use** (DRUG) **when you were around people with whom you used** (DRUG)**?**	4. Craving, or a strong desire or urge to use the substance.	– +

During the past 12 months, since (12 MONTHS AGO)... **...have you missed work or school or often arrived late because you were intoxicated, high, or recovering from the night before?** IF NO: **How about doing a bad job at work or school, or failing courses or getting kicked out of school because of your use of** [DRUG]? IF NO: **How about getting into trouble at work or school because of your use of** [DRUG]? IF NO: **How about not taking care of things at home because of your use of** (DRUG), **like making sure there is food and clean clothes for your family and making sure your children go to school and get medical care? How about not paying your bills?** IF YES TO ANY: **How often?**	5. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household).	–	+
...has your use of [DRUG] **caused problems with other people, such as with family members, friends, or people at work? (Have you found yourself regularly getting into arguments about your** [DRUG] **use? Have you gotten into physical fights when you were taking** [DRUG]?) IF YES: **Did you keep on using** [DRUG] **anyway? (Over what period of time?)**	6. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights).	–	+
...have you had to give up or reduce the time you spent at work, with family or friends, or on your hobbies because you were using [DRUG] **instead?**	7. Important social, occupational, or recreational activities given up or reduced because of substance use.	–	+
...have you ever gotten high before doing something that requires coordination and concentration like driving, boating, climbing on a ladder, or operating heavy machinery? IF YES (FOR SUBSTANCES OTHER THAN STIMULANTS): **Would you say that your use of** (DRUG) **affected your coordination or concentration so that it was more likely that you or someone else could have been hurt?** IF YES: (FOR STIMULANTS ONLY): **Would you say that your being high on stimulants made you drive recklessly like driving very fast or taking unnecessary risks?** IF YES TO EITHER AND UNKNOWN: **How many times?**	8. Recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use).	–	+

During the past 12 months, since (12 MONTHS AGO)... **...has your use of** [DRUG] **caused you any problems like making you very depressed, anxious, paranoid, very irritable or extremely agitated? What about triggering panic attacks, making it difficult for you to sleep, putting you into a "mental fog," or making it so you couldn't recall what happened while you were using** [DRUG]? **Has your use of** [DRUG] **ever caused physical problems, like heart palpitations, coughing or trouble breathing, constipation, or skin infections?** IF YES TO EITHER OF ABOVE: **Did you keep on using** [DRUG] **anyway?**	9. Substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., recurrent cocaine use despite recognition of cocaine-related depression).	–	+
...have you found that you needed to use much more [DRUG] **in order to get the feeling you wanted than when you first started using it?** IF YES: **How much more?** IF NO: **What about finding that when you used the same amount, it had much less effect than before?** IF PRESCRIBED MEDICATION: **Were you taking** (DRUG) **exactly as your doctor told you to? (Did you ever take more of it than was prescribed or run out of your prescription early? Did you ever go to more than one doctor in order to get the amount of medication you wanted?)**	10. Tolerance, as defined by either of the following: a. A need for markedly increased amounts of the substance to achieve intoxication or desired effect. b. Markedly diminished effect with continued use of the same amount of the substance.	–	+
THE FOLLOWING ITEM DOES NOT APPLY TO PCP, HALLUCINOGENS, AND INHALANTS. **Have you ever had any withdrawal symptoms, in other words felt sick when you cut down or stopped using** [DRUG]? IF YES: **What symptoms did you have?** (Refer to list of withdrawal symptoms on page 35) IF NO: **After not using** [DRUG] **for a few hours or more, did you sometimes use it or something like it to keep yourself from getting sick with** (WITHDRAWAL SYMPTOMS)? IF PRESCRIBED MEDICATION: **Were you taking this exactly as your doctor told you to? (Did you ever take more of it than was prescribed or run out of your prescription early? Did you ever have to go to more than one doctor to make sure you didn't run out?)**	11. Withdrawal, as manifested by either of the following: a. The characteristic withdrawal syndrome for the substance (see page 35). b. The same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms Note: This criterion does not apply to PCP, hallucinogens, or inhalants. Note: This criterion is not considered met for those taking opioids, sedatives, hypnotics or anxiolytics, or stimulant medications solely under medical supervision	–	+


IF UNKNOWN: When did (SXS RATED "+" ABOVE) occur? (Did they all happen within the past 12 months?)
AT LEAST TWO SUBSTANCE USE ITEMS CODED "+" AND ITEMS OCCURRED DURING THE LAST 6 MONTHS.
NO
YES
If there is significant use of other drug classes in past 12 months, return to page 30 and re-assess the criteria for each drug class in sequence until either criteria are met for a Substance Use Disorder in the past 12 months or else none of the drug classes meet criteria. If no drug class ultimately meets criteria, END OF SCID..
COUNT THE NUMBER OF SYMPTOMS RATED "+." IF TWO OR MORE, EXCLUDE FROM STUDY

LIST OF GENERAL MEDICAL CONDITIONS AND SUBSTANCES FOR MANIA

Etiological general medical conditions include: Alzheimer's disease, vascular dementia, HIV-induced dementia, Huntington's disease, Lewy body disease, Wernicke-Korsakoff, Cushing's disease, multiple sclerosis, ALS, Parkinson's disease, Pick's disease, Creutzfelt-Jakob disease, stroke, traumatic brain injuries, hyperthyroidism.

Etiological substances include alcohol (I/W), phencyclidine (I), hallucinogens (I), sedatives, hypnotics, anxiolytics (I/W), amphetamines (I/W), cocaine (I/W), corticosteroids, androgens, isoniazid, levodopa, interferon alpha, varenicline, procarbazine, clarithromycin, ciprofloxacin

LIST OF GENERAL MEDICAL CONDITIONS AND SUBSTANCES FOR PSYCHOTIC SYMPTOMS:

Etiological general medical conditions include: neurological conditions (e.g., neoplasms, cerebrovascular disease, Huntington's disease, multiple sclerosis, epilepsy, auditory or visual nerve injury or impairment, deafness, migraine, central nervous system infections), endocrine conditions (e.g., hyper- and hypothyroidism, hyper- and hypoparathyroidism, hyper- and hypoadrenocorticism), metabolic conditions (e.g., hypoxia, hypercarbia, hypoglycemia), fluid or electrolyte imbalances, hepatic or renal diseases, and autoimmune disorders with central nervous system involvement (e.g., systemic lupus erythematosus).

Etiological substances include alcohol(I/W); cannabis(I); hallucinogens(I), phencyclidine (and related substances(I); inhalants(I); sedatives, hypnotics, and anxiolytics(I/W); and stimulants (including cocaine)(I); anesthetics and analgesics, anticholinergic agents, anticonvulsants, antihistamines, antihypertensive and cardiovascular medications, antimicrobial medications, antiparkinsonian medications, chemotherapeutic agents (e.g., cyclosporine, procarbazine), corticosteroids, gastrointestinal medications, muscle relaxants, nonsteroidal anti-inflammatory medications, other over-the-counter medications (e.g., phenylephrine, pseudoephedrine), antidepressant medication, and disulfiram. Toxins include anticholinesterase, organophosphate insecticides, sarin and other nerve gases, carbon monoxide, carbon dioxide, and volatile substances such as fuel or paint.

LIST OF WITHDRAWAL SYMPTOMS (FROM DSM-5 CRITERIA)

Listed below are the characteristic withdrawal syndromes for those classes of psychoactive substances for which a withdrawal syndrome has been identified. (NOTE: A specific withdrawal syndrome has not been identified for PCP, HALLUCINOGENS, and INHALANTS). Withdrawal symptoms may occur following the cessation of prolonged moderate or heavy use of a psychoactive substance or a reduction in the amount used.

SEDATIVES, HYPNOTICS, AND ANXIOLYTICS:

Two (or more) of the following, developing within several hours to a few days after cessation of (or reduction in) sedative, hypnotic, or anxiolytic use, that has been prolonged:

1. Autonomic hyperactivity (e.g., sweating or pulse rate greater than 100 bpm).
2. Hand tremor.
3. Insomnia.
4. Nausea or vomiting.
5. Transient visual, tactile, or auditory hallucinations or illusions.
6. Psychomotor agitation.
7. Anxiety.
8. Grand mal seizures.

CANNABIS :

Three (or more) of the following signs and symptoms developing within approximately one week after cessation of cannabis use that has been heavy and prolonged (i.e., usually daily or almost daily use over a period of at least a few months):

1. Irritability, anger, or aggression.
2. Nervousness or anxiety.
3. Sleep difficulty (e.g., insomnia, disturbing dreams).
4. Decreased appetite or weight loss.
5. Restlessness.
6. Depressed mood.
7. At least one of the following physical symptoms causing significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills, or headache.

STIMULANTS/COCAINE

Dysphoric mood AND two (or more) of the following physiological changes, developing within a few hours to several days after cessation of (or reduction in) prolonged amphetamine-type substance, cocaine, or other stimulant use:
1. Fatigue.
2. Vivid, unpleasant dreams.
3. Insomnia or hypersomnia.
4. Increased appetite.
5. Psychomotor retardation or agitation.

OPIOIDS:

Three (or more) of the following, developing within minutes to several days after cessation of (or reduction in) opioid use that has been heavy and prolonged (i.e., several weeks or longer) or after administration of an opioid antagonist after a period of opioid use:

1. Dysphoric mood.
2. Nausea or vomiting.
3. Muscle aches.
4. Lacrimation or rhinorrhea.(runny nose)
5. Pupillary dilation, piloerection ("goose bumps"), or sweating.
6. Diarrhea.
7. Yawning.
8. Fever.
9. Insomnia.

A11–8 BECK ANXIETY INVENTORY (BAI)

(Sample; Not to Be Used to Enter Subject Data)

BAI

Below is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by each symptom during the PAST WEEK, INCLUDING TODAY, by placing an X in the corresponding space in the column next to each symptom.

	NOT AT ALL	MILDLY It did not bother me much.	MODERATELY It was very unpleasant, but I could stand it.	SEVERELY I could barely stand it.
1. Numbness or tingling.				
2. Feeling hot.				
3. Wobbliness in legs.				
4. Unable to relax.				
5. Fear of the worst happening.				
6. Dizzy or lightheaded.				
7. Heart pounding or racing.				
8. Unsteady.				
9. Terrified.				
10. Nervous.				
11. Feelings of choking.				
12. Hands trembling.				
13. Shaky.				
14. Fear of losing control.				
15. Difficulty breathing.				
16. Fear of dying.				
17. Scared.				
18. Indigestion or discomfort in abdomen.				
19. Faint.				
20. Face flushed.				
21. Sweating (not due to heat).				

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Page 1 of 1

A11–9 PITTSBURGH-SLEEP QUALITY INDEX (PSQI)

(Sample; Not to Be Used to Enter Subject Data)

Pittsburgh Sleep Quality Index (PSQI)

Instructions: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. **Please answer all questions.**

1. During the past month, what time have you usually gone to bed at night? _____
2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night? _____
3. During the past month, what time have you usually gotten up in the morning? _____
4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.) _____

5. During the past month, how often have you had trouble sleeping because you…	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
a. Cannot get to sleep within 30 minutes				
b. Wake up in the middle of the night or early morning				
c. Have to get up to use the bathroom				
d. Cannot breathe comfortably				
e. Cough or snore loudly				
f. Feel too cold				
g. Feel too hot				
h. Have bad dreams				
i. Have pain				
j. Other reason(s), please describe:				
6. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
	No problem at all	Only a very slight problem	Somewhat of a problem	A very big problem
8. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?				
	Very good	Fairly good	Fairly bad	Very bad
9. During the past month, how would you rate your sleep quality overall?				

	No bed partner or room mate	Partner/room mate in other room	Partner in same room but not same bed	Partner in same bed
10. Do you have a bed partner or room mate?				
	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
If you have a room mate or bed partner, ask him/her how often in the past month you have had:				
a. Loud snoring				
b. Long pauses between breaths while asleep				
c. Legs twitching or jerking while you sleep				
d. Episodes of disorientation or confusion during sleep				
e. Other restlessness while you sleep, please describe:				

A11–10 SHEEHAN DISABILITY SCALE (SDS)

(Sample; Not to Be Used to Enter Subject Data)

STABLE RESOURCE TOOLKIT

Sheehan Disability Scale

A brief, patient rated, measure of disability and impairment.

Please mark ONE circle for each scale.

WORK* / SCHOOL

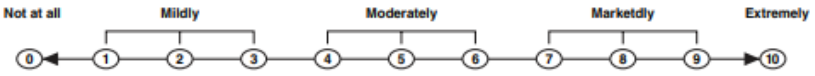
The symptoms have disrupted your work / school work:

☐ I have not worked / studied at all during the past week for reasons unrealted to the disorder.

* Work includes paid, unpaid volunteer work or training

SOCIAL LIFE

The symptoms have disrupted your social life / leisure activities:



FAMILY LIFE / HOME RESPONSIBILITIES

The symptoms have disrupted your family life / home responsibilities:

Days Lost

On how many days in the last week did your symptoms cause you to miss school or work or leave you unable to carry out your normal daily responsibilities? _____

Days Unproductive

On how many days in the last week did you feel so impaired by your symptoms, that even though you went to school or work, your productivity was reduced? _____

A11–11 COGNITION AND PHYSICAL FUNCTIONING QUESTIONNAIRE (CPFQ)

(Sample; Not to Be Used to Enter Subject Data)

(a) How has your motivation/interest/enthusiasm been over the past month?					
1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent
(b) How has your wakefulness/alertness been over the past month?					
1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent
(c) How has your energy been over the past month?					
1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent
(d) How has your ability to focus/sustain attention been over the past month?					
1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent
(e) How has your ability to remember/recall information been over the past month?					
1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent
(f) How has your ability to find words been over the past month?					
1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent
(g) How has your sharpness/mental acuity been over the past month?					
1	2	3	4	5	6
greater than normal	normal	minimally diminished	moderately diminished	markedly diminished	totally absent

Please answer all questions by *circling* the *correct answer* or the answer which seems the most *appropriate* to you (consider 'normal' the time in your life prior to the past month when you were most satisfied with your cognitive and physical functioning). Copyright: Massachusetts General Hospital.

A11–12 PATIENT-GLOBAL IMPRESSION OF SEVERITY (PGI-S)

(Sample; Not to Be Used to Enter Subject Data)

Patient Global Impression of Severity (PGI-S)

Thinking about all aspects of your PTSD symptoms, please rate the overall severity of your symptoms during the past 7 days? Do not consider other conditions or comorbidities unrelated to PTSD.

- ☐ No symptoms
- ☐ Very mild
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

A11–13 PATIENT-GLOBAL IMPRESSION OF CHANGE (PGI-C)

(Sample; Not to Be Used to Enter Subject Data)

Patient Global Impression of Change (PGI-C)

Thinking about all aspects of your PTSD symptoms, how much would you rate the overall change in your PTSD symptoms since starting the study? Do not consider other conditions or comorbidities unrelated to PTSD.

- ☐ Very much improved
- ☐ Much improved
- ☐ Minimally improved
- ☐ No change
- ☐ Minimally worse
- ☐ Much worse
- ☐ Very much worse

A11–14 COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS), BASELINE

(Sample; Not to Be Used to Enter Subject Data)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Lifetime: Time He/She Felt Most Suicidal

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
If yes, describe:
Yes ☐ No ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan.
Have you actually had any thoughts of killing yourself?
If yes, describe:
Yes ☐ No ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."*
Have you been thinking about how you might do this?
If yes, describe:
Yes ☐ No ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
If yes, describe:
Yes ☐ No ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
If yes, describe:
Yes ☐ No ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

Most Severe

Most Severe Ideation: ____ _____
Type # (1-5) ***Description of Ideation***

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm,*** just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

A11–15 COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS), SINCE LAST VISIT

(Sample; Not to Be Used to Enter Subject Data)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

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For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

Appendix 12
Abbreviations

Abbreviation or Term	Definition
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
ASD	autism spectrum disorder
AVP	(arginine) vasopressin
BAI	Beck Anxiety Inventory
CBT	cognitive-behavioral therapy
CAPS-5	Clinician-Administered PTSD scale for DSM-5
CGI-C	Clinician-Global Impression of Change
CGI-S	Clinician-Global Impression of Severity
CI	confidence interval
ClinRO	clinician-reported outcome
COVID-19	Coronavirus Disease 2019
CPFQ	Cognitive and Physical Functioning Questionnaire
CPK	creatine phosphokinase
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP3A4	cytochrome P450 3A4
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Version 5
EC	Ethics Committee
eCRF	electronic Case Report Form
EMDR	eye movement desensitization and reprocessing
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HPA	hypothalamic-pituitary adrenocortical
hs-cTnT	high-sensitivity-cardiac troponin T
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IRB	Institutional Review Board
MAO	monoamine oxidase
M2	metabolite 2
M3	metabolite 3
NGS	next-generation sequencing

Appendix 12: Abbreviations

Abbreviation or Term	Definition
NCS-R	National Comorbidity Survey Replication
PCL-5	PTSD Checklist for DSM-5
PerfO	performance outcome
PGI-C	Patient-Global Impression of Change
PGI-S	Patient-Global Impression of Severity
P-gp	P-glycoprotein
PHQ-9	Patient Health Questionnaire-9
PK	pharmacokinetic
PRO	patient-reported outcome
PSQI	Pittsburgh Sleep Quality Index
PTSD	post-traumatic stress disorder
QD	quaque die (once a day)
QTc	corrected QT interval
QTcF	QT interval corrected through use of Fridericia's formula
RBR	Research Biosample Repository
REC	recording eyes closed
REO	recording eyes open
rTMS	transcranial magnetic stimulation
SCID-5	Structured-Clinical Interview for DSM-5
SDCR	study drug or condition related
SDS	Sheehan Disability Scale
SNRI	serotonin and norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCAs	tricyclic antidepressants
TF	trauma-focused
ULN	upper limit of normal
V1a	vasopressin 1a
V1b	vasopressin 1b
V2	vasopressin 2
WES	whole exome sequencing
WGS	whole genome sequencing

Appendix 13
Protocol Amendment History

A rationale for the current amendment precedes the Table of Contents.

PROTOCOL AMENDMENT, VERSION 2: 23 FEBRUARY 2022

Protocol BN43546 has been amended to reflect recent feedback from the U.S. Food and Drug Administration (FDA) after submission of the Investigational New Drug Application. In addition, Sponsor-initiated modifications have been incorporated including clarification of non-pharmacological interventions and the number of interim analyses to be performed. Substantive changes to the protocol, along with a rationale for each change, are summarized below.

- The exclusion criterion for moderate or severe hepatic and renal impairment was updated to include specific grading criteria; Child-Pugh classification, and eGFR, respectively (Section 5.2).
- An exclusion criterion was added for participants with current or past gastrointestinal disease that could potentially limit the absorption of study drug. Some reduction in gastrointestinal absorption is considered acceptable since the brain receptor occupancy is predicted to remain relatively high with even moderate reduction in absorption (Section 5.2).
- The exclusion criterion for participants currently receiving trauma-based psychotherapy was removed (Section 5.2) and clarification language was added describing the types and frequency of non-pharmacological interventions for post-traumatic stress disorder that are permitted during the study (Section 6.8.1).
- Language on screen failures was updated to more closely align with Roche Global Data Standards (Section 5.4).
- Following FDA comment to include structured questions about general and upper extremity neuropathy symptoms and to include upper extremity testing as part of the neurological evaluation, the following sections in the protocol have been updated. Section 7.1.5 now has a section describing considerations for treatment discontinuation regarding emerging AE of peripheral neuropathy. Text was updated to include both upper and lower limbs in neurological examinations (Section 8.2.3). In Appendix 7, details of the structured brief interview and examination for peripheral neuropathy were updated to include upper extremity sensory and motor testing.
- The randomization ratio was updated from 3:1 to 1:1 (Sections 4.1, 6.3.1, and 9.2), which will allow for a more robust comparison between balovaptan and placebo arms based on the data collected in the study.
- Text was added describing the rationale for the target number of enrolled participants, which is based on drop-out rates seen in similar clinical studies (Section 9.2).
- Language has been revised to include only one interim analysis instead of two. The information will be used for internal purposes and planning of future development of the compound; sample size re-estimation may be performed (Section 9.5.1).

- Language was updated to clarify that electrocardiogram parameters will be provided as non-eCRF data (Section 8.2.4).
- Language has been clarified in Appendix 1, Section A1-1 to indicate that any substantial amendments to the protocol will require IRB/EC and health authority approval (as locally required) before implementation of changes, with the exception of administrative changes or changes necessary to eliminate an immediate hazard to study participants.
- Due to administrative changes “serious adverse event reporting form” has been updated to “Clinical Trial Adverse Event/Special Situations Form” and “Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form” has been updated to “Clinical Trial Adverse Event/Special Situations Form” throughout the protocol.

Signature Page for Protocol - BN43546 - BALOVAPTAN - v3 - Global/Core - Publishe
System identifier: RIM-CLIN-459544

Approval Task	[redacted] Company Signatory 09-Jan-2023 21:23:14 GMT+0000