DRUG:	**COMP360**
STUDY NUMBER:	**COMP 201**
PROTOCOL TITLE:	**The Safety and Tolerability of COMP360 in Participants with Post-traumatic Stress Disorder**
CLINICAL PHASE	**II**
ClinicalTrials.gov IDENTIFIER:	**NCT05312151**
EudraCT NUMBER:	**2021-002621-19**
SPONSOR:	**COMPASS Pathfinder Limited** [redacted]
VERSION NUMBER:	**V 5.0 (USA)**
VERSION DATE:	**09 June 2023**

CONFIDENTIALITY STATEMENT

The information provided in this document is strictly confidential and is available for review to Investigators, potential Investigators, appropriate ethics committees and other national authorities. No disclosure should take place without the written authorisation from the sponsor, except to the extent necessary to obtain informed consent from potential participants.

CLINICAL PROTOCOL APPROVAL FORM

Protocol Number: COMP 201

Protocol Title: The Safety and Tolerability of COMP360 in Participants with Post-traumatic Stress Disorder

Original Protocol Date: 13 May 2021

Protocol Version No: V 5.0 (USA)

Protocol Version Date: 09 June 2023

This study protocol was reviewed and approved by the sponsor. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational product.
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and principles of Good Clinical Practices (GCP) as described in the Code of Federal Regulations (CFR) 21 CFR parts 50, 54, 56 and 312 and according to applicable local requirements.

The investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

Sponsor Approval: [redacted]

Signature: [redacted] Date: 6/20/2023 | 14:06 EDT

Name (print) [redacted]

Title: Chief Medical Officer
COMPASS Pathfinder Limited

STUDY NUMBER: COMP 201

THE SAFETY AND TOLERABILITY OF COMP360 IN PARTICIPANTS WITH POST-TRAUMATIC STRESS DISORDER

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to COMP360 are the confidential and proprietary information of COMPASS Pathfinder Limited (COMPASS), and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of COMPASS.

I have read the protocol, including all appendices, and I agree that it contains all the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Code of Federal Regulations (CFR) for Good Clinical Practices (GCP) and International Council for Harmonisation (ICH) guidelines and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by COMPASS or specified designees. I will discuss the material with them to ensure that they are fully informed about COMP360 and the study.

Principal Investigator Name (printed)	**Signature**
Date	**Site Number**

PROTOCOL SYNOPSIS

Protocol number	COMP 201
Protocol Title:	The Safety and Tolerability of COMP360 in Participants with Post-traumatic Stress Disorder
EudraCT Number:	2021-002621-19
Investigational Medicinal Product:	COMP360
ClinicalTrials.gov Identifier:	**NCT05312151**
Clinical Phase:	II
Rationale:	The Post-traumatic Stress Disorder (PTSD) Psychopharmacology Working Group has recently called for novel, effective and efficient trauma-focused interventions and has labelled current treatment outcomes as "the Crisis in the Pharmacotherapy of Post-traumatic Stress Disorder".[1] MDMA-assisted psychotherapy has recently received Breakthrough Therapy designation (BTD) by the FDA for PTSD, implying that psychedelic-assisted psychotherapies may provide better outcomes for patients than the current standard of care. Psilocybin therapy with COMP360 (COMPASS Pathways' proprietary synthetic psilocybin formulation) has received similar BTD for treatment-resistant depression, a condition often comorbid with PTSD. It is therefore reasonable to obtain proof of feasibility for COMP360 therapy for PTSD. If demonstrated safe and well tolerated, COMP360 therapy may offer a powerful alternative to MDMA-assisted psychotherapy in reducing PTSD symptoms.
Target Population:	PTSD
Number of Participants:	Up to 20 participants
Objectives:	**Primary Objective** • To assess the safety and tolerability of COMP360 administered under supportive conditions in PTSD participants **Secondary Objectives** • To assess the efficacy of COMP360 administered under supportive conditions in reducing PTSD symptoms • To assess the effects of COMP360 administered under supportive conditions on quality of life and participant functional impairment **Exploratory Objectives** • To assess participants subjective experience of COMP360 administered under supportive conditions

- To assess participants perceived growth and resilience after COMP360 therapy
- To evaluate the impact of COMP360 on real life functional activity estimated from passive data streams collected on the Cue app on participants' mobile phones
- Natural language processing on the participant narrative during the interactions with the therapist
- To assess the influence of COMP360 therapy on blood biomarkers
- To assess the influence of COMP360 therapy on brain activity

Study Design and Procedures:

This is a phase II, multicentre, fixed-dose open label trial. The study population will include adult men and women outpatients, 18 years of age and older meeting Diagnostic and Statistical Manual of Mental Disorders (5th Edition; DSM-5) diagnostic criteria for PTSD after a traumatic event experienced during adulthood.

After signing the informed consent form (ICF), participants will be assessed for their eligibility with the Mini International Neuropsychiatric Interview, version 7.0.2 (MINI 7.0.2), the PTSD Checklist for DSM-5 (PCL-5), Life Events Checklists for DSM-5 (LEC-5), the Childhood Trauma Questionnaire (CTQ) and the Columbia- Suicide Severity Rating Scale (C-SSRS). Those who meet the eligibility criteria will enter the screening period. Additionally, a medical history, an electrocardiogram (ECG), blood tests, and vital signs will be obtained. Participants will be offered the option of enrolling in the neuroimaging component of the study. Participation in this part of the study is optional, and participants who do not consent to neuroimaging will not be excluded from the study. If participants consent to neuroimaging, they will be assessed for additional eligibility criteria for the Magnetic Resonance Imaging (MRI) scan.

During the screening period, participants who are on antidepressant and/or antipsychotic medications will be expected to complete tapering of these medications at least 2 weeks prior to baseline. Participants will be given a choice of the tapering rate. During the tapering period all participants will be supported by the study clinician.

Once the participant has been evaluated as eligible, they are invited to enter the screening period visits. During the first of these visits the participant begins tapering off their antidepressant and/or antipsychotic medications, if appropriate. The participant must complete the taper within the first 4 weeks of this period, prior to 2 weeks completely off antidepressant and/or antipsychotic medications, before the baseline visit. Section 10.3 describes guidance for antidepressant and antipsychotic medications requiring immediate cessation at screening V1a followed by at least four weeks of washout prior to baseline.

The designated study team member will be in frequent contact with the participants to monitor for withdrawal and worsening of symptoms. The participant will meet with a therapist during screening. These are safety sessions and will contribute to the participant's preparation for the COMP360 administration session.

Participants discontinuing antidepressant and/or antipsychotic medications during the screening period will be evaluated for safety at the clinic weekly for a minimum of three weeks prior to COMP360 administration to ensure safe discontinuation of current antidepressant therapy required by the protocol. Participants not discontinuing antidepressant and/or antipsychotic medications during the screening period will visit the clinic weekly for a minimum of two weeks prior to COMP360 administration. For all participants, preparation sessions with a therapist will take place at the final two screening period visits and a final preparation session will take place at baseline. Participants discontinuing antidepressant and/or antipsychotic medications must have completed washout before the first preparation session. Participants' companions (carers, friends, or family members) may be educated about the signs of worsening of PTSD and suicidality and instructed on ways to contact the study team in case of significant worsening. During these visits the C-SSRS, the Modified Discontinuation Emergent Signs and Symptoms Scale (mDESS), and any changes in medications since the previous visit will be obtained in addition to other assessments at the study clinician's discretion. The designated study team member will contact the participant by phone calls in between in clinic visits during screening period to monitor for withdrawal and worsening of symptoms.

The day before the administration session, the participants will undergo a baseline assessment (2 to 6 weeks after beginning screening period) that will consist of the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), Sheehan Disability Scale (SDS), EuroQuol-5 Dimensions- 5 Levels (EQ-5D-5L), C-SSRS, Brief Psychiatric Rating Scale – Positive symptom subscale (BPRS+), Perceived Ability to Cope with Trauma (PACT), Resilience Adult Scale (RAS), a semi-structured interview on the management of their PTSD, vital signs, urinalysis, urine drug screen, and urine pregnancy test (only for women of childbearing potential). After baseline data are collected and entered in the Electronic Data Capture (EDC), the Clinical Assessment Technologies Team (CAT) team will complete a final review to ensure the participant's continued eligibility. Participants cannot be progressed to the administration session until this approval is received. Full descriptions of the activities carried out during the therapist sessions can be found in the Therapist Manual. Those who agreed to take part in the optional neuroimaging component of the study and met the eligibility criteria will be offered an MRI scan. To reduce participant burden on baseline visit, the MRI scan can be organised within 7 days prior to the baseline visit. The investigator will be responsible for confirming eligibility of the participant before MRI.

The following day, the participants will attend the clinic for the dosing session that will last approximately 6-8 hours and will be supported by two designated trained therapists. Participants will receive 25 mg COMP360. A full description of the activities of the administration session is found in the Therapist Manual. After the acute effects of COMP360 pass, participants will complete the Five-Dimensional Altered States of Consciousness (5D-ASC), and will be evaluated for safety and accompanied home. On the following day, participants will be seen in person for a safety check, assessment of suicidality, and to discuss their experience during the dosing session (integration). During this visit,

participants will complete a semi-structured interview on the acceptability of the therapeutic intervention and the severity of PTSD symptoms will be evaluated using the PCL-5. All sessions between the therapists and the participant may be audio recorded, and the administration session may be video recorded, for research, adherence monitoring, and quality assurance. Audio and video recording of the sessions are subject to participant consent. Participants who do not consent to either or all recordings will not be excluded from the study.

All participants will be asked to remain off medications for their PTSD symptoms for at least 4 weeks following the administration session. Rescue medications are allowed as noted in the protocol. Participants who restart their medications during the first 4 weeks after the dosing session will be assessed for reasons of resuming their medications and followed until 12 weeks post COMP360 administration. Participants will be seen at the clinic for screening (plus visits during the screening period as required by the protocol), baseline, day 1, day 2, week 1, week 2, week 4, and week 12 visits. Participants will also be contacted for a remote follow-up at week 6 and week 9. The option of an in clinic visit at weeks 6 and 9 will also be available. See Section 5.3 for a full schedule of assessments. Participants who agreed to the optional neuroimaging component of the study will be offered an MRI scan at week 4.

Eligibility Criteria:

Inclusion Criteria

To be eligible for the study, participants must meet the following criteria:

1. Signed ICF
2. 18 years of age or older at screening
3. Meet DSM-5 criteria for current PTSD resulting from a trauma experienced during adulthood measured via the PCL-5 in combination with the LEC-5 at screening
4. Meet DSM-5 criteria for current PTSD resulting from a trauma experienced during adulthood as assessed by the CAPS-5, with a minimum score of 25 at baseline
5. Able to identify a next of kin who is willing and able to be reached by the investigators in case of emergency
6. Have successfully discontinued all prohibited medications at least two weeks prior to baseline visit. Section **10.3** describes guidance for antidepressant and antipsychotic medications requiring immediate cessation at Screening V1a followed by at least four weeks of washout prior to baseline.
7. Able to complete all protocol required assessment tools without any assistance or alteration to the copyrighted assessments, and to comply with all study visits

Inclusion Criteria for subset of participants agreeing to the optional MRI scan:

1. Have consented to take part in the neuroimaging component of the study

Exclusion Criteria

Exclusion of potentially confounding psychiatric diseases and therapies:

1. Current or past history of schizophrenia, schizoaffective disorder or any other form of psychotic disorder, obsessive compulsive disorder, personality disorders, bipolar disorder, or any other significant disorder as assessed by clinician judgement and a structured clinical interview (MINI 7.0.2)
2. Diagnosis of complex PTSD based on medical records and clinician judgement
3. Borderline Personality Disorder as demonstrated by both the McLean Screening Instrument for Borderline Personality Disorder (MSI- BPD) score ≥ 7 and clinical confirmation of diagnosis by the study clinician and Medical Monitor
4. Significant suicide risk as defined by (1) suicidal ideation as endorsed on items 4 or 5 on the C-SSRS within the past year, during screening or at baseline, or; (2) suicidal behaviours within the past year, or; (3) history of serious suicide attempt that required a rescuing medical intervention, or; (4) clinical assessment of significant suicidal risk during participant interview
5. Current (within the last year) alcohol or substance use disorder as informed by DSM-5 assessed via the MINI 7.0.2 at screening
6. Other personal circumstances and behaviour judged to be incompatible with establishment of rapport or safe exposure to psilocybin
7. Exposure to 3,4-methylenedioxymethamphetamine (MDMA), psilocybin, or any other psychedelics, such as ayahuasca, mescaline, lysergic acid diethylamide (LSD), or peyote in the past year
8. Primary diagnosis of major depressive disorder within 6 months of study entry
9. Exposure to a traumatic experience in the past 3 months
10. Significant childhood physical or sexual abuse based on clinician judgment with the use of CTQ
11. Enrolment in a psychological therapy programme that will not remain stable for the duration of the study. Psychological therapies cannot have been initiated within 21 days of baseline

General Medical Exclusion Criteria:

12. Women who are pregnant, nursing or planning a pregnancy. Male and female participants who engage in sexual intercourse which could result in pregnancy, must agree to use a highly effective contraceptive method (as listed in Section 10.2) throughout their participation in the study. Women of

childbearing potential must have a negative serum pregnancy test at screening and negative urine pregnancy test at baseline

13. Cardiovascular conditions: recent stroke (< 1year from signing of ICF, recent myocardial infarction (<1 year from signing of ICF), hypertension (blood pressure >140/90 mmHg) or clinically significant arrhythmia within 1 year of signing the ICF
14. Uncontrolled diabetes for whom hypoglycaemia during a prolonged fasting period could be a concern
15. Seizure disorder
16. Positive urine drug screen for illicit drugs or drugs of abuse at screening and/or baseline. Any positive urine drug test will be reviewed with participants to determine the pattern of use and eligibility will be determined at the investigator's discretion in conjunction with the medical monitor
17. Current enrolment in an interventional study or participation in such within 30 days of screening
18. Abnormal and clinically significant results on vital signs, ECG, or laboratory tests at screening and baseline
19. Any other clinically significant cardiovascular, pulmonary, gastrointestinal, hepatic, renal or any other major concurrent illness that, in the opinion of the investigator, may interfere with the interpretation of the study results or constitute a health risk for the participant if he/she takes part in the study
20. Hypersensitivity to the IMP or any of the excipients
21. Unwilling to consent to information sharing with the participant's usual general practitioner or family physician
22. Any other history, medical or psychological conditions that, in the opinion of the investigator, impede the ability to establish therapeutic alliance leading to psilocybin session

Exclusion Criteria for subset of participants agreeing to the optional MRI scan:

1. Had a serious head injury, according to their medical history that, in the opinion of the investigator will interfere with the interpretation of the MRI scan
2. Have an MRI incompatible implant, including dental metal implant, contraceptive coil containing metal, pacemaker, vascular clips, artificial heart valves, or any other foreign body that might not be safe for MRI
3. Have tattoos or permanent make up on head, or neck
4. Being claustrophobic
5. Have a false limb, brace, or body piercings, hair extensions containing metal that cannot be removed
6. Had an eye injury involving metal

7. Any other factor deemed to be incompatible with MRI in the opinion of the investigator

Study Drug(s): Single, 5 capsule dose of COMP360:

- 25 mg COMP360 treatment: 5 x 5mg capsules

Primary Endpoint: The safety and tolerability endpoints include:

- AEs
- 12-lead ECGs
- Clinical laboratory tests
- Vital signs
- Suicidality measured via the C-SSRS
- BPRS+

Secondary Endpoints:

- Change in CAPS-5 total score from baseline
- Change in PCL-5 total score from baseline
- Change in SDS total score from baseline
- Change in EQ-5D-5L total score from baseline
- Proportion of participants with response (defined as a ≥ 15 point improvement on the CAPS-5 total score from baseline)
- Proportion of participants with remission (defined as CAPS-5 total score ≤ 20)

Exploratory Endpoints:

- Change in PACT total score from baseline
- Change in RAS total score from baseline
- 5D-ASC on day 1
- Summary of the Emotional Breakthrough Inventory (EBI) total score on day 2
- Participant acceptability of the treatment assessed via a semi-structured qualitative interview *
- Quantitative and descriptive characterisation of changes in the participant narrative as a result of treatment *
- Measures derived from the Cue app installed on the participant's smart phone *
- Changes in blood biomarkers after COMP360 therapy, as well as any relationship between biomarkers pre- and post-treatment, and clinical outcomes

- Brain activation during fMRI tasks relating to trauma-related events and an emotional go/no-go task *

*Data from the semi-structured qualitative interview and data generated from the Cue app and the MRI and blood biomarker components of study will be assessed outside of the Clinical Study Report (CSR)

Estimand framework

An estimand framework will not be used for this study since it is a descriptive, exploratory study.

Statistical Procedures

Sample Size Determination

No formal sample size calculation has been performed for this exploratory study.

Analysis Sets

The Screening Analysis Set will consist of all participants who signed the ICF.

The Safety Analysis Set will consist of all participants who receive study drug.

The Full Analysis Set (FAS) will consist of all participants in the Safety Analysis Set who have at least one post-baseline efficacy assessment.

Safety Analysis

The Safety Analysis Set will be used. Safety will be evaluated based on AEs, ECG findings, clinical laboratory assessments, vital signs, BPRS+ and suicidality (as measured via the C-SSRS).

Efficacy Analyses

The FAS will be used. Efficacy endpoints will be summarised using descriptive statistics.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
5D-ASC	**Five-Dimensional altered states of consciousness**
AE	**adverse event**
AESI	**adverse event of special interest**
ALT	**alanine aminotransferase**
AST	**aspartate aminotransferase**
bpm	**Beats per minute**
BPRS+	**Brief Psychiatric Rating Scale – Positive symptom subscale**
BTD	**Breakthrough Therapy designation**
CAPS-5	**Clinician-Administered PTSD Scale for DSM-5**
CBT	**Cognitive behavioural therapy**
CFR	**Code of Federal Regulations**
CI	**confidence interval**
COMPASS	**COMPASS Pathfinder Limited**
CSR	**Clinical Study Report**
C-SSRS	**Columbia-Suicide Severity Rating Scale**
CTQ	**Childhood Trauma Questionnaire**
CYP	**cytochrome P450**
DSM-5	**Diagnostic and Statistical Manual of Mental Disorders, 5th edition**
DSMB	**Data and Safety Monitoring Board**
EBI	**Emotional Breakthrough Inventory**
EC_{50}	**half-maximal effective concentration**
ECG	**electrocardiogram**
eCRF	**electronic Case Report Form**
EIU	**Exposure in Utero**
EOS	**End of Study**
EQ-5D-5L	**Euro QoL-5 dimension-5 level**
EQ VAS	**Euro QoL visual analogue scale**
ET	**early termination**
FAS	**full analysis set**
GCP	**Good Clinical Practice**

H	**hour(s)**
HDPE	**high density polyethylene**
IB	**Investigator's Brochure**
ICF	**informed consent form**
ICH	**The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use**
IEC	**Independent Ethics Committee**
IMP	**Investigational Medicinal Product**
IRB	**Institutional Review Board**
IV	**intravenous**
Kg	**Kilogram**
L	**Litres**
LEC-5	**Life Events Checklist for DSM-5**
MDD	**major depressive disorder**
mDESS	**Modified Discontinuation Emergent Signs and Symptoms scale**
MedDRA	**Medical Dictionary for Regulatory Activities**
min	**minute(s)**
mg	**milligram**
MINI 7.0.2	**Mini International Neuropsychiatric Interview, Version 7.0.2**
mL	**millilitre**
mmHg	**millimetres of mercury**
MRI	**Magnetic Resonance Imaging**
ng	**Nanogram**
PACT	**Perceived Ability to Cope with Trauma**
PCL-5	**PTSD Checklist for DSM-5**
PRN	***Pro re nata,* as needed**
PS	**Prescreen**
PT	**Preferred Term**
PTSD	**Posttraumatic Stress Disorder**
RAS	**Resilience Adult Scale**
SAE	**Serious Adverse Event**
SAF	**Safety Analysis Set**
SAP	**Statistical Analysis Plan**
SD	**standard deviation**

SDS	**Sheehan Disability Scale**
TRD	**Treatment-resistant depression**
UK	**United Kingdom**
ULN	**upper limit of normal**
US	**United States**

1 INTRODUCTION AND RATIONALE

Background information for the investigational product is provided in the current Investigator's Brochure (IB).[2]

1.1 Background

COMP360 is COMPASS' proprietary formulation of synthetic psilocybin. Psilocybin belongs to a class of drugs referred to as psychedelics (meaning 'mind manifesting'). Specifically, psilocybin is considered a 5-hydroxytryptaminergic (serotonergic) psychedelic, along with other tryptamines such as dimethyltryptamine (DMT), ergolines such as lysergic acid diethylamide (LSD), and phenethylamines such as mescaline.

1.2 Study Rationale

PTSD is a serious debilitating condition, highly impactful on quality of life, resulting in diminished cognitive and psychosocial functioning, fractured relationships, inability to maintain employment, substance abuse, high healthcare utilisation costs, increased depression, and suicide risk. People who experience PTSD relive their traumatic experience(s) through nightmares and flashbacks, have difficulty sleeping, and feel detached or estranged. Despite the fact that symptoms can be severe and long lasting, there are currently no effective treatments for PTSD.[1]

International guidelines recommend psychological interventions (such as trauma-focused cognitive behavioural therapy or eye movement desensitisation and reprocessing) as first-line treatments for PTSD followed by pharmacological approaches, aiming to improve mood and reducing hyperarousal.[3,4] Serotonin-reuptake inhibitors (SSRIs) are recommended by guidelines as second-line treatments, but despite being effective in some cases, about 40% of those with PTSD will not improve after treatment.[5]

The PTSD Psychopharmacology Working Group has recently called for novel, effective and efficient trauma-focused interventions and has labelled current treatment outcomes as "the Crisis in the Pharmacotherapy of Post-traumatic Stress Disorder".[1] MDMA-assisted psychotherapy has recently been designated as a Breakthrough Therapy designation (BTD) by the Food and Drug Administration (FDA) for PTSD, implying that psychedelic-assisted psychotherapies may provide better outcomes for patients than the current standard of care. COMP360 therapy has received similar BTD for treatment-resistant depression, a condition often comorbid with PTSD. It is therefore reasonable to obtain proof of feasibility for COMP360 for PTSD. If demonstrated to be safe and well tolerated, COMP360 may offer a powerful alternative to MDMA-assisted psychotherapy in reducing PTSD symptoms.

In this study, the aim is to assess the safety and tolerability, and explore efficacy of administration of a single dose of COMP360 25 mg under supportive conditions in participants with PTSD.

1.2.1 Pharmacokinetics and Pharmacodynamics

The pharmacokinetics of a different form of psilocybin (non-COMP360) were studied in 12 healthy adult subjects who received single oral doses of 0.3, 0.45, or 0.6 mg/kg at minimal intervals of 4 weeks.[6] The results suggested rapid luminal and first pass dephosphorylation of psilocybin to its active metabolite, psilocin. Plasma exposures of psilocin were linear within the dose range tested and the elimination half-life of psilocin was 3 h (standard deviation [SD] ± 1.1 h). Variation in psilocin exposure was not predicted by body weight; therefore, a fixed oral psilocybin dose of 25 mg is expected to result in psilocin exposure (based on the area under the curve [AUC] and C_{max}) similar to that demonstrated after an individualised 0.3 mg/kg oral dose. At the 0.3 mg/kg dose, the AUC was 140 µg h/L (interquartile range [IQR] 102 - 175), the plasma psilocin C_{max} was 16 µg/L (IQR 14.5-17.2) and T_{max} was 2.03 h (1.15 - 2.07). No psilocybin was found in plasma or urine, and renal clearance of intact psilocin accounted for less than 2% of the total clearance. An extended elimination phase in some subjects suggests potential for hydrolysis of psilocin glucuronide metabolite.

Available results of COMP360 and previously published information on different forms of psilocybin from *in vitro* assays and rodent studies demonstrate broadly similar pharmacokinetics to human studies after a single dose.

The subjective intensity of the psychedelic effects of a different form of psilocybin (non-COMP360) have been shown to correlate with plasma levels of psilocin and its levels of occupancy of 5-HT_{2A} receptors.[7] The psychedelic effects of psilocybin can be blocked with ketanserin, a 5-HT_{2A} receptor antagonist.[8] Thus, the pharmacokinetics of psilocin and concomitant activation of 5-HT_{2A} receptors appears to be closely associated with the psychedelic effects of psilocybin.

1.2.2 Clinical Adverse Event Profile

The safety of COMP360 should be considered in terms of benefit and risk. Within the context of COMP360 administration in a controlled setting with psychological support, a participant may report visual or auditory disturbances, perceptual distortions, altered sense of time, and other changes in mood or affect amongst other neuropsychiatric observations which have been previously described.[15] These effects are both expected, and may be a necessary component of therapeutic response. Investigators must follow regulatory guidance for AE reporting which addresses untoward medical occurrences associated with the use of a drug in humans, whether or not considered drug related. An AE can be any unfavourable and unintended sign (eg an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality.

Results from COMPASS' completed trial in healthy volunteers (COMP 002, EudraCT number: 20180999878-30) suggests that COMP360 is generally well tolerated. There were no SAEs and no AEs led to study withdrawal. In total, 511 TEAEs were reported over the 12-week study duration across the 89 participants. Of the 511 TEAEs, the majority had an onset and resolution on day 1. Of the 403 TEAEs that started on the day of dosing, 343 (85.4%) were resolved the same day.

1.2.3 Dosing Regimen

This study will evaluate a 25 mg single COMP360 dose administered under supportive conditions.

Carhart-Harris- successfully evaluated two oral doses of psilocybin (non-COMP360) (10 mg and 25 mg) administered seven days apart to patients with unipolar TRD. Minimal AEs were reported in this study.[9] Work by the Griffiths group showed that under supportive conditions, psilocybin at doses of 20 to 30 mg/70 kg can dose dependently occasion mystical- -type experiences.[10] The doses successfully explored in cancer patients with mood and/or anxiety symptoms range between 14-30 mg/70 kg.[10-12]

COMPASS is currently running a phase IIb study to measure COMP360 efficacy on TRD symptoms using doses of 1 mg, 10 mg, and 25 mg. Considering that depression is highly comorbid with PTSD, we expect a 25 mg dose to be adequate in this population for safety purposes.

2 STUDY OBJECTIVES

2.1 Primary

To assess the safety and tolerability of COMP360 administered under supportive conditions in PTSD participants

2.2 Secondary

- To assess the efficacy of COMP360 administered under supportive conditions in reducing PTSD symptoms
- To assess the effects of COMP360 administered under supportive conditions on quality of life and participant functional impairment

2.3 Exploratory

- To assess participants subjective experience of COMP360 administered under supportive conditions
- To assess participants perceived growth and resilience after COMP360 therapy
- To evaluate the impact of COMP360 on real life functional activity estimated from passive data streams collected on the Cue app on participants' mobile phones
- Natural Language Processing on the participant narrative during the interactions with the therapist
- To assess the influence of COMP360 therapy on blood biomarkers
- To assess the influence of COMP360 therapy on brain activity

3 STUDY ENDPOINTS

3.1 Primary

The safety and tolerability endpoints include:

- AEs
- 12-lead ECGs
- Clinical laboratory tests
- Vital signs
- Suicidality measured via the C-SSRS
- Brief Psychiatric Rating Scale – Positive symptom subscale (BPRS+)

3.2 Secondary

- Change in CAPS-5 total score from baseline
- Change in PCL-5 total score from baseline
- Change in SDS total score from baseline
- Change in EQ-5D-5L total score from baseline
- Proportion of participants with response (defined as a ≥ 15 point improvement on the CAPS-5 total score from baseline)
- Proportion of participants with remission (defined as CAPS-5 total score ≤ 20)

3.3 Exploratory

- Change in PACT total score from baseline
- Change in RAS total score from baseline
- 5D-ASC on day 1
- Summary of the Emotional Breakthrough Inventory (EBI) total score on day 2
- Participant acceptability of the treatment assessed via a semi-structured qualitative interview *
- Quantitative and descriptive characterisation of changes in the participant narrative as a result of treatment *
- Measures derived from the Cue app installed on the participant's smart phone *
- Changes in blood biomarkers after COMP360 therapy, as well as any relationship between biomarkers pre- and post-treatment, and clinical outcomes *

- Brain activation during fMRI tasks relating to trauma-related events and an emotional go/no-go task *

*Data from the semi-structured qualitative interview and data generated from the Cue app and the MRI and blood biomarker components of study will be assessed outside of the CSR.

4 ESTIMAND FRAMEWORK

An estimand framework will not be used for this study since it is a descriptive, exploratory study.

5 STUDY PLAN

5.1 Study Design

This is a phase II, multicentre, fixed-dose open label trial. The study population will include adult men and women outpatients, 18 years of age and older meeting Diagnostic and Statistical Manual of Mental Disorders (5th Edition; DSM-5) diagnostic criteria for PTSD after a traumatic event experienced during adulthood.

After signing the informed consent form (ICF), participants will be assessed for their eligibility with the Mini International Neuropsychiatric Interview, version 7.0.2 (MINI 7.0.2), the PTSD Checklist for DSM-5 (PCL-5), Life Events Checklists for DSM-5 (LEC-5), the Childhood Trauma Questionnaire (CTQ) and the Columbia- Suicide Severity Rating Scale (C-SSRS). Those who meet the eligibility criteria will enter the screening period. Additionally, a medical history, an electrocardiogram (ECG), blood tests, and vital signs will be obtained. Participants will be offered the option of enrolling in the neuroimaging component of the study. Participation in this part of the study is optional, and participants who do not consent to neuroimaging will not be excluded from the study. If participants consent to neuroimaging, they will be assessed for additional eligibility criteria for the Magnetic Resonance Imaging (MRI) scan.

During the screening period, participants who are on antidepressant and/or antipsychotic medications will be expected to complete tapering of these medications at least 2 weeks prior to baseline. Participants will be given a choice of the tapering rate. During the tapering period all participants will be supported by the study clinician.

Once the participant has been evaluated as eligible, they are invited to enter the screening period visits. During the first of these visits the participant begins tapering off their antidepressant and/or antipsychotic medications, if appropriate. The participant must complete the taper within the first 4 weeks of this period, prior to 2 weeks completely off antidepressant and/or antipsychotic medications, before the baseline visit. Section 10.3 describes guidance for antidepressant and antipsychotic medications requiring immediate cessation at Screening V1a followed by at least four weeks of washout prior to baseline.

The designated study team member will be in frequent contact with the participants to monitor for withdrawal and worsening of symptoms. The participant will meet with a therapist during screening. These are safety sessions and will contribute to the participant's preparation for the COMP360 administration session.

Participants discontinuing antidepressant and/or antipsychotic medications during the screening period will be evaluated for safety at the clinic weekly for a minimum of three weeks prior to COMP360 administration to ensure safe discontinuation of current antidepressant therapy required by the protocol. Participants not discontinuing antidepressant and/or antipsychotic medications during the screening period will visit the clinic weekly for a minimum of two weeks prior to COMP360 administration. For all

participants, preparation sessions with a therapist will take place at the final two screening period visits and a final preparation session will take place at baseline. Participants discontinuing antidepressant and/or antipsychotic medications must have completed washout before the first preparation session. Participants' companions (carers, friends, or family members) may be educated about the signs of worsening of PTSD and suicidality and instructed on ways to contact the study team in case of significant worsening. During these visits the C-SSRS, the Modified Discontinuation Emergent Signs and Symptoms Scale (mDESS), and any changes in medications since the previous visit will be obtained in addition to other assessments at the study clinician's discretion. The designated study team member will contact the participant by phone calls in between in clinic visits during screening period to monitor for withdrawal and worsening of symptoms.

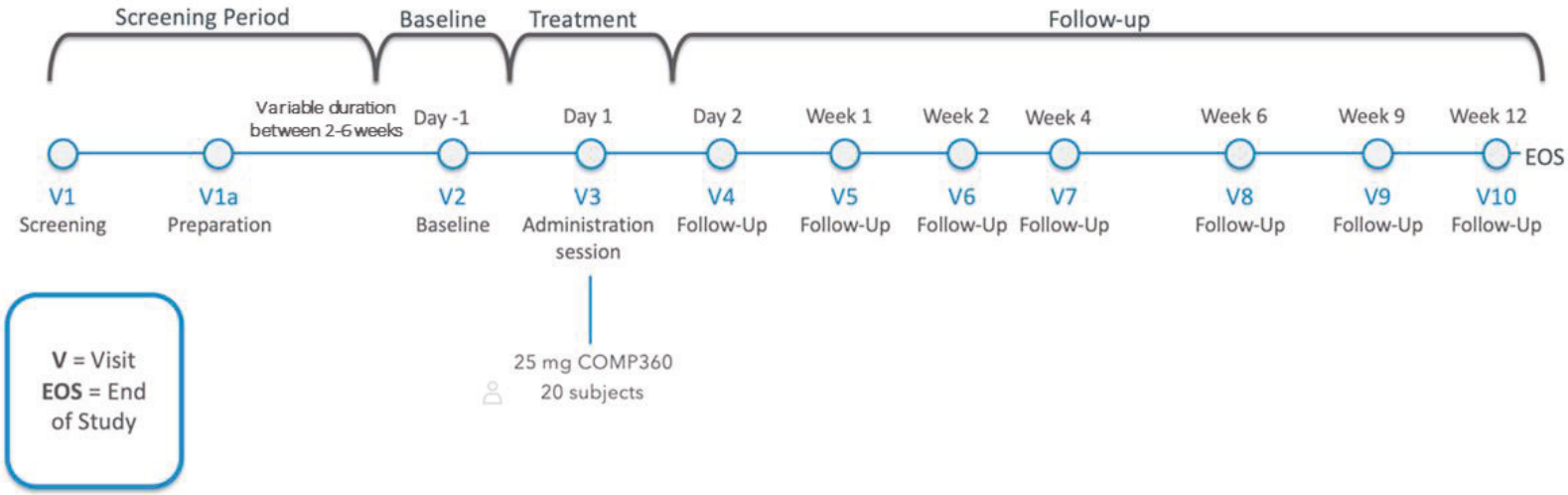
The day before the administration session, the participants will undergo a baseline assessment (2 to 6 weeks after beginning screening period) that will consist of the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), Sheehan Disability Scale (SDS), EuroQuol-5 Dimensions- 5 Levels (EQ-5D-5L), C-SSRS, BPRS+, Perceived Ability to Cope with Trauma (PACT), Resilience Adult Scale (RAS), a semi-structured interview on the management of their PTSD, vital signs, urinalysis, urine drug screen, and urine pregnancy test (only for women of childbearing potential). After baseline data are collected and entered in the Electronic Data Capture (EDC), the Clinical Assessment Technologies Team (CAT) team will complete a final review to ensure the participant's continued eligibility. Participants cannot be progressed to the administration session until this approval is received. Full descriptions of the activities carried out during the therapist sessions can be found in the Therapist Manual. Those who agreed to take part to the optional neuroimaging component of the study and met the eligibility criteria will be offered an MRI scan. To reduce participant burden on baseline visit, the MRI scan can be organised within 7 days prior to the baseline visit. The investigator will be responsible for confirming eligibility of the participant before MRI.

The following day, the participants will attend the clinic for the dosing session that will last approximately 6-8 hours and will be supported by two designated trained therapists. Participants will receive 25 mg COMP360. A full description of the activities of the administration session is found in the Therapist Manual. After the acute effects of COMP360 pass, participants will complete the Five-Dimensional Altered States of Consciousness (5D-ASC), and will be evaluated for safety and accompanied home. On the following day, participants will be seen in person for a safety check, assessment of suicidality, and to discuss their experience during the dosing session (integration). During this visit, participants will complete a semi-structured interview on the acceptability of the therapeutic intervention and the severity of PTSD symptoms will be evaluated using the PCL-5. All sessions between the therapists and the participant may be audio recorded, and the administration session may be video recorded, for research, adherence monitoring, and quality assurance. Audio and video recording of the sessions are subject to participant consent. Participants who do not consent to either or all recordings will not be excluded from the study.

All participants will be asked to remain off medications for their PTSD symptoms for at least 4 weeks following the administration session. Rescue medications are allowed as noted in the protocol. Participants who restart their medications during the first 4 weeks after the dosing session will be assessed for reasons of resuming their medications and followed until 12 weeks post COMP360 administration. Participants will be seen at the clinic for screening (plus safety visits during the screening period as required by the protocol), baseline, day 1, day 2, week 1, week 2, week 4, and week 12 visits. Participants will also be contacted for a remote follow-up at week 6 and week 9. The option of an in clinic visit at weeks 6 and 9 will also be available. See Section 5.3 for a full schedule of assessments. Participants who agreed to the optional neuroimaging component of the study will be offered an MRI scan at week 4.

The study schematic is presented in Section 5.2 and the schedule of assessments is presented in Section 5.3.

5.2 Study Schematic



5.3 Schedule of Assessments

	Screening (≥2 weeks Prior COMP360)		Baseline		Time Since COMP360 Treatment						
	Screen Visit[1]	Screening Period	Day -1	Administration Session (Day 1)	Day 2	Week 1	Week 2	Week 4	Week 6	Week 9	Week 12 (ET)
Allowable Window	N/A	weekly	N/A	≤ 7 days	none	± 1 day	± 1 day	± 1 day	± 3 days	± 3 days	± 7 days
Visit	1	1a, 1b, etc	2	3	4	5	6	7	8	9	10
Location Visit	Clinic	Clinic[2]	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Remote/Clinic	Remote/Clinic	Clinic
Clinical Assessments and Procedures											
Informed Consent	✓										
Medical History	✓		✓								
Inclusion/exclusion Criteria review	✓		✓								
C-SSRS[3]	✓	✓	✓	✓[4]	✓	✓	✓	✓	✓	✓	✓
MINI v7.0.2	✓										
MSI-BPD	✓										
BPRS+			✓	✓[4]	✓	✓	✓	✓	✓	✓	✓
Semi-structured PTSD management interview			✓								
Vital signs	✓		✓	✓[5]	✓						
ECG	✓		✓		✓						
Weight	✓										

	Screening (≥2 weeks Prior COMP360)		Baseline		Time Since COMP360 Treatment						
	Screen Visit[1]	Screening Period	Day -1	Administration Session (Day 1)	Day 2	Week 1	Week 2	Week 4	Week 6	Week 9	Week 12 (ET)
Allowable Window	N/A	weekly	N/A	≤ 7 days	none	± 1 day	± 1 day	± 1 day	± 3 days	± 3 days	± 7 days
Visit	1	1a, 1b, etc	2	3	4	5	6	7	8	9	10
Location Visit	Clinic	Clinic[2]	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Remote/Clinic	Remote/Clinic	Clinic
Height	✓										
Urinalysis[6]	✓		✓								
Urine drug screen[6]	✓		✓		✓	✓	✓	✓	✓	✓	✓
Urine pregnancy test[7]			✓		✓						
Serum pregnancy test[7]	✓										
Clinical Laboratory tests [6]	✓[8]		✓		✓			✓			✓
Biomarkers analysis			✓[9]					✓			✓
MRI scan[9]			✓[10]					✓			
Activate/deactivate Cue app[9]	✓										✓
Prior/Concomitant Medication Review	✓	✓	✓	✓[4]	✓	✓	✓	✓	✓	✓	✓
Documentation of contraceptive method to be used[7]	✓										
IMP administration				✓							

	Screening (≥2 weeks Prior COMP360)		Baseline		Time Since COMP360 Treatment						
	Screen Visit[1]	Screening Period	Day -1	Administration Session (Day 1)	Day 2	Week 1	Week 2	Week 4	Week 6	Week 9	Week 12 (ET)
Allowable Window	N/A	weekly	N/A	≤ 7 days	none	± 1 day	± 1 day	± 1 day	± 3 days	± 3 days	± 7 days
Visit	1	1a, 1b, etc	2	3	4	5	6	7	8	9	10
Location Visit	Clinic	Clinic[2]	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Remote/Clinic	Remote/Clinic	Clinic
Preparation[11]		✓	✓								
Psychoeducational information [12]		✓									
Integration					✓	✓	✓				
AEs	✓	✓	✓	✓[4]	✓	✓	✓	✓	✓	✓	✓
CAPS-5			✓					✓			✓
CTQ	✓										
Participant Completed Assessments											
PCL-5	✓		✓		✓	✓	✓	✓	✓	✓	✓
LEC-5	✓										
mDESS[13]		✓	✓								
EQ-5D-5L			✓					✓			✓
SDS			✓					✓			✓
PACT			✓					✓			✓
RAS			✓					✓			✓
EBI					✓[14]						
5D-ASC				✓[4]							

	Screening (≥2 weeks Prior COMP360)		Baseline		Time Since COMP360 Treatment						
	Screen Visit[1]	Screening Period	Day -1	Administration Session (Day 1)	Day 2	Week 1	Week 2	Week 4	Week 6	Week 9	Week 12 (ET)
Allowable Window	N/A	weekly	N/A	≤ 7 days	none	± 1 day	± 1 day	± 1 day	± 3 days	± 3 days	± 7 days
Visit	1	1a, 1b, etc	2	3	4	5	6	7	8	9	10
Location Visit	Clinic	Clinic[2]	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Remote/Clinic	Remote/Clinic	Clinic
Semi-structured qualitative interview					✓						✓

Abbreviations: AE, adverse event; BPRS+, Brief Psychiatric Rating Scale – Positive Symptom subscale; CAPS-5, Clinician Administered PTSD Scale for DMS-5; C-SSRS, Columbia-Suicide Severity Rated Scale; CTQ, Childhood Trauma Questionnaire; EBI, Emotional Breakthrough Inventory; ECG, electrocardiogram; EQ5D-5L, EuroQoL 5dimension 5-levels; ET, early termination; IMP, Investigational Medicinal Product; mDESS=Modified Discontinuation Emergent Signs and Symptoms scale; MRI, Magnetic Resonance Imaging; MSI-BPD, McLean Screening Instrument for Borderline Personality Disorder; LEC-5, Life Events Checklist for DSM-5; MINI, Mini International Neuropsychiatric Interview; PACT, Perceived Ability to Cope with Trauma scale; PCL-5, PTSD Checklist for DSM-5; SDS, Sheehan Disability Scale; 5D-ASC. Five Dimensional Altered States of Consciousness

[1] If additional visits are needed to ensure adequate time for discontinuation of prior antidepressant therapy, visits should occur weekly prior to the dosing session (V3). At subsequent screening visits (V1a, V1b, etc), medications taken and any changes in medications since the previous visit and C-SSRS will be obtained, in addition, to other assessments at the study clinician's discretion. Assessments may be performed over several days, but all scales should be completed on the same day.
[2] Telephone check-ins will be completed in between clinic visits.
[3] The "Last 12 Months" version will be administered at screening and the "Since Last Visit" version will be administered at all other visits.
[4] This assessment will be administered at the end of the admnistration session.
[5] Body temperature and respiratory rate will be measured before and at the end of the COMP360 administration session. Blood pressure and pulse rate measurements will be collected via an automatic arm cuff, with measurements collected supine at rest, in triplicate approximately one minute apart, at 15 minutes before COMP360 administration, and at one hour, three hours and six hours after COMP360 administration. Measurements should be collected within a ±10-minute time window. At the end of the COMP360 administration session, a final triplicate measurement will be taken after the participant has rested for at least five minutes in the sitting position.
[6] See Section 8.2.4 for complete list of required tests to be performed.
[7] For women of child-bearing potential only.
[8] Only clinical laboratory tests will be tested at this visit.
[9] Optional components of the study.
[10] Baseline MRI scan can be completed within ≤ 7 days prior to baseline visit.
[11] Participants will have two preparation sessions during the screening period and one on day -1.
[12] Psychoeducational information will be provided by the therapist during the preparation sessions in the screening period.
[13] Collection starting from V1b through to Baseline for those participants requiring withdrawal from prohibited medications.
[14] The EBI must be performed after integration on day 2.

6 POPULATION

6.1 Number of Participants

A total of up to 20 participants will be included with the below eligibility criteria.

6.2 Inclusion Criteria

To be eligible for the study, participants must meet the following criteria:

1. Signed ICF
2. 18 years of age or older at screening
3. Meet DSM-5 criteria for current PTSD resulting from a trauma experienced during adulthood measured via the PCL-5 in combination with the LEC-5 at screening
4. Meet DSM-5 criteria for current PTSD resulting from a trauma experienced during adulthood as assessed by the CAPS-5, with minimum score of 25 at baseline
5. Able to identify a next of kin who is willing and able to be reached by the investigators in case of emergency
6. Have successfully discontinued all prohibited medications at least two weeks prior to baseline visit. Section 10.3 describes guidance for antidepressant and antipsychotic medications requiring immediate cessation at Screening V1a followed by at least four weeks of washout prior to baseline.
7. Able to complete all protocol required assessment tools without any assistance or alteration to the copyrighted assessments, and to comply with all study visits

Inclusion Criteria for subset of participants agreeing to the optional MRI scan:

1. Have consented to take part in the neuroimaging component of the study

6.3 Exclusion Criteria

Exclusion of potentially confounding psychiatric diseases and therapies:

1. Current or past history of schizophrenia, obsessive compulsive disorder, personality disorders, bipolar disorder, or psychotic disorder as assessed by clinician judgement and a structured clinical interview (MINI 7.0.2)
2. Diagnosis of complex PTSD based on medical records and clinician judgement
3. Borderline Personality Disorder as demonstrated by both the McLean Screening Instrument for Borderline Personality Disorder (MSI- BPD) score ≥ 7 and clinical confirmation of diagnosis by the study clinician and Medical Monitor
4. Significant suicide risk as defined by (1) suicidal ideation as endorsed on items 4 or 5 on the C-SSRS within the past year, at screening or at baseline, or; (2) suicidal behaviours within the past year, or; (3) history of serious suicide attempt that required a rescuing medical intervention, or; (4) clinical assessment of significant suicidal risk during participant interview
5. Current (within the last year) alcohol or substance use disorder as informed by DSM-5 assessed via the MINI 7.0.2 at screening
6. Other personal circumstances and behaviour judged to be incompatible with establishment of rapport or safe exposure to psilocybin

7. Exposure to 3,4-methylenedioxymethamphetamine (MDMA), psilocybin, or any other psychedelics, such as ayahuasca, mescaline, lysergic acid diethylamide (LSD), or peyote in the past year
8. Primary diagnosis of major depressive disorder within 6 months of study entry
9. Exposure to a traumatic experience in the past 3 months
10. Significant childhood physical or sexual abuse based on clinician judgment with the use of CTQ
11. Enrolment in a psychological therapy programme that will not remain stable for the duration of the study. Psychological therapies cannot have been initiated within 21 days of baseline

General Medical Exclusion Criteria:

1. Women who are pregnant, nursing or planning a pregnancy. Male and female participants who engage in sexual intercourse which could result in pregnancy, must agree to use a highly effective contraceptive method (as listed in Section 10.2) throughout their participation in the study. Women of childbearing potential must have a negative serum pregnancy test at screening and negative urine pregnancy test at baseline
2. Cardiovascular conditions: recent stroke (< 1year from signing of ICF, recent myocardial infarction (<1 year from signing of ICF), hypertension (blood pressure >140/90 mmHg) or clinically significant arrhythmia within 1 year of signing the ICF
3. Uncontrolled diabetes for whom hypoglycaemia could be a concern
4. Seizure disorder
5. Positive urine drug screen for illicit drugs or drugs of abuse at screening and/or baseline. Any positive urine drug test will be reviewed with participants to determine the pattern of use and eligibility will be determined at the investigator's discretion in conjunction with the medical monitor
6. Current enrolment in an interventional study or participation in such within 30 days of screening
7. Abnormal and clinically significant results on vital signs, ECG, or laboratory tests at screening
8. Any other clinically significant cardiovascular, pulmonary, gastrointestinal, hepatic, renal or any other major concurrent illness that, in the opinion of the investigator, may interfere with the interpretation of the study results or constitute a health risk for the participant if he/she takes part in the study
9. Hypersensitivity to the IMP or any of the excipients
10. Unwilling to consent to information sharing with the participant's usual general practitioner or family physician
11. Any other history, medical or psychological conditions that, in the opinion of the investigator, impede the ability to establish therapeutic alliance leading to psilocybin session

Exclusion Criteria for subset of participants agreeing to the optional MRI scan:

1. Had a serious head injury, according to their medical history that, in the opinion of the investigator will interfere with the interpretation of the MRI scan

2. Have an MRI incompatible implant, including dental metal implant, contraceptive coil containing metal, pacemaker, vascular clips, artificial heart valves, or any other foreign body that might not be safe for MRI
3. Have tattoos or permanent make up on head, or neck
4. Being claustrophobic
5. Have a false limb, brace, or body piercings, hair extensions containing metal that cannot be removed
6. Had an eye injury involving metal
7. Any other factor deemed to be incompatible with MRI in the opinion of the investigator

6.4 Participant Screening

Participants will be recruited primarily from the community and referring healthcare providers. Those participants considered potentially eligible for the study will be assessed to confirm eligibility after the participant has signed an ICF. Rescreening of participants considered not eligible for the study will be allowed. Decisions to rescreen will be discussed on a case-by-case basis with the Medical Monitor and study investigators. Participants who consent to take part in the optional neuroimaging portion of the study will be assessed to confirm eligibility with additional criteria specific for MRI. If the participant does not meet the eligibility criteria for the neuroimaging, they will not be able to participate to the MRI scanning, but they will still take part in the main study.

6.5 Deviation from Inclusion/Exclusion Criteria

No deviations will be permitted from the inclusion or exclusion criteria. The investigator may call the Medical Monitor to discuss the eligibility of any given participant.

7 STUDY CONDUCT

The procedures to be performed throughout the study are outlined in the Schedule of Assessments (Section 5.3). A detailed description of each assessment may be found in Section 8.

7.1 General Instructions

Participants will be outpatients and will be recruited primarily from the community and referring healthcare providers. Those participants considered eligible for the study will be further assessed to confirm eligibility after the participant has signed an ICF.

7.2 Study Procedures by Time Point

7.2.1 Screening Period

The participant will be seen initially to evaluate suitability for the study. Participants requiring medication washout will be seen at the clinic weekly for a minimum of three weeks prior to the baseline visit to ensure safe discontinuation of current antidepressant/antipsychotic medications required by the protocol, and to conduct psychoeducation and preparation sessions. Participants not requiring medication washout will be seen at the clinical weekly for a minimum of two visits to conduct psychoeducation and preparation sessions. At the first screening visit (V1), the following assessments will be performed and recorded:

- ICF
- Medical history
- Prior and current medications; the participant will be tapered from prohibited medications (see Section 10.3), if any, under the supervision of the study clinician
- Review of inclusion/exclusion criteria (Section 6)
- MINI version 7.0.2
- MSI-BPD
- PCL-5
- LEC-5
- CTQ
- C-SSRS (Last 12 months)
- Vital signs (ie, supine, after at least five mins of rest, diastolic and systolic blood pressure, pulse, and body temperature)
- Weight

- Height
- 12-lead ECG
- Blood and urine samples for:
  - Clinical laboratory tests
  - Urinalysis
  - Urine drug screen
  - Serum pregnancy test for all women of childbearing potential
- Document contraceptive method to be used by the participant
- If the participant opts to participate to use the Cue app, the app will be uploaded on the participant's mobile phone and activated

All participants will undergo two in-person preparation sessions during the screening period, where the designated therapist will use psychoeducational material. More details on the preparation sessions are in the Therapist Manual.

Once a participant completes all screening assessments and all screening data is entered into the EDC, the Medical Monitor, and CAT Team will review data entered and issue approval, if the patient is eligible. Once approval is issued, the participant should then be invited for a screening V1a visit. The V1a visit is the point at which the patient begins tapering off their antidepressant and/or antipsychotic medications, if appropriate. The participant must complete the taper within the first 4 weeks of this period, prior to 2 weeks completely off antidepressant and/or antipsychotic medications, before baseline. The tapering period used in the study is set at the industry standard for depression trials. The study team will complete telephone check-ins in between the weekly in clinic visits.

At subsequent screening period visits (V1a, V1b, etc), medications taken and any changes in medications since the previous visit, and the C-SSRS and mDESS (if the participant is withdrawing from prohibited medications) will be obtained.

7.2.2 Baseline Visit – Visit 2 – Day -1

The baseline visit should occur within 2 to 6 weeks after beginning of screening period. At baseline visit, the participant's eligibility will be confirmed by reviewing the Inclusion/Exclusion Criteria (Sections 6.2 and 6.3) and updating medical history.

The following procedures will be performed and recorded at this visit:

- C-SSRS (Since Last Visit)
- BPRS+
- CAPS-5

- PCL-5
- mDESS (if applicable)
- EQ-5D-5L
- SDS
- RAS
- PACT
- Semi-structured PTSD management interview
- Vital signs (ie supine, after at least five mins of rest, diastolic and systolic blood pressure, pulse, and body temperature)
- Blood and urine samples for:
  - Clinical laboratory tests
  - Biomarkers, if the participant opts to participate in this part of the study
  - Urine drug screen
  - Urinalysis
  - Urine pregnancy test for all women of childbearing potential
- Medications taken and any changes in medications since the previous visit
- AEs and Serious AEs (SAEs) (Sections 11 and 12)

If the participant continued to meet the eligibility criteria, the trained therapist will review psychoeducational material and the anticipated psilocybin session with the participant. If the participant remains eligible, arrangements will be made for the participant to return to the study site for IMP administration the next day. After baseline data is entered into EDC, the CAT team will complete a final review to ensure the participant's continued eligibility. Participants cannot be progressed to the administration session until this approval is received.

If the participant opts to participate in the neuroimaging part of the study, specific eligibility criteria will be reviewed by the investigator (Section 6). If considered eligible, the participant will undergo an MRI scan (within ≤7 days prior to baseline).

7.2.3 Visit 3 – Day 1 – Administration Session

The administration session should occur the day after baseline visit. During this session (the day of COMP360 administration), the following are to be obtained:

- Vital signs (ie supine after at least five mins of rest diastolic and systolic blood pressure, pulse, body temperature, and respiratory rate). Blood pressure and pulse rate measurements will be collected supine, in triplicate approximately one minute apart, at 15 minutes before COMP360 administration, and one, three and six hours after COMP360 administration. Measurements should be collected within a ±10-minute time window. At the end of the COMP360 administration session, a final triplicate measurement will be taken after the participant has rested for at least five minutes in the sitting position (see Section 8.2.2 for details).

- Administration of study drug (Section 9.4). The dosing session may be video recorded for research, training, and adherence monitoring. A full description of the activities of the dosing session is found in the Therapist Manual. After approximately 6-8 h, participants will be assessed for safety and to ensure the acute drug effects have subsided before being accompanied home.

- C-SSRS (Since Last Visit), after dosing

- BPRS+, after dosing

- 5D-ASC, after dosing

- Medications taken and any changes in medications since the previous visit

- AEs and SAEs (Sections 11 and 12) after dosing

7.2.4 Visit 4 – Day 2

On the day following IMP administration, the participant will return to the study site for a safety check and to discuss their experience during the administration session. The following will be obtained at this visit:

- C-SSRS (Since Last Visit)

- BPRS+

- PCL-5

- Vital signs (ie, supine, after at least five mins of rest, diastolic and systolic blood pressure, pulse, and body temperature)

- 12-lead ECG

- Blood samples for clinical laboratory tests

- Urine drug screen

- Urine pregnancy test for all women of childbearing potential

- Medications taken and any changes in medications since the previous visit

- AE and SAE (Sections 11 and 12)
- Semi-structured qualitative interview
- Integration session with the trained therapist
- EBI. Note that this assessment must be completed after the integration session

Participants will be asked to remain off medications for PTSD until after week 4.

7.2.5 Visit 5 – 1 Week Post-administration

The participant will visit the clinic 1 week (± 1 day) following study drug administration; the following assessments will be obtained at this visit:

- C-SSRS (Since Last Visit)
- BPRS+
- PCL-5
- Urine drug screen
- Medications taken and any changes in medications since the previous visit
- AE and SAE (Sections 11 and 12)
- Integration session with the trained therapist

Participants will be reminded to remain off medications for PTSD until after week 4.

7.2.6 Visit 6 – 2 Weeks Post-administration

The participant will visit the clinic 2 weeks (± 1 day) following study drug administration; the following assessments will be obtained at this visit:

- C-SSRS (Since Last Visit)
- BPRS+
- PCL-5
- Urine drug screen
- Medications taken and any changes in medications since the previous visit
- AE and SAE (Sections 11 and 12)
- Integration session with the trained therapist

Participants will be reminded to remain off medications for PTSD until after week 4.

7.2.7 Visit 7 – 4 Weeks Post-administration

The participant will visit the clinic 4 weeks (± 1 day) following study drug administration; the following assessments will be obtained at this visit:

- C-SSRS (Since Last Visit)
- BPRS+
- CAPS-5
- PCL-5
- EQ-5D-5L
- SDS
- RAS
- PACT
- Blood samples for:
  - Clinical laboratory tests
  - Biomarkers, if the participant opts to participate in this part of the study
- Urine drug screen
- Medications taken and any changes in medications since the previous visit
- AE and SAE (Sections 11 and 12)

If the participant opts to participate in the neuroimaging part of the study, they will undergo an MRI scan.

7.2.8 Visit 8 – 6 Weeks Post-administration

The participant will be telephoned by site staff 6 weeks (± 3 days) following study drug administration; the following assessments will be obtained at this visit:

- C-SSRS (Since Last Visit)
- BPRS+
- PCL-5

- Urine drug screen (if visit is conducted in clinic)
- Medications taken and any changes in medications since the previous visit
- AE and SAE (Sections 11 and 12)

7.2.9 Visit 9 – 9 Weeks Post-administration

The participant will be telephoned by site staff 9 weeks (± 3 days) following study drug administration; the following assessments will be obtained at this visit:

- C-SSRS (Since Last Visit)
- BPRS+
- PCL-5
- Urine drug screen (if visit is conducted in clinic)
- Medications taken and any changes in medications since the previous visit
- AE and SAE (Sections 11 and 12)

7.2.10 Visit 10 – 12 Weeks Post-administration- End of Study

The participant will visit the clinic 12 weeks (± 7 day) following study drug administration for the End of Study visit (EOS); this visit is also to be completed if the participant is discontinued from the study early (early termination [ET]). The following assessments will be obtained at this visit:

- C-SSRS (Since Last Visit)
- BPRS+
- CAPS-5
- PCL-5
- EQ-5D-5L
- SDS
- RAS
- PACT
- Semi-structured qualitative interview
- Blood samples for:
  - Clinical laboratory tests

- Biomarkers, if the participant opts to participate in this part of the study

- Urine drug screen
- Deactivate Cue app, if appropriate
- Medications taken and any changes in medications since the previous visit
- AE and SAE (Sections 11 and 12)

7.3 Premature Discontinuation

If a participant's participation in the study is terminated prematurely for any reason, the reason for such ET should be documented and the V10 (EOS) procedures should be performed as noted in Section 7.2.10.

A termination form should be completed for every participant who is enrolled, whether the participant completes the study or not. The reason for any ET should be indicated on this form; as much information should be provided as possible. The primary reason for a participant discontinuing early should be selected from the following standard categories of ET:

- *Screen Failure:* Participant does not qualify to participate in the study.
- *Lack of efficacy*
- *Adverse Event*: Clinical or laboratory events occurred that, in the medical judgment of the investigator for the best interest of the participant, are grounds for discontinuation. This includes serious and nonserious AEs regardless of relation to the IMP.
- *Death:* The participant died.
- *Withdrawal of Consent*: The participant desired to withdraw from further participation in the study in the absence of an investigator-determined medical need to withdraw. If the participant gave a reason for withdrawing, it should be recorded.
- *Lost to Follow-up*: The participant stopped coming for visits and study personnel were unable to contact the participant.
- *Non-compliance:* The participant was non-compliant with study visits or procedures.
- *Other*: The participant was discontinued for a reason other than those listed above, such termination of the study by the sponsor.

8 DESCRIPTION OF STUDY PROCEDURES

8.1 Efficacy Assessments

8.1.1 Clinician-Administered PTSD Scale for DSM-5

The CAPS-5 is the gold standard clinician rated assessment for PTSD. It consists of 30 items and can be used for diagnostic purposes as well as monitoring PTSD symptoms severity over time. Each item could be rated as 0=absent, 1=mild/subthreshold, 2=moderate/subthreshold, severe/markedly elevated, 4=extreme/ incapacitating. At baseline visit the last month version of CAPS-5 will be used for diagnostic purposes. The last month version of the assessment will be administered to monitor participant symptoms improvement after treatment at weeks 4 and 12.[13]

8.1.2 PTSD Checklist for DSM-5

The PCL-5 is a 20-item self-reported scale, used for provisional PTSD diagnosis, screening and symptoms monitoring purposes. The participant will complete the past month version of this assessment at screening, scoring the severity of their symptoms on a 5-points Likert scale where 0 = not at all and 4 = extremely.[14] The screener should help the participant understanding this scale and in its correct completion to ensure the PCL-5 is used to measure the relevant Criterion A for the trauma. The past day version of the assessment will be used at day 2. The past week version of the assessment will be administered at baseline and weeks 1, 2, 4, 6, 9, and 12.

8.1.3 EuroQoL5dimension 5level Scale

The EQ-5D-5L was introduced by the EuroQoL Group in 2009.[21] The EQ-5D-5L consists of 2 sections: the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ VAS).

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

The EQ VAS records the participant's self-rated health on a vertical VAS, where the endpoints are labelled 'The best imaginable health state' and 'The worst imaginable health state'. The VAS can be used as a quantitative measure of health outcome that reflect the participant's own judgement.

The EQ-5D-5L will be obtained at baseline, week 4, and week 12 visits.

8.1.4 Sheehan Disability Scale

The SDS is a brief, 5-item inventory that assesses functional impairment in work/school, social life, and family life. The total score ranges from 0 to 30 with 0 representing no impairment and

30 representing severe impairment. The last two items of the scale (Days Lost and Days Unproductive) do not count toward the total score. Each domain is rated on a 10-point visual analogue scale (VAS).[15] The SDS will be completed by participants at baseline, week 4 and week 12.

8.1.5 Resiliance Adult Scale

The RAS was developed to capture a set of fundamental protective factors based on resilience research. It includes 33 items, in a six-factors structure including (1) perception of self, (2) planned future, (3) social competence, (4) structured style, (5) family cohesion, (6) social recourses.[16]

8.1.6 Perceived Ability to Cope with Trauma Scale

The PACT scale is a self-reported, 20 items scale, organised in two sub-scales, (1) Forward focus and (2) Trauma focus. The first subscale measures the ability of the individual to move beyond their trauma, while the second measures the perceived ability to focus on processing the trauma. Overall the scales provides a quantification of the individual's coping flexibility.[17]

8.2 Safety Assessments

8.2.1 Columbia-Suicide Severity Rating Scale

The C-SSRS will be used to assess suicide potential or tendency as a study entry criterion and monitored throughout the study.

The C-SSRS is a semi-structured interview designed to assess the severity and intensity of suicidal ideation, suicidal behaviour, and non-suicidal self-injurious behaviour over a specified time period. The measurement of suicidal ideation is based on five "yes" or "no" questions with accompanying descriptions arranged in order of increasing severity. If the patient answers "yes" to either questions 1 or 2, the intensity of ideation is assessed in five additional questions related to frequency, duration, controllability, deterrents, and reasons for the most severe suicidal ideation. Suicidal behaviour is assessed by asking questions categorising behaviours into actual, aborted, and interrupted attempts; preparatory behaviour; and non-suicidal self-injurious behaviour.

If any item(s) on the C-SSRS are answered "yes", the primary investigator or physician investigator must review the patient's responses in order to (a) at screening and day-1 determine the patient's study eligibility and potential need for referral to a mental health professional, and (b) during the study evaluate the patient's need for appropriate medical management such as a referral to a mental health professional.

A significant risk of suicide is defined as a "yes" in answer to (a) questions 4 or 5 on the suicidal ideation section; or (b) any questions on any item in the suicidal behaviour section. This must be reported as an AE or SAE as appropriate and followed up accordingly. Additionally, if a patient responds "yes" to any of the suicidal ideation questions 1 through 3, the investigator should apply clinical judgment to determine the need for reporting this as an AE or SAE and the need for any appropriate referral.

The C-SSRS will be collected at every visit.

8.2.2 Vital Signs

Blood pressure will be measured supine, after at least 5 min at rest. The three measurements should be recorded 1 to 2 min apart, and the results averaged to inform eligibility at screening and baseline. Blood pressure, body temperature, and pulse rate will be obtained at screening, baseline, administration session, and day 2.

On Day 1 (administration session), body temperature and respiratory rate will be measured before and after COMP360 administration. On Day 1, blood pressure and pulse rate will be monitored via an automatic arm cuff, with measurements collected supine at rest, in triplicate approximately one minute apart, at 15 minutes before COMP360 administration, and one, three and six hours after COMP360 administration. Measurements should be collected within a ±10-minute time window. At the end of the COMP360 administration session, a final triplicate measurement will be taken after the participant has rested for at least five minutes in the sitting position.

Any AEs related to blood pressure and pulse rate will be recorded. Investigators should not inform participants of any blood pressure or pulse rate changes unless clinically warranted.

All extreme high blood pressure values (systolic >160 mmHg or diastolic >110 mmHg) should be double-checked before the values are recorded. If blood pressure remains high, the Investigator should consider seeking assistance from health care providers experienced in managing elevated blood pressure and refer participants with signs or symptoms of hypertensive crisis (eg chest pain, shortness of breath, visual disturbance, neurological deficits, etc) immediately for emergency care.

8.2.3 Electrocardiogram

Standard 12-lead ECGs will be obtained at screening, baseline, and day 2.

8.2.4 Clinical Laboratory Tests

Clinical laboratory evaluations will be performed including blood chemistry, haematology, urinalysis, urine drug screen, and serum and urine pregnancy tests (for women of childbearing potential). Blood samples for clinical laboratory tests will be collected at screening, baseline, and day 2, week 4, and week 12. Urine samples for urinalysis will be collected at screening and baseline. Urine samples for urine drug screen will be collected at screening, baseline, day 2, and weeks 1 to 12. For urine drug screen, a dipstick will be performed as standard test. If the dipstick results at screening, day 2, or weeks 1 to 12 are positive, the sample will be sent to the central lab for a confirmatory assessment. The study doctor will discuss the results of the urine drug screen with the participant, if deemed necessary. The details of the analyses are listed in Table 8.1. and in the Schedule of Assessments in Section 5.3.

Table 8.1 List of clinical laboratory evaluations

Haematology	**Chemistry**
Haemoglobin	Albumin
Haematocrit	Alkaline phosphatase
Red blood cell count	Alanine aminotransferase (ALT)
Mean corpuscular haemoglobin	Amylase
Mean corpuscular volume	Aspartate aminotransferase (AST)
Mean corpuscular haemoglobin concentration	Bicarbonate
White blood cell count (with differential)	Bilirubin (direct, indirect, and total)
Platelet count	Calcium
	Chloride
	Creatine kinase
	Creatinine
	Gamma-glutamyl transferase
	Glucose
	Lactate dehydrogenase
	Lipase
	Magnesium
	Phosphate
	Potassium
	Protein-total
	Sodium
	Urea (blood urea nitrogen)
	Uric acid
Urinalysis (dipstick)	**Urine Drug screen**
Blood	Amphetamines
Glucose	Barbiturates
Ketone	Benzodiazepines
Protein	Cocaine
pH	Cannabinoids
Specific gravity	Opiates
Nitrite	
Leukocytes	
Bilirubin	
Urobilinogen	
Others	
Urine pregnancy dipstick	
Serum pregnancy test	

8.2.5 Adverse Events

All AEs occurring after the participant signs the ICF and up to the last study event will be recorded. Any AEs occurring before the start of treatment (eg, before the dose of the IMP on day 1) will be recorded as pre-treatment AEs. Any SAE ongoing at V12 (EOS/ET) will be followed until resolution or no longer considered clinically significant.

See Sections 11 and 12 for additional information.

8.2.6 Brief Psychiatric Rating Scale – Positive Symptom Subscale

The BPRS+ is a four-item, clinician administered subscale of the 18-item, clinician-administered Brief Psychiatric Rating Scale (BPRS), used to assess symptoms of

psychosis, anxiety and depression [18]. The sensitivity to change of the BPRS in individuals with depression has been previously demonstrated [19]. The four-item positive symptom subscale assesses conceptual disorganisation, unusual thought content, suspiciousness, and hallucinatory behaviour, which are scored on a scale from 1 (not present) to 7 (extremely severe) with a score range of 4-28. A score of 0 will be recorded if the symptom was not assessed.

8.2.7 Modified Discontinuation Emergent Signs and Symptoms Scale

The mDESS is a 15-item, self-reported scale, listing typical symptoms that can arise from antidepressant withdrawal.[20] It is a modified version of the 43-item Discontinuation Emergent Signs and Symptoms Scale.[21] If participants will be required to withdraw from prohibited medications, they will be asked to class each of the 15 symptoms as new, old but worse, old but improved, old but not changed, or not present. A total score ranging from 0 to 15 is calculated by summing the number of 'new symptom(s)' and the number of 'old symptom(s) but worse'. The mDESS will be performed at each visit during the Screening Period (V1b onwards) and at Baseline in the subset of participants who are withdrawing from prohibited medication/s during the Screening Period.

8.3 Other Assessment Instruments

8.3.1 Mini International Neuropsychiatric Interview, Version 7.0.2

The MINI was designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-5 and International Classification of Diseases-10. Validation and reliability studies have been done comparing the MINI to the Structured Clinical Interview for DSM-5 Patient Edition and the Composite International Diagnostic Interview (a structured interview developed by the World Health Organisation). Version 7.0.2 of the MINI will be used for this study. The results of these studies show that the MINI has similar reliability and validity properties, but can be administered in a much shorter period (mean 18.7 ± 11.6 min, median 15 min) than the above referenced instruments. It can be used by clinicians after a brief training session.[27]

At screening, the presence of inclusionary and lack of exclusionary psychiatric diagnoses will be confirmed by use of the MINI 7.0.2.[27]

8.3.2 McLean Screening Instrument for Borderline Personality Disorder

The MSI-BPD is a commonly used measure to assess for BPD. The scale consists of 10 items based on the DSM-5 BPD criteria; the first 8 items represent the first eight criteria in the DSM-5 for BPD diagnosis, while the last two questions assess the paranoia and dissociation criteria for BPD. Scores for the MSI-BPD range from 0 to 10, with each item rated as "1" if present and "0" if absent. A score of 7 or higher indicates a likelihood for the participant to meet criteria for BPD. The MSI-BPD will be collected at Screening only and participants positive for BPD will be subject to clinical confirmation of diagnosis by the study clinician and Medical Monitor.

8.3.3 Life Event Checklist for DSM-5

LEC-5 is a self-report measure designed to screen for potentially traumatic events in a respondent's lifetime. The LEC-5 assesses exposure to 16 events known to potentially result in PTSD or distress and includes one additional item assessing any other extraordinarily stressful event not captured in the first 16 items. For each item in the list the participant has the option to reply, "happened to me", "witnessed it", "learned about it", "part of my job", "not sure", "doesn't apply". The LEC-5 will be administered at screening together with the PCL-5.[22]

8.3.4 Childhood Trauma Questionnaire

The CTQ is a 28-item self-report measure validated to screen for history of childhood abuse and the meaning given to the abuse by the participant. It consists of 5 subscales measuring, physical abuse, sexual abuse, emotional abuse, physical neglect, and emotional neglect. The CTQ will be used at screening to exclude participants with childhood trauma.[23]

8.3.5 Semi-structured PTSD management interview

Participants will be asked at baseline about their PTSD symptoms and feelings at the time of diagnosis and the type of treatments and support offered to them before joining the study.

8.3.6 Semi-structured qualitative interview

Participants will be asked their overall opinion of their experience with COMP360 therapy, if they consider a single dose enough, the impact of the experience on their lives and any feedback on the study design. This will occur at day 2 and week 12.

8.3.7 Five Dimensional Altered States of Consciousness Questionnaire

The 5D-ASC measures the acute drug effects using 5 primary dimensions and respective subdimensions to assess alterations in mood, perception, and experience of self in relation to environment and thought disorder. The 5 dimensions include *oceanic boundlessness*, *anxious ego dissolution*, *visionary restructuralization*, *auditory alterations*, and *reduction of vigilance.*[24,25] This will be administered immediately after the psilocybin session on day of COMP360 administration.

8.3.8 Emotional Breakthrough Inventory

The EBI is an eight-item brief measure intended to index the degree to which an individual experiences their emotion during the study drug administration session. Each of the items is a VAS, with units from 0 to 100. A total score can be derived by averaging individual item responses.[26]

8.3.9 Cue app

If the participant opts to participate in the Cue app portion of the study, the app will be activated on the participant's mobile phone at the screening visit; it will be deactivated at the EOS. Participants who do not consent to the app installation, or do not have a smart phone, will not be excluded from the study.

Mobile data collection: The Cue app will collect data from the participant's smart phone and periodically send these data back to the HealthRhythms' highly secured servers. Once the app is installed on the phone, the participant would use their phone as they normally would and keep their phone with them as often as possible. The data collected from the participant's phone will include:

- Activity data based on CoreMotion on iOS and the Activity Transition API on Android.
- Location information from the Location API on both iOS and Android, which uses GPS and/or cell tower location information.
- Device display status from Springboard on iOS and display on/off broadcast events on Android. These data are used to approximate when a user is actively using their phone.
- Pedometer data ("steps") based on CoreMotion on iOS and Google Fit on Android.

No personally identifiable information is captured, and all captured data are encrypted on the smartphone before upload to HealthRhythms' cloud storage servers, and the data remain encrypted in transit and at rest.

8.3.10 Biomarkers measurements

If the participant opts to participate in this portion of the study, additional blood samples will be drawn. Participants who do not consent to blood withdrawal for biomarkers will not be excluded from the study, and clinical laboratory tests will still be run for safety purposes.

Blood samples to measure biomarkers levels will be collected at baseline, week 4, and week 12 after COMP360 administration. Up to 100mL of blood will be collected at each time point: five X 10ml EDTA tubes, one X 8.5ml serum tube, two X 2.5ml RNA PAXGene tube, and two X 8.5ml DNA PAXGene tube will be collected.

In addition to clinical laboratory measurements, the biomarkers measured will include biomarkers related to stress and inflammation such as plasma or serum cortisol, oxytocin, ACTH, catecholamines, BDNF, NPY, and cytokines; telomere length and telomerase activity; and the expression levels of stress-relevant mRNAs through transcriptomics and candidate gene analyses.

In addition, aliquots of the samples will be bio-banked for future studies, such as for genome-wide methylation, genome-wide expression, genotyping/GWAS (psych chip).

8.3.11 Magnetic Resonance Imaging

If the participant opts to participate in this portion of the study, brain imaging via MRI will be performed at baseline and week 4. To reduce participant burden at baseline visit, the baseline MRI can be carried out ≤ 7 days prior to the baseline visit. The activity of brain regions will be

monitored during the performance of an emotional go/no-go task. Participants who do not consent to the MRI scan will not be excluded from the study.

8.4 Protocol Deviations

All protocol deviations will be assessed and documented on a case-by-case basis before the database lock.

9 INVESTIGATIONAL PRODUCT MANAGEMENT

9.1 Description

Information about the IMP is provided in Table 9.1.

Table 9.1 Details of Investigational Medicinal Product (IMP)

	COMP360
Ingredient	**Synthetic psilocybin**
Manufacturer	[redacted]
Dose	**25 mg**
Route	**Oral**
Formulation	**Capsule**
Strength	**5 mg**

9.2 Storage

All IMP must be kept in a locked area with limited access. The high-density polyethylene (HDPE) bottles of IMP are to be stored as indicated in the IMP Handling Manual. Deviations of storage temperature outside this required range should be documented and COMPASS or its designee should be notified promptly. Bottles of IMP should not be frozen. If any component of the IMP is damaged, COMPASS or its designee must be notified as soon as possible.

9.3 Packaging

COMP360 capsules are packaged into HDPE containers with child-resistant, tamper-evident screw cap lids with a mounted desiccant by [redacted] Each bottle contains 5 capsules for a single dose administration. Labels are affixed on to the bottles consistent with regulations in participating countries. Single individual bottles will be provided for use by a given participant.

9.4 Dose and Administration

Each participant will be assigned 1 treatment bottle containing the following:

- 5 x 5mg COMP360 capsules

After a light breakfast taken at least 2 h prior to IMP administration and under observation of study staff, the 5-capsule dose is to be swallowed with a full glass of water; due to the number of capsules in a dose, additional water may be necessary to swallow the dose. Study staff will ensure the entire 5-capsule dose has been swallowed.

To prepare for the drug experience, the participant will take the IMP and lie down in a room with dim lights and a standard playlist of relaxing music playing quietly. Two trained therapists will be present with the participant at all times.

The effects of COMP360 usually start about 20 to 30 min after administration, become most intense in the first 90 to 120 min, and gradually subside after 5 to 6 h. The participants will be asked to remain in the room for the duration of the session regardless of the intensity of the effects, preferably lying down. A light meal and fruit will be available for the participant.

About 5 to 6 h after dosing, a trained therapist will discuss the study drug administration experience with the participant. The participant is to be discharged 6 to 8 h post-dosing when, in the opinion of the investigator, the acute effects of COMP360 are resolved. The participant will be accompanied home. The site is to be notified that they have returned home safely, and in the absence of receiving a phone call, site staff will directly contact the participant.

More details on preparation, administration, and integration sessions are available in the Therapist Manual.

9.5 Accountability

The investigator must keep an accurate account of the number of IMP units delivered to the site, administered to participants, and returned to COMPASS or its designee during and at the completion of the study. The IMP must be administered to participants only by an appropriately qualified person. The IMP is to be used in accordance with the protocol by participants who are under the direct supervision of the investigator. Investigators should maintain records that document adequately that the participants were administered the IMP dose specified by the protocol and reconcile all IMPs received at the site before final disposition. At the end of the study, or as directed, all IMP, including unused, partially used, and empty containers, will be returned to the sponsor or its designee.

9.6 Compliance

Administration of the IMP will be supervised by study personnel to ensure compliance.

10 CONCOMITANT THERAPY

All prescription and non-prescription medications (eg over-the-counter drugs and herbal supplements) that participants report taking during the 30 days prior to screening will be assessed and recorded at that visit. For each medication, documentation should list the trade or generic name, the total daily dose including units (or the dose, units and scheduled and actual frequency of administration if the medication is not taken daily), the route of administration, and the reason for use.

Concomitant medication refers to all drugs and therapies used from the time the ICF was signed through the end of study participation.

Changes, additions, or discontinuations to medications will be assessed and recorded in the eCRF during each study visit. All as-needed (*pro re nata*, PRN) prescriptions should be converted to reflect actual number of pills or dose taken per day.

10.1 Permissible Medications

All concurrent non-serotonergic medications are allowed.

Medications for the management of concurrent anxiety and insomnia, or nonpsychiatric medications that have a potential psychotropic effect are permitted with the following limitations. From the initial screening visit through final study visit (EOS), participants are permitted to remain on the same regular dose regimen of benzodiazepines they were already on in order to avoid withdrawal symptoms. Participants who were not taking benzodiazepines before screening may take up to 2 mg of lorazepam equivalents per day for anxiety emerging during the withdrawal of antidepressant and antipsychotic medications. Benzodiazepines may not be taken within 8 hours before COMP360 administration. Hypnotics such as zopiclone, eszopiclone or zolpidem are allowed for insomnia. Prescription and non-prescription medications with psychoactive properties that are used as needed for nonpsychiatric conditions (eg pseudoephedrine for allergies or cold symptoms;) can be used daily but not within 12 hours before dosing. Documentation of the use of adjunctive anxiolytics, hypnotics or medication with potential psychotropic properties (including over-the-counter preparations) will be obtained at each clinic visit. Ongoing, stably-dosed medications prescribed for attention deficit hyperactivity disorder, including psychostimulants, atomoxetine, clonidine, and guanfacine, are permitted alone or in combination. Atomoxetine use should be avoided for 12 hours prior to and six hours post COMP360 administration (see Section 10.3).

Therapy considered necessary for the participant's welfare may be given at the discretion of the study clinician.

10.2 Definition of Women of Childbearing Potential and/or Acceptable Contraceptive Methods

A woman is considered of childbearing potential (eg fertile) following menarche and until becoming postmenopausal unless permanently sterilised (eg participant had hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).

A woman who is not of childbearing potential is considered to be postmenopausal after at least 12 months without menstruation.

The following methods of contraception, if used properly and used for the duration of the study, are generally considered highly effective:

- Combined oestrogen- and progestogen-containing hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence is considered a highly effective method only in case of refraining from heterosexual intercourse during the entire period of the clinical trial and when in line with the preferred and usual lifestyle of the subject

Periodic abstinence (eg calendar, symptothermal, or post-ovulation methods) is not an acceptable form of contraception for this study.

These methods of contraception also apply to partners of male participants.

The investigator and each participant will determine the appropriate method of contraception for the participant during the participation in the study. This will be documented at screening.

If a participant or the partner of a male participant becomes pregnant during the study, the investigator will notify the PI, study sponsor and COMPASS immediately after the pregnancy is confirmed according to Section 14.5.

10.3 Prohibited Medications

Participants are to be discontinued from antidepressant and/or antipsychotic medications at least two weeks prior to baseline visit. These medications include the following two classes of the Anatomical Therapeutic Chemical (ATC) Classification System: - NO5A Antipsychotics & NO6A Antidepressants. Participants should also discontinue prazosin one week before COMP360 administration session. For fluoxetine, aripiprazole, brexpiprazole, and cariprazine, immediate cessation at screening V1a followed by at least four weeks of washout will be required prior to baseline.

Opioid medications (all classes) are prohibited in the two-weeks prior to baseline and if taken for >3 consecutive days in the post-administration follow-up period.

In vitro inhibition studies suggest that psilocin, the active metabolite of psilocybin, may be an inhibitor of cytochrome P450 (CYP)2D6 at clinically relevant concentrations. In the absence of formal drug-drug interaction studies yet to be completed, it is recommended to avoid the use of medications that are sensitive substrates of CYP2D6 (eg atomoxetine, desipramine, dextromethorphan, eliglustat, nebivolol, nortriptyline, perphenazine, R-venlafaxine, tolterodine) or substrates with a narrow therapeutic index (dosulepin) for 12 hours prior to and six hours post COMP360 administration. As COMP360 is a single dose treatment, the risk for any clinically important drug-drug interactions is considered low. After a single oral administration of COMP360, the half-life of psilocin, the active metabolite of psilocybin, is approximately three hours. Therefore, drug interaction potential would be greatly diminished by day 2.

The medical monitor should be contacted if there is any question that a used medication is thought to be in one of these classes. These medications are not to be reintroduced to the participant until after week 4. Participants who require concomitant medication(s) specifically for the treatment of PTSD at any time through the duration of the study will be assessed for reasons of resuming their medications and followed until 12 weeks post COMP360 administration. Participants can resume taking prazosin the day after administration session, if necessary. The study clinician should initiate treatment of symptoms of PTSD as deemed appropriate and may change the venue of therapy (eg outpatient to inpatient) if deemed clinically necessary. The intervention may be a combination of somatic (eg approved antidepressant medication) and non-somatic (various forms psychotherapy, eg TF- CBT) whose therapeutic intention is remediation of PTSD symptoms. Because the anticipated half-life of COMP360 is approximately 3 h, and only 1 administration of test product is permitted, no known issues regarding pharmacokinetics or pharmacodynamic interactions are envisioned within approximately 7 days of product administration.

10.4 Rescue Medication

Rescue medications may be used during and after the administration session.

The decision to medicate a participant will depend on whether the responsible physician judges that they are capable of maintaining the safety of the participant and others without medical intervention.

- Benzodiazepine anxiolytics are the pharmacological intervention of choice in case of acute psychological distress (eg medications such as lorazepam or alprazolam that have a rapid onset, a short time until peak plasma concentration, and a short duration of therapeutic action; the oral route is preferable because IV injection procedures may further exacerbate the participant's anxiety)
- Antipsychotic medications (eg risperidone) should be available in the event that an adverse reaction escalates to unmanageable psychosis.

In case of the development of acute anxiety or psychotic symptoms requiring pharmacological intervention, the participant will be managed appropriately. The participant may be discharged from the clinic when, in the opinion of investigator, the condition has stabilised. The participant will be accompanied home. The site is to be notified by the participant that they have returned home safely, and in the absence of receiving a phone call site staff will directly contact the participant.

Information for how to manage participants during difficult psychological states are detailed in the Therapist Manual.

11 ADVERSE EVENTS

Throughout the course of the study, all AEs will be monitored and recorded in the eCRF, including the AE's description, start and end date, seriousness, severity, action taken, and relationship to the IMP. If AEs occur, the first concern will be the safety of the study participants.

Per ICH E2A: An AE is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether considered related to the medicinal product.

Medical interventions such as surgeries, diagnostic procedures, and therapeutic procedures are not AEs, but the action taken to treat the medical condition. They should be recorded as treatment of the AEs.

The investigator will promptly notify COMPASS or ICON of all SAEs and nonserious AEs occurring during the clinical trial so that legal obligations and ethical responsibilities towards the safety of participants and the safety of the product under clinical investigation are met.

COMPASS or ICON has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. COMPASS or ICON will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and investigators. These will be detailed in the safety plan.

11.1 Documenting Adverse Events

AEs occurring from when the participant signs the ICF until the last study event will be recorded. Any AEs occurring before the start of treatment (eg before the dose of the IMP on day 1) will be recorded as pre-treatment AEs. Also, the sign, symptom, or disease present before starting the treatment period are only considered AEs if they worsen after starting the treatment period. Investigators should document all significant illnesses that the participant has experienced within 3 months of the screening and up to the day of inclusion. Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs.

All clinical laboratory results, vital signs, and ECG results or findings should be appraised by the investigator to determine their clinical significance. Isolated abnormal clinical laboratory test results, vital sign findings, or ECG findings (eg not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to IMP discontinuation/study withdrawal, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

At each time point, the investigator will determine whether any AEs have occurred by evaluating the participant. AEs may be directly observed, reported spontaneously by the participant or by questioning the participant at each time point. Participants should be

questioned in a general way, without asking about the occurrence of any specific symptoms. The investigator must assess all AEs to determine intensity, causality and seriousness, in accordance with the definitions in Sections 11.2, 11.3, and 12.1, respectively. The investigator's assessment must be clearly documented in the study site's source documentation with the investigator's signature.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

The investigator should report all AEs on the AE page(s) of the eCRF and source documents, regardless of seriousness, severity, and causality. Whenever possible, an AE will be reported using a diagnostic term, (eg "common cold" or "upper respiratory infection" rather than "runny nose, cough, mild fever") and should be described with the attributes described in Sections 11.2 and 11.3.

11.2 Assessment of Intensity

Each AE will be classified according to the following criteria:

Mild:	The AE does not interfere in a significant manner with the participant's normal level of functioning.
Moderate:	The AE produces some impairment of functioning but is not hazardous to the participant's health.
Severe:	The AE produces significant impairment of functioning or incapacitation and is a definite hazard to the participant's health.

Severity versus Seriousness: Severity is used to describe the level of functional impairment and hazardousness due to the intensity of a specific event while the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "seriousness". An SAE is one that results in death, is life-threatening, causes hospitalisation or prolongs hospitalisation, causes significant or persistent disability, results in a congenital disorder or is otherwise medically significant (see Section 12 for details).

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the experience should be noted. If the intensity category changes over several days, those changes should be recorded separately (with distinct onset dates).

11.3 Assessment of Causality

Each AE will be assessed as to its relationship to the IMP, based on the following criteria. Although the attribution by the investigator will be collected for reported events, for analytic purposes a temporal association with the use of the IMP will be assumed sufficient for at least plausible association. All noxious and unintended responses to the IMP related to the dose should be reported as Adverse Drug Reactions (ADR).

Not related:	No causal relationship exists between the IMP and the AE, but an obvious alternative cause exists, eg the participant's underlying medical condition or concomitant therapy.
Possibly related:	A connection with the administration of the IMP appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the IMP; (2) it could not readily have been produced by the participant's clinical state, environmental or toxic factors, or other modes of therapy administered to the participant; or (3) it follows a known pattern of response to the IMP.
Related:	There is a reasonable/plausible possibility that the AE may have been caused by the IMP.

When assessing the relationship to the IMP, the following criteria will be considered:

- Known class effect
- Biological plausibility
- Lack of alternative explanation—concomitant drug or disease

11.4 Action Taken Regarding Investigational Medicinal Product

Dose modifications of IMP (eg dose not changed, drug withdrawn, drug interrupted, or dose increased) are not applicable as this is a single dose study.

- Not Applicable: Participant died, study treatment had been completed prior to reaction/event, or reaction/event occurred prior to start of treatment

11.5 Other Action Taken for Event

Other possible actions that can be taken for event are the following:

- None (eg no treatment was required)
- Medication required (eg prescription and/or OTC medication was required to treat the AE)
- Hospitalisation or prolongation of hospitalisation required (eg hospitalisation was required or prolonged because of the AE, whether medication was required)
- Other

11.6 Adverse Event Outcome

The outcome of AEs can be defined as one of the following:

- Recovered/Resolved (eg the participant fully recovered from the AE with no residual effect observed)
- Recovering/Resolving (eg the AE improved but has not fully resolved)
- Not Recovered/Not Resolved (eg the AE itself is still present and observable)
- Recovered/Resolved with Sequelae (eg the residual effects of the AE are still present and observable, including sequelae/residual effects)
- Fatal (eg 'fatal' should be used when death is a direct outcome of the AE)
- Unknown

11.7 Clinical Laboratory Changes

Clinically significant abnormalities in a laboratory value that is new in onset or which has worsened in severity or frequency from the baseline condition and meets one of the following criteria will be recorded and reported as an AE:

- Requires therapeutic intervention or diagnostic tests
- Has accompanying or inducing symptoms or signs
- Is judged by the investigator as clinically significant

Combined elevations of aminotransferases and bilirubin, either serious or nonserious, and whether causally related, meeting the criteria of a potential Hy's Law case (total bilirubin level ≥ 3 × upper limit of normal [ULN] with simultaneous ALT or AST ≥ 3 × ULN) should always be reported to the sponsor as soon as possible following the procedures outlined in Section 12.3 for SAE reporting, with the investigator's assessment of seriousness, causality, and a detailed narrative.

11.8 Overdose

Any instance of overdose (suspected or confirmed) must be communicated to the CRO, within 24 hours and be fully documented as an AE or SAE if it meets the SAE criteria. Details of any signs or symptoms and their management should be recorded including details of any antidote(s) administered.

11.9 Adverse Events of Special Interest

An adverse event of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to the study drug, for which ongoing monitoring and immediate notification by the investigator to COMPASS and the CRO is required. Such AEs may require further investigation to characterise and understand them.

The following events will be reported as AESI:

AESI term	MedDRA Preferred Terms
Manic and bipolar mood disorders and disturbances	Euphoric mood; Grandiosity; Bipolar disorder; Bipolar I disorder; Bipolar II disorder; Cyclothymic disorder; Hypomania; Mania; Manic symptoms
Dissociative disorder	Dissociative disorder; Dissociative identity disorder; Dissociative amnesia; Dissociation; Depersonalisation/derealisation disorder
Hallucination	Hallucination; Hallucination, auditory; Hallucination, synaesthetic; Hallucination, tactile; Hallucination, visual; Hallucination, olfactory; Hallucinations, mixed; Somatic hallucination; Hallucination, gustatory; Illusion; Pseudohallucination
Psychotic disorder	Psychotic disorder; Psychotic behaviour; Acute psychosis; Hysterical psychosis; Reactive psychosis; Substance-induced psychotic disorder; Brief psychotic disorder with marked stressors; Brief psychotic disorder without marked stressors; Transient psychosis; Cotard's syndrome; Delusions; Delusion of grandeur; Delusion of parasitosis; Delusion of reference; Delusion of replacement; Delusion of theft; Depressive delusion; Erotomanic delusion; Jealous delusion; Mixed delusion; Persecutory delusion; Somatic Delusion; Thought broadcasting; Thought insertion; Thought withdrawal; Delusional disorder, erotomanic type; Delusional disorder, grandiose type; Delusional disorder, jealous type; Delusional disorder, mixed type; Delusional disorder, persecutory type; Delusional disorder, somatic type; Delusional disorder, unspecified type
Cognitive disorder	Cognitive disorder
Disturbance in attention	Disturbance in attention
Mood altered	Mood altered; Depressed mood; Affect lability; Fluctuating mood symptoms
Psychomotor skills impaired	Psychomotor skills impaired
Inappropriate affect	Inappropriate affect
Overdose	Overdose; Accidental overdose; Intentional overdose
Intentional product misuse	Intentional product misuse
Suicidal behaviour	Suicidal behaviour; Intentional self-injury; Completed suicide; Suicide attempt; Suspected suicide; Suspected suicide attempt
Suicidal ideation	Suicidal ideation; Depression suicidal; Suicide threat

The final list of preferred terms corresponding to AESIs will be provided in the study Statistical Analysis Plan (SAP). The investigator must report to COMPASS and the CRO all the above events within 24 hours of learning about the event regardless of relationship to study drug.

The report should include the following minimum information:

- Participant number
- Event
- Date/time of onset

- Duration of the event
- Dose of drug taken
- Severity
- Outcome

11.10 Adverse Event Follow-up

All SAEs related to the IMP will be followed until resolved or stable and the outcome documented. All AESIs will be followed up until the end of the study.

If the investigator detects an AE in a study participant after the last scheduled follow-up visit and considers the event possibly related or related to prior study treatment, the investigator should report it to COMPASS and the CRO.

12 SERIOUS ADVERSE EVENTS

12.1 Definition of Serious Adverse Event

An SAE is any event that meets any of the following criteria:

- Death
- Life-threatening
- Inpatient hospitalisation or prolongation of existing hospitalisation
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a participant who received psilocybin.
- Other: Important medical events that may not result in death, be life-threatening, or require hospitalisation, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Suicidal behaviours (which do not include non-suicidal self-injurious behaviours) must be classified as important medical events if they do not otherwise meet SAE criteria. Examples of important medical events are:
  - Intensive treatment in an emergency room or at home for allergic bronchospasm
  - Blood dyscrasias or convulsions that do not result in inpatient hospitalisation
  - Development of drug dependency or drug abuse

12.2 Definition of Terms

Life-threatening: An AE is life-threatening if the participant was at immediate risk of death from the event as it occurred; eg it does not include a reaction that if it had occurred in a more serious form might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

Hospitalisation: AEs requiring hospitalisation should be considered SAEs. Hospitalisation for elective surgery or routine clinical procedures that are not the result of AEs (eg elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'nonserious' according to the usual criteria.

In general, hospitalisation signifies that the participant has been detained (usually involving at least one 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. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any serious, untoward event that may occur subsequent to the reporting period that the investigator assesses as related to IMP should also be reported and managed as an SAE.

The investigator should follow participants with AEs until the event has resolved or the condition has stabilised. In case of unresolved AEs, including significant abnormal clinical laboratory values at the end of study assessment, these events will be followed until resolution or until they become clinically not relevant.

Disability/incapacitating: An AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the participant's ability to carry out normal life functions.

12.3 Reporting Serious Adverse Events

Each AE will be assessed to determine whether it meets seriousness criteria (Section 12.1). If the AE is considered serious, the investigator should report this event to the CRO, and to the IRB/IEC according to its standard operating procedures.

If the investigator detects an SAE in a study participant after the last scheduled follow-up visit, and considers the SAE related or possibly related to this study's IMP administration, the investigator should report it to the CRO.

The investigator must report to the sponsor all SAEs on the eCRF page within 24 hours of learning about the event regardless of relationship to IMP.

All information about SAEs will be collected and reported via paper SAE form and sent by e-mail message or facsimile (contact information will be contained in the investigator site file). The investigator should send the initial report within 24 h of becoming aware of the SAE. At minimum, the initial report should include the following information:

- Event and brief description of the SAE (including diagnosis or signs/symptoms)
- Study code
- Participant identification number, initials, gender, and date of birth
- IMP
- Reporter name and contact information

  • Site staff will complete the paper SAE report form and e-mail it within 24 h to the following address: [redacted]

  • In cases where the email system is unavailable, site staff will send the SAE by fax to: [redacted]

If the SAE has not resolved at the time the investigator submits an initial SAE report, the investigator must provide a follow-up report as soon as the event resolves (or upon receipt of

significant information if the event is still ongoing). Additional follow-up information must be reported on the SAE report form and emailed or faxed as specified above within 24 h of awareness following investigator (or site) awareness of the information. The investigator should not delay reporting an SAE in order to obtain additional information. Additional information, when available, should be reported per the reporting procedures described above.

All SAEs shall be followed until resolution, until the condition stabilises, or until the participant is lost to follow-up, or otherwise explained. Once the SAE is resolved, the corresponding AE eCRF page shall be updated. Additionally, any relevant laboratory test reports, consultation reports from other health care professionals, discharge summaries, or other information that has been gathered about the event may be requested by the CRO as part of SAE follow-up activities.

In the case of a "minimum report" (one that solely comprises the information bulleted above), a more detailed follow-up report should be sent as soon as more information becomes available but no later than 7 calendar days after the date of the initial report. Each SAE should be followed up until resolution or stabilisation and for reported deaths, the investigator should supply the CRO and the IRB/IEC with any additional requested information (eg, autopsy reports and terminal medical reports).

The original SAE form should be kept at the study site. The sponsor or its representative will be responsible for determining and in turn, reporting SAEs to regulatory authorities according to the applicable regulatory requirements.

All SAEs will be followed until resolved or stable and the outcome documented on the eCRF.

Investigator safety reports will be prepared for suspected unexpected serious adverse reactions (those not listed in the IB) according to local regulatory requirements and COMPASS/the CRO policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (eg summary or listing of SAEs) from COMPASS or the CRO will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

13 STATISTICS

13.1 Hypotheses and Treatment Comparisons

There are no formal hypotheses being tested in this study.

13.2 Sample Size Considerations

The sample size is not based on a formal statistical evaluation but is considered to be adequate to meet the objectives of the study.

13.3 Analysis Sets

Analysis Population	Definition
Screening Analysis Set	All participants who signed the ICF
Safety Analysis Set	All participants who receive study drug
Full Analysis Set (FAS)	All participants in the Safety Analysis Set who have at least one post-baseline efficacy assessment

The Safety Analysis Set will be used for all safety-related evaluations and study population-related evaluations. The FAS will be used for all efficacy-related evaluations.

13.4 General Considerations

A detailed SAP will be finalised and signed before database lock. Any deviations from the methods described below will be included in the SAP and considered final, which will be included in the Clinical Study Report (CSR).

All TFLs will be created using SAS® version 9.4 or higher.

Unless otherwise specified, "baseline" is defined as the last observed value of the parameter of interest prior to dosing. For numerical variables, change from baseline will be calculated as the difference between the value of interest and the corresponding baseline value.

Continuous data will be summarised descriptively using N (number of participants), n (number of observations), mean, standard deviation (SD), median, minimum and maximum. Categorical data will be summarised using frequency counts and percentages. Confidence intervals for selected endpoints will also be displayed.

All individual participant data will be listed.

13.5 Data Handling

Procedures for the handling of any missing, unused or spurious data will be described in the SAP.

13.5.1 Analysis of Efficacy

Since this is a single treatment open-label study, no statistical testing will be performed.

The FAS will be used for all efficacy-related endpoints, if the two sets are not identical. For each of the secondary (CAPS-5, PCL-5, SDS and EQ-5D-5L (including EQ VAS)) and some exploratory endpoints (PACT, RAS) measuring changes from baseline, summary statistics will be provided. In addition, 95% confidence intervals for changes from baseline as well as for proportions of responders and remitters based on the CAPS-5 will be provided. Graphical displays will also be created for a subset of the efficacy endpoints to visualise their profile over time.

Analysis of all exploratory endpoints will be further detailed in the SAP.

13.5.2 Analysis of Safety

13.5.2.1 Adverse Events

AEs will be coded by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) classification.

A TEAE is defined as any AE that has an onset on or after taking study drug, or any pre-existing condition that has worsened on or after taking study drug.

The frequency and incidence of TEAEs will be summarised by SOC and PT. Summaries will also include, but not limited to, relationship to study drug and maximum severity. The summary will be sorted by International Agreed Order for SOC and alphabetical order for Preferred Term.

For each of the summaries produced at the participant level, multiple occurrences of the same event within a participant will be counted once in the summaries by SOC and Preferred Term; multiple occurrences of the same event within a participant will be counted once in the maximum severity category (severe > moderate > mild) and/or maximum drug relationship category (reasonable possibility/no reasonable possibility). If severity or relationship is found to be missing, the most severe occurrence will be imputed for that particular summary.

AESIs will also be presented using the same logic as for general AE summary tables, including patient incidence and event counts.

These summaries will also present the number of events that occurred, so multiple occurrences of the same event within a participant will all be accounted for in the maximum intensity category and maximum relationship category they were classed as.

13.5.2.2 Electrocardiogram Data

ECG data and changes from baseline/screening will be summarised by visit. Frequency tabulations of the abnormalities will be provided, as well a summary using the ICH E14 Guideline: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. ECG variables to be analysed will include heart rate (bpm), RR interval (ms), PR interval (ms), QRS interval (ms), QT interval (ms), and corrected

QT interval using the following correction methods: QT corrected according to Bazett's formula [QTcB (ms)] and QT corrected according to Fridericia's formula [QTcF (ms)].

13.5.2.3 Vital Signs

Vital signs data and changes from baseline/screening will be summarised by visit. Frequency tabulations of the abnormalities will be provided. Vital sign variables to be analysed will include blood pressure [systolic (mmHg) and diastolic (mmHg)], body temperature (°C), and pulse rate (beats/min). The percentage of participants with values outside clinically important limits will be summarised, using the following limits:

Vital sign	Lower Limit	Upper Limit
Systolic blood pressure (mmHg)	90 mmHg	160 mmHg
Diastolic blood pressure (mmHg)	50 mmHg	100 mmHg
Pulse rate (bpm)	50 bpm	100 bpm
Respiration rate (breaths/min)	11 breaths/min	20 breaths/min
Body temperature (degrees Celsius)	-	37.5 °C

13.5.2.4 Laboratory Data

Observed values and changes from baseline for haematology and blood chemistry parameters will be summarised by visit. All presentations will be based on the International System of Units. The frequency of laboratory abnormalities will be tabulated.

By-participant data listings will flag laboratory values that are outside normal reference ranges or markedly abnormal findings.

13.5.2.5 Columbia-Suicide Severity Rating Scale

C-SSRS data, including item scores, suicidal ideation, and suicidal behaviour, will be summarised by visit.

13.5.2.6 mDESS

Data listings will present mDESS data at the Screening and Baseline visits.

13.5.2.7 BPRS+

Data listings will present BPRS+ data by visit.

13.5.3 Participant Disposition, Demographic and Baseline Characteristics

Participant disposition, including number of screen failures, participants in each analysis set, completers and early discontinuation as well as reason, will be summarised.

Demographic data and baseline characteristics, including age at screening, gender, race, ethnicity, height, body weight, BMI and duration of PTSD will be summarised.

13.5.4 Medical History

Medical history will be coded using MedDRA latest version and summarised and listed for all participants.

13.5.5 Prior and Concomitant Medication

Prior and concomitant medications will be summarised and listed.

Prior medication refers to any medication that was stopped prior to the start of taking study drug/ taken during the 30-day period before signing the ICF. Concomitant medication refers to the use of any ongoing medication use at the time of the start of the study /all medications taken after the ICF has been signed.

13.6 Interim Analysis

No interim analysis is planned for this study.

14 ETHICS AND RESPONSIBILITIES

14.1 Good Clinical Practice

The study will be performed in accordance with this protocol, US investigational new drug (IND) regulations (21 Code of Federal Regulations [CFR] 312), ICH guidelines for Good Clinical Practice (GCP), the regulations on electronic records and electronic signature (21 CFR 11), and the most recent guidelines of the Declaration of Helsinki (Section 21.2). These guidelines are on file at the CRO.

The study will also be performed in accordance with any laws and regulations in force in the country in which the research is carried out.

14.2 Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will periodically review and evaluate the accumulated study data for participant safety, study conduct and progress and when appropriate, efficacy. The DSMB will make recommendations concerning the continuation, modification or termination of the trial, always ensuring participant safety is paramount. As outlined in the DSMB charter, the DSMB can recommend modifying or stopping the study if the risks to participants appear to exceed the benefits by following the below guidance:

- Any participant who experiences increases in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥5-fold upper limit of normal (ULN), or ≥3-fold ULN with concomitant serum total bilirubin ≥2-fold the ULN and ≥35% direct, will be withdrawn from the study and will be followed until resolution of the abnormal laboratory values.
- Any participant who experiences clinically significant suicidal risk or risk of self-injury during study participation will be withdrawn from the study and followed until resolution.

Other stopping criteria will include:

- A ‘serious’ adverse reaction in two participants, ie, an SAE that is considered at least possibly related to IMP administration.
- If there is an unacceptable tolerability profile based on the nature, frequency and intensity of observed AEs and/or clinical safety monitoring in the opinion of the investigator.
- If any of the above study stopping criteria are fulfilled, all dosing will be stopped immediately in all study participants. No further dosing will be permitted at a group or individual level. If the trial is halted due to safety concerns, or because the stopping criteria are fulfilled, the trial will only resume after Research Ethics Committee (REC) and regulatory authority approval via a substantial amendment.

The composition, the frequency of the review, range of decisions permitted, and the methods for dissemination of information will be addressed in a separate charter.

14.3 Institutional Review Board/ Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted IRB/ IEC. Approval is required for the study protocol, protocol amendments, ICFs, participant information sheets, and advertising materials.

14.4 Informed Consent

Written, informed consent will be obtained from all study participants. Participants should be informed that they may withdraw from the study at any time. They will receive all information that is required by local regulations and ICH guidelines. The Principal Investigator or a designated representative will provide the sponsor or its representative with a copy of the IRB approved ICF before the start of the study.

14.5 Exposure in Utero During Clinical Studies

Sponsor must be notified of any participant who becomes pregnant within 30 days of receiving the IMP. Reporting after the follow-up visit or ET is done voluntarily by the investigator.

Sponsor must be notified of any male participant whose partner becomes pregnant within 30 days of the participant receiving the IMP. Reporting after any follow-up visit or ET is done voluntarily by the investigator.

Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the investigator, or designee, to report any pregnancy in a participant or the partner of a male participant using the eCRF pregnancy within 24 h of becoming aware of the event. Exposure in Utero (EIU) Reporting form. Please contact your study monitor to receive the EIU Reporting form upon learning of a pregnancy. The investigator should make every effort to follow the participant until completion of the pregnancy and complete the EIU Reporting form eCRF with complete pregnancy outcome information, including normal delivery and induced abortion. The adverse pregnancy outcome, either serious or nonserious, should be reported in accordance with study procedures. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie post-partum complications, spontaneous or induced abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted foetus), the investigator should follow the procedures for reporting SAEs outlined in Section 12. In the event the eCRF system is unavailable, a back-up paper Pregnancy Reporting Form will be available for site staff to complete following the reporting guidelines as outlined in Section 12.2.

For reports of pregnancy in the partner of a male participant within 30 days from receiving the IMP, the pregnancy eCRF page EIU form (or SAE form if associated with an adverse outcome) should be completed with the participant's initials, and date of birth, and details regarding the partner of the male participant should be entered in the narrative section.

14.6 Records Management

By signing this protocol, the investigator grants permission to personnel from the sponsor, its representatives, and appropriate regulatory authorities, for on-site monitoring of all appropriate study documentation, paper and electronic, as well as on-site review of the procedures employed in eCRF generation, where clinically appropriate.

14.7 Source Documentation

Note that a variety of original documents, data, and records will be considered as source documents in this trial. The eCRF itself is not to be used as a source document under any circumstances.

14.8 Study Files and Record Retention

The investigator must arrange for retention of study records at the site. The nature of the records and the duration of the retention period must meet the requirements of the relevant regulatory authority. In addition, because this is an international study, the retention period must meet the requirements of the most stringent authority. The investigator should take measures to prevent accidental or premature destruction of these documents.

15 AUDITING AND MONITORING

This study will be monitored for quality assurance at all stages of its development by the clinical research personnel employed by the sponsor or its representative. Monitoring will include personal visits and telephone communication to assure that the investigation is conducted according to the protocol, standard operating procedures, GCP guidelines, and applicable regulatory requirements. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. On-site review of eCRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each participant.

The investigator and appropriate personnel will be periodically requested to attend meetings/workshops organised by the sponsor to assure acceptable protocol execution. The study may be audited by the sponsor or by regulatory authorities. If such an audit occurs, the investigator must agree to allow access to required participant records. By signing this protocol, the investigator grants permission to personnel from the sponsor, its representatives, and appropriate regulatory authorities, for on-site monitoring of all appropriate study documentation, as well as on-site review of the procedures employed in eCRF generation, where clinically appropriate.

16 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study participants, may be made only by COMPASS. A protocol change intended to eliminate an apparent immediate hazard to participants may be implemented immediately, provided the IRB/IEC is notified within five days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the investigator must await approval before implementing the changes. COMPASS will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/IEC, the investigator, and/or COMPASS the amendment to the protocol substantially changes the study design and/or increases the potential risk to the participant and/or has an impact on the participant's involvement as a study participant, the currently approved written ICF will require similar modification. In such cases, informed consent will be renewed for participants enrolled in the study before continued participation.

17 STUDY REPORT AND PUBLICATIONS

COMPASS is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

The publication policy of COMPASS is discussed in the investigator's Clinical Research Agreement.

18 STUDY DISCONTINUATION

Both COMPASS and the Principal Investigator reserve the right to terminate the study at any time. Should this be necessary, COMPASS or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the Principal Investigator will inform the IRB/IEC of the same. In terminating the study, COMPASS and the Principal Investigator will assure that adequate consideration is given to the protection of the participants' interests.

19 CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from COMPASS. However, authorised regulatory officials, IRB/IEC personnel, COMPASS and its authorised representatives are allowed full access to the records.

Identification of participants and CRFs shall be by initials, screening and treatment numbers only. If required, the participant's full name may be made known to an authorised regulatory agency or other authorised official.

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21 APPENDICES

21.1 APPENDIX I – Names of Study Personnel

Sponsor:	[redacted] Chief Medical Officer COMPASS Pathfinder Limited [redacted]
Medical Monitor:	[redacted], Medical Director, Medical Affairs Worldwide Clinical Trials [redacted]
Clinical Research Organisations:	Worldwide Clinical Trials [redacted] ICON plc [redacted]
Clinical Laboratory:	ACM Global Laboratories [redacted]
Investigational Product Distribution:	[redacted]

21.2 APPENDIX II – Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles

for

Medical Research Involving Human Participants

Adopted by the 18th WMA General Assembly

Helsinki, Finland, June 1964

and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington DS, USA, October 2002

55th WMA General Assembly, Tokyo, Japan, October 2004

59th WMA General Assembly, Seoul, Republic of Korea, October 2008

and the

64th WMA General Assembly, Fortaleza, Brazil, October 2013

A. INTRODUCTION

The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human participants. Medical research involving human participants includes research on identifiable human material or identifiable data.

It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my participant will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the participant's interest when providing medical care which might have the effect of weakening the physical and mental condition of the participant."

Medical progress is based on research, which ultimately must rest in part on experimentation involving human participants.

In medical research on human participants, considerations related to the well-being of the human participant should take precedence over the interests of science and society.

The primary purpose of medical research involving human participants is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best-proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

Medical research is participant to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognised. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be participant to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

Research investigators should be aware of the ethical, legal and regulatory requirements for research on human participants in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human participants set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human participant.

Medical research involving human participants must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

Appropriate caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.

The design and performance of each experimental procedure involving human participants should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially

appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any SAEs. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for participants.

The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

Medical research involving human participants should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human participant must always rest with a participant of the research, even though the participant has given consent.

Every medical research project involving human participants should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the participant or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

Physicians should abstain from engaging in research projects involving human participants unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

Medical research involving human participants should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the participant. This is especially important when the human participants are healthy volunteers.

Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

The participants must be volunteers and informed participants in the research project.

The right of research participants to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the participant, the confidentiality of the participant’s information and to minimise the impact of the study on the participant's physical and mental integrity and on the personality of the participant.

In any research on human beings, each potential participant must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The participant should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the participant has understood the information, the physician should then obtain the participant's freely-given informed consent, preferably in writing. If the consent

cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

When obtaining informed consent for the research project the physician should be particularly cautious if the participant is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

For a research participant who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorised representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

When a participant deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorised representative.

Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research participants with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorised surrogate.

Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the participants who are research participants.

The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

At the conclusion of the study, every participant entered into the study should be assured of access to the best-proven prophylactic, diagnostic and therapeutic methods identified by the study.

The physician should fully inform the participant which aspects of the care are related to the research. The refusal of a participant to participate in a study must never interfere with the participant-physician relationship.

In the treatment of a participant, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the participant, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.