STATISTICAL ANALYSIS PLAN (SAP) FOR COMP 201 THE SAFETY AND TOLERABILITY OF COMP360 IN PARTICIPANTS WITH POST-TRAUMATIC STRESS DISORDER

DRUG:	COMP360
TITLE:	COMP 201
CLINICAL PHASE	II
SPONSOR:	Compass Pathfinder Limited [redacted]
VERSION NUMBER:	Final Version 1.0
VERSION DATE:	05 March 2024

CONFIDENTIALITY STATEMENT

SAP APPROVAL FORM

Protocol Number: COMP 201

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

SAP Version and Date: Version 1.0 05 March 2024

This SAP was authored and approved by the sponsor. The information contained in this SAP 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.

Compass Study Statistician Details and Signature:

Signature: [redacted] Date: 05-Mar-2024

Name (print) [redacted]

Title: Statistician

Worldwide Reviewer Details and Signature:

Signature: [redacted] Date: 05-Mar-2024

Name (print) [redacted]

Title: Senior Principal Statistician

Compass Approval Details and Signature:

Signature: [redacted] Date: 06-Mar-2024

Name (print) [redacted]

Title Senior Director, Statistics and Data Management

SAP SYNOPSIS

Study Number:	COMP 201
Protocol Title:	The Safety and Tolerability of COMP360 in Participants with Post-traumatic Stress Disorder
EudraCT Number:	2021-002621-19
ClinicalTrials.gov Identifier:	NCT05312151
Investigational Medicinal Product:	COMP360
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". 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.
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 **Additional 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.
Primary Endpoint(s):	The safety and tolerability endpoints include: • AEs • 12-lead ECGs • Clinical laboratory tests • Vital signs • Suicidality measured via the C-SSRS • BPRS+
Secondary Endpoint(s):	<u>Secondary Endpoint(s)</u> • 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)
Additional Endpoint(s):	<u>Additional Endpoint(s)</u> • 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.
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.
Hypothesis	There are no formal hypotheses being tested in this study.
Primary Endpoint Analyses	Safety will be evaluated based on AEs, ECG findings, clinical laboratory assessments, vital signs, BPRS+, and suicidality (as measured via the C-SSRS).
Secondary Endpoint Analyses	Efficacy endpoints will be summarised using descriptive statistics, using the FAS.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ATC	Anatomical Therapeutic Chemical
BPD	borderline personality disorder
bpm	beats per minute
CI	confidence interval
Compass	Compass Pathfinder Limited
CR	code review
CS	clinically significant
CSR	clinical study report
dps	decimal places
DSMB	Data and Safety Monitoring Board
eCRF	electronic case report form
EOS	end of study
ET	early termination
FAS	Full Analysis Set
ICF	informed consent form
IProg	independent programming
MedDRA	Medical Dictionary for Regulatory Activities
MR	manual review
NCS	not clinically significant
PT	preferred term
PTSD	post-traumatic stress disorder
QC	quality control
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
Stat IProg	Independent programming by a statistician
TFLs	tables, figures, and listings
UK	United Kingdom
VAS	Visual Analogue Scale
WHO	World Health Organization
Worldwide	Worldwide Clinical Trials, Inc.

LIST OF PARAMETERS

Parameter	Definition
Study Disposition	
BMI	body mass index
CTQ	Childhood Trauma Questionnaire
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
LEC-5	Life Event Checklist for DSM-5
MINI	Mini International Neuropsychiatric Interview
MSI-BPD	McClean Screening Instrument for Borderline Personality Disorder
Safety	
AE	adverse event
AESI	adverse event of special interest
BPRS+	Brief Psychiatric Rating Scale – Positive Symptom Subscale
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
mDESS	Modified Discontinuation Emergent Signs and Symptoms Scale
QTcB	QT interval corrected by Bazett's formula
QTcF	QT interval corrected by Fridericia's formula
SAE	Serious Adverse Event
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
Efficacy	
5D-ASC	Five-Dimensional Altered States of Consciousness questionnaire
CAPS-5	Clinician-Administered PTSD Scale for DSM-5
EBI	Emotional Breakthrough Inventory
EQ-5D-3L	EQ-5D 3-level version
EQ-5D-5L	EQ-5D 5-level version
PACT	Perceived Ability to Cope with Trauma
PCL-5	PTSD Checklist for DSM-5
RAS	Resilience Adult Scale
SDS	Sheehan Disability Scale

1 INTRODUCTION

This statistical analysis plan (SAP) is based on the final United Kingdom (UK) protocol (V5.0) and the final United States (US) protocol (V5.0), both dated 09 June 2023. The plan covers the tables, figures and listings (TFLs) of the study data to investigate the safety and tolerability of COMP360 administered under supportive conditions in post-traumatic stress disorder (PTSD) participants.

The SAP is prepared by Compass Pathfinder Limited (Compass). The statistical analyses and production of the outputs described in the SAP, as well as the quality check (QC), will be conducted by Worldwide Clinical Trials, Inc. (Worldwide), using SAS® Version 9.4 or later.[1] The final analyses and outputs will be approved by Compass.

Any statistical analysis details described in this document supersede any description of statistical analysis in the protocol.

2 STUDY OBJECTIVES AND ENDPOINTS

The study objectives and their corresponding endpoints are presented in Table 1.

Table 1: Study Objectives and Endpoints

Objectives	**Endpoints/Variables**
Primary:	
To assess the safety and tolerability of COMP360 administered under supportive conditions in PTSD participants	The safety and tolerability endpoints include: • AEs • 12-lead ECGs • Clinical laboratory tests • Vital signs • Suicidality measured via the C-SSRS • BPRS+
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	• 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)
Additional:	

• 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	• 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 characterization 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 and thus will not be in scope of this SAP.

5D-ASC=Five-Dimensional Altered States of Consciousness; AE=adverse event; BPRS+=Brief Psychiatric Rating Scale; CAPS-5=Clinical Administered PTSD Scale for DSM-5; CSR=clinical study report; C-SSRS=Columbia-Suicide Severity Rated Scale; EBI=Emotional Breakthrough Inventory; ECG=electrocardiogram; EQ-5D-5L=5-level EQ-5D version; fMRI=functional magnetic resonance imaging; PACT=Perceived Ability to Cope with Trauma; PCL-5=PTSD Checklist for DSM-5; PTSD=post-traumatic stress disorder; RAS=Resilience Adult Scale; SAP=statistical analysis plan; SDS=Sheehan Disability Scale.

3 ESTIMAND FRAMEWORK

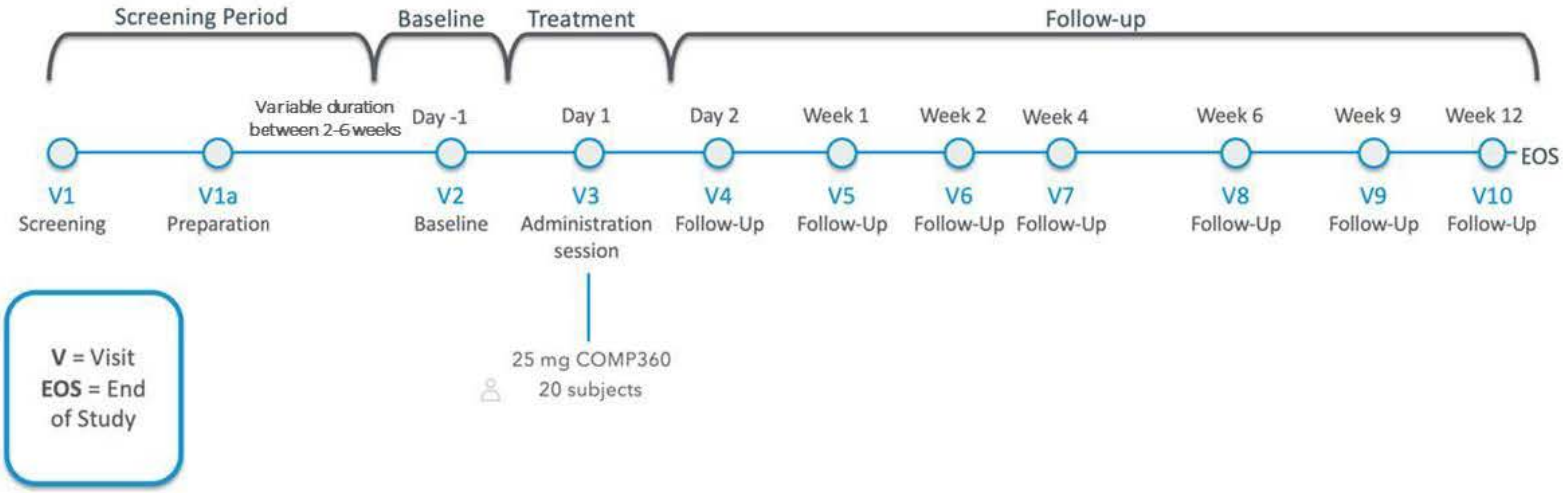
An estimand framework will not be used for this study since it is a descriptive, exploratory study.

4 STUDY DESIGN

4.1 Study Design

The study schematic is presented in Section 4.2 and the schedule of assessments is presented in Section 4.3, Table 2.

4.2 Study Schematic



4.3 Schedule of Assessments

Table 2: Schedule of Assessments for COMP 201

	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	✓		✓		✓						

	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
Weight	✓										
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]	✓	✓	✓	✓	✓	✓	✓

	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
Documentation of contraceptive method to be used[7]	✓										
IMP administration				✓							
Preparation [11]		✓	✓								
Psychoeducational information [12]		✓									
Integration					✓	✓	✓				
AEs	✓	✓	✓	✓[4]	✓	✓	✓	✓	✓	✓	✓
CAPS-5			✓					✓			✓
CTQ	✓										
Participant Completed Assessments											
PCL-5	✓		✓		✓	✓	✓	✓	✓	✓	✓
LEC-5	✓										
mDESS[13]		✓	✓								
EQ-5D-5L			✓					✓			✓

	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
SDS			✓					✓			✓
PACT			✓					✓			✓
RAS			✓					✓			✓
EBI					✓[14]						
5D-ASC				✓[4]							
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; 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 protocol 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.

4.4 Hypotheses and Treatment Comparisons

There are no formal hypotheses being tested in this study.

4.5 Multiplicity

There are no formal hypotheses being tested, so no multiplicity adjustments are needed for this study.

4.6 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. Approximately 20 participants are expected to be enrolled in the study.

4.7 Randomisation

Not applicable.

5 PLANNED ANALYSES

5.1 Final Analysis

The SAP will be finalised before database lock. Final data analysis will be conducted after database lock. The TFLs planned in this document will be included in the final analysis.

5.2 Interim Analysis

No interim analysis is planned for this study.

5.3 Data Safety Monitoring Board (DSMB)

An independent DSMB, composed of experts in the management of participants with the disease under study and a biostatistician, will review selected safety data at predefined intervals during the study. The primary purpose of this committee will be to review safety data for the protection of participant safety. A DSMB Charter will define the primary responsibilities of the DSMB, Compass, and Worldwide, the purpose and timing of meetings, quorum, and voting details. The Charter will also provide the procedures for confidentiality, communication, and a description of the deliverables that will be provided to and reviewed by the DSMB.

A separate DSMB SAP will define the outputs the DSMB will review.

In general, the DSMB will advise Compass and make recommendations regarding continuation of the study and any modification to the protocol or study procedures in order to protect the participants enrolled in the study.

6 ANALYSIS SETS

Table 3: Analysis Sets

Analysis Set	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

ICF: Informed consent form

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

The Full Analysis Set (FAS) will be used for all efficacy-related evaluations.

7 GENERAL CONSIDERATIONS

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

Listings will be sorted in the following order: participant, visit, and parameter unless otherwise stated. All data will be listed.

Unless otherwise specified, "baseline" is defined as the last observed value of the parameter of interest prior to dosing. This includes values collected at both scheduled and unscheduled visits. 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 observations), mean, standard deviation (SD), median, minimum. and maximum.

Categorical data will be summarised using frequency counts and percentages. The denominator for a percentage will be the total number of participants in the relevant treatment group or analysis set (N), unless otherwise specified (on some occasions, percentages may be calculated using the total number of participants with available data at a particular visit or time point as the denominator [n]).

Unscheduled visits and retests (same visit number assigned) will not be displayed in by-visit summary tables but will be included in the data listings.

All individual participant data will be listed. Listings will include scheduled, unscheduled, retest and early discontinuation data.

All medical histories, adverse events (AEs), and prior and concomitant non-drug therapy will be coded from the actual verbatim term using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.1 or later.

All prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Global Dictionary (Sep-2023 version or later).

8 DATA DERIVATIONS

This section describes the derivations required for statistical analysis. Unless otherwise stated, variables derived in the source data will not be re-calculated.

8.1 General

8.1.1 Change from Baseline

Table 4: Change from Baseline Definition

Definition	Derivation
Change from baseline	*= post-baseline visit value – baseline value*

If there is no baseline or post-dose visit value, then the absolute and change from baseline will be set to missing.

8.1.2 Missing and Partial Dates

All rules explained in Section 8.2.10 for partial / missing dates will be followed unless contradicted by any other data recorded on the electronic Case Report Form (eCRF).

All dates presented in the individual participant listings will be as recorded on the eCRF. In case of partial eCRF entries, the rules described in Sections 8.2.10.1 will be used for date imputation for the purposes of deriving ancillary quantities (e.g. study day, duration of an event, etc) but only partial dates will be presented in the listings.

8.1.3 Treatment Exposure and Compliance

Since the frequency of administration of COMP360 is only once, calculations of treatment exposure and compliance are not applicable.

8.1.4 Inexact Values

In the case where a variable is recorded as "> x", "≥ x", "< x" or "≤ x", the value of x will be taken for analysis purposes. This rule will be applied to continuous laboratory parameter values only for summary tables and figures, whereas listings will show the actual value recorded (inclusive of the non-numeric symbol).

8.2 Study Participants

8.2.1 Protocol Deviations

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

8.2.2 Age Categories

The following age categories will be derived:

- 18-34 years
- 35-64 years
- 65-84 years
- > 84 years

8.2.3 Body Mass Index (BMI)

The BMI will be calculated at screening using the formula:

$$weight\ (kg)/height\ (m)^2$$

The BMI will be categorised as follows:

- < 18.5 kg/m^2 (underweight)
- ≥ 18.5 to < 25 kg/m^2 (healthy)
- ≥ 25 to < 30 kg/m^2 (overweight)
- ≥ 30 kg/m^2 (obese)

8.2.4 Duration of PTSD

The length in months of the duration of PTSD will be calculated as follows:

$$12 \times [\frac{screening\ date - start\ \ date\ of\ PTSD}{365.25}]$$

8.2.5 Prior and Concomitant Treatments

Prior treatments refer to all prescription and non-prescription treatments (medications including over-the-counter drugs and herbal supplements, psychological and somatic therapies) that participants report taking and stopping during the 30 days prior to signing the ICF.

Concomitant treatments refer to all prescription and non-prescription treatments (medications including over-the-counter drugs and herbal supplements, psychological and somatic therapies) used from the time the ICF was signed through to the end of study (EOS) visit.

8.2.6 Mini International Neuropsychiatric Interview (MINI), Version 7.0.2

The MINI[Error! Reference source not found.] is a brief structured interview for the major psychiatric disorders in the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th

Edition) and International Classification of Diseases[Error! Reference source not found.,2] Version 7.0.2 of the MINI will be used for this study.

MINI version 7.0.2 data will be obtained at Screening (Visit 1) only.

8.2.7 McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD)

The MSI-BPD is a commonly used measure to assess for borderline personality disorder (BPD). The scale consists of 10 items; 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. Each item has a score 0=absent or 1=present, a total score is derived as the sum of each item, with the total score ranging from 0-10. A score of 7 or higher indicates a likelihood for the participant to meet criteria for BPD. [3]

MSI-BPD data will be obtained at Screening (Visit 1) only.

8.2.8 Life Event Checklist for DSM-5 (LEC-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.[4]

LEC-5 data will be obtained at Screening (Visit 1) only.

8.2.9 Childhood Trauma Questionnaire (CTQ)

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.[5]

The only item being collected from this assessment is 'Did the participant experience significant childhood physical or sexual abuse that resulted in PTSD based on the CTQ?'.

CTQ data will be obtained at Screening (Visit 1) only.

8.2.10 Missing Data

8.2.10.1 Missing PTSD Start Date

If the month and year for PTSD start date are present but the day is missing, the start date will be set to the first day of the relevant month. If only the year is recorded the start date will be set as "01-Jan" for that year.

This imputation rule will only be implemented to derive the PTSD start date, and the imputed date will not be used elsewhere (ie partial dates will be presented in the listings, as recorded).

8.2.10.2 Missing/Partial Start/Stop Dates of Prior/Concomitant Treatments

Missing and partial start and stop dates will be imputed for analysis purposes as detailed below.

Partial or missing stop date will be imputed as follows:

- If the stop date is completely missing and the event has resolved, or the participant has stopped taking the concomitant treatment, the stop date will be imputed as the date of the participant's last clinic visit in the study.
- If only the stop date year is known, and it is equal to the year of the participant's last clinic visit in the study, the stop date will be imputed as the date of the participant's last clinic visit date, otherwise if the year differs it will be imputed as "31-Dec".
- If the stop date month and year are known, the stop date will be imputed as the last day of that month unless the stop date is in the same month as the participant's last clinic visit in which case the date of participant's last clinic visit in the study will be used.

Missing start date will be imputed as follows:

- If the stop date occurs on or after the first dose of COMP360 or the AE / treatment is ongoing, the start date will be imputed as the date of the first dose of COMP360.
- If the stop date occurs before the first dose of COMP360, the start date of the treatment will be imputed as the participant's Screening date or the stop date of the AE whichever the earlier

Partial start date (year present, but month and day missing) will be imputed as follows:

- If the stop date occurs on or after the first dose of COMP360 or the treatment is ongoing, and the year is the same as the year of dosing the start date will be imputed as the date of the first dose of COMP360. If the year is different from the year of dosing "01-Jan" will be used.
- If the stop date occurs before the first dose of COMP360, the start date of the treatment will be imputed as the "01-Jan" of the same year.

Partial start date (month and year present, but day missing) will be imputed as follows:

- If the stop date occurs on or after the first dose of COMP360 or the treatment is ongoing, the start date will be imputed as the first day of the same month and year unless this partial start date is in same month as the first dose of COMP360 in which case the date of first dose of COMP360 will be used.

- If the stop date occurs before the first dose of COMP360, the start date will be imputed as the first day of the same month and year of the partial start date.

8.3 Safety

8.3.1 Adverse Events

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. A treatment-emergent adverse event (TEAE) is defined as any AE that has an onset on or after the dose of COMP360, or any pre-existing AE condition that has worsened on or after the dose of COMP360.

A treatment-related TEAE is defined as an AE reported by the investigator to be possibly related or related to COMP360. If an AE has a missing relationship, it will be assumed to be related to the study drug for analysis purposes.

Maximum severity will be assumed for an AE with missing severity.

TEAEs, treatment emergent serious adverse events (TESAEs), and adverse events of special interest (AESIs) will be categorised by time of onset (Day 1, Day 2 to Week 4, after Week 4 to Week 12, and after Week 12) and duration ($\leq$ 1 day, $>$ 1 and $\leq$ 2 days, $>$ 2 to $\leq$ 7 days, >7 days or ongoing).

AESIs will be identified as follows:

Table 5: AESI terms and MedDRA preferred terms

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 symptom
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; Synaesthesia
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; Delusion; 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; Psychotic symptom; Paranoia
Cognitive disorder	Cognitive disorder
Disturbance in attention	Disturbance in attention
Mood altered	Mood altered; Depressed mood; Affect lability; Mood swings; Tearfulness; Crying
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

AESI=adverse event of special interest; MedDRA=Medical Dictionary for Regulatory Activities.

AEs, serious adverse events (SAEs), and AESIs with an onset within 24 hours of COMP360 administration will be categorised by the start time and stop time as outlined in Table 6.

Table 6: Start Time and Stop Time Categories for Adverse Events With Onset Within 24 Hours of COMP360 Administrations

Start time (hours)	Stop time (hours)
< 6	< 8 ≥ 8 to < 12 ≥ 12 to < 24 ≥ 24
≥ 6 to ≤ 15	< 24 ≥ 24
> 15 to ≤ 24	< 24 ≥ 24

8.3.2 Laboratory Tests

The full list of parameters and their units (where applicable) are reported in Table 7.

Table 7: Laboratory Tests

Category	Parameter (Unit)
Haematology	Basophils (10^9/L) Basophils/Leukocytes (%) Eosinophils (10^9/L) Eosinophils/Leukocytes (%) Mean corpuscular haemoglobin concentration (g/L) Mean corpuscular haemoglobin (pg) Mean corpuscular volume (fL) Erythrocytes (10^{12}/L) Haematocrit (%) Haemoglobin (g/L) Leukocytes (10^9/L) Lymphocytes (10^9/L) Lymphocytes /Leukocytes (%) Monocytes (10^9/L) Monocytes/Leukocytes (%) Neutrophils (10^9/L) Neutrophils/Leukocytes (%) Platelets (10^9/L)
Chemistry	Alanine aminotransferase (ALT) (U/L) Albumin (g/L) Alkaline phosphatase (ALP) (U/L) Amylase (U/L) Aspartate aminotransferase (AST) (U/L) Bicarbonate (mmol/L) Bilirubin (direct, indirect, and total) (mg/dL) Calcium (mg/dL) Chloride (mmol/L) Creatine Kinase (U/L) Creatinine (mg/dL) Gamma-glutamil transferase (U/L) Glucose (mg/dL) Lactate dehydrogenase (U/L) Lipase (U/L) Magnesium (mg/dL) Phosphate (mg/dL) Potassium (mmol/L) Protein total (g/L) Sodium (mmol/L) Urate (mg/dL) Urea nitrogen (mg/dL)
Urinalysis	Bilirubin Glucose Ketones Leukocytes

	Nitrite Blood Protein Specific Gravity Urobilinogen pH

The laboratory tests data will be obtained at Screening, Baseline, Day 2, Week 4, and Week 12 (Visits 1, 2, 4, 7, and 10 respectively).

8.3.3 Vital Signs Parameters

The full list of vital signs parameters and their units are reported below:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (bpm [beats per minute])
- Respiration rate (breath / min)
- Body temperature (°C)

The vital signs data will be obtained at Screening, Baseline, Day 1, and Day 2 (Visits 1, 2, 3, and 4 respectively). On COMP360 administration day (Day 1), body temperature and respiratory rate will be measured before and after COMP360 administration. 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 study drug administration, and one, three and, six hours after COMP360 administration. Measurements should be collected within a ±10-minute time window. Blood pressure measurement is to be repeated until normalised if found to be elevated at the six-hour measurement.

8.3.3.1 Vital Signs Ranges of Clinical Importance

Values outside the following ranges for the vital signs parameters will be considered clinically important (Table 8):

Table 8: Vital Signs Parameters Ranges of Clinical Importance

Vital Sign (Units)	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 (breath / min)	11 breath/min	20 breath/min
Body temperature (°C)	-	37.5 °C

8.3.4 ECG Parameters

The full list of ECG parameters and their units are reported below:

- Heart rate (bpm)
- PR interval (msec)
- RR interval (msec)
- QRS interval (msec)
- QT interval (msec)
- QT interval corrected by Fridericia's formula (QTcF) (msec)
- QT interval corrected by Bazett's formula (QTcB) (msec)

The ECG data will be obtained at Screening, Baseline, and Day 2 (Visits 1, 2, and 4 respectively).

8.3.4.1 ECG Categorical Intervals

The ECG categorical intervals of interest are:

- QTcF $\leq$ 450 msec
- 450 msec < QTcF $\leq$ 480 msec
- 480 msec < QTcF $\leq$ 500 msec
- QTcF > 500 msec

Change from baseline in QTcF:

- QTcF increase from baseline > 30 and $\leq$ 60 msec
- QTcF increase from baseline > 60 msec

8.3.5 Columbia-Suicide Severity Rating Scale (C-SSRS)

The following outcomes are C-SSRS categories and have binary responses (yes / no)[6]:

Table 9: C-SSRS Categories

Category	Question
Category 1	Wish to be Dead
Category 2	Non-Specific Active Suicidal Thoughts

Category 3	Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Category 4	Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Category 5	Active Suicidal Ideation with Specific Plan and Intent
Category 6	Actual Attempt
Category 7	Has Subject Engaged in Non-suicidal Self-injurious Behaviour?
Category 8	Interrupted Attempt
Category 9	Aborted Attempt
Category 10	Preparatory Acts or Behaviour
Category 11	Suicidal Behaviour
Category 12	Suicide

The C-SSRS 'past 12 months' and 'lifetime' versions will be used at Screening, and subsequently the 'since last visit' version of the C-SSRS will be used at every other clinic visit.

There will be no imputation of missing data for the C-SSRS.

8.3.6 Brief Psychiatric Rating Scale – Positive Symptom Subscale (BPRS+)

The BPRS+ is a four-item, clinician administered subscale of the 18-item, clinician-administered Brief Psychiatric Rating Scale, used to assess symptoms of psychosis, anxiety and depression.[7] 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)**Error! Reference source not found.**.

A total score is calculated by taking the sum of the four individual items, with a total score range of 4-28. A score of 0 will be recorded if the symptom was not assessed, and a total score will not be calculated.

The BPRS+ data will be obtained at Baseline, Day 1 (conducted at the end of the COMP360 administration session), Day 2, Week 1, Week 2, Week 4, Week 6, Week 9, and Week 12 (Visits 2, 3, 4, 5, 6, 7, 8, 9, and 10 respectively).

There will be no imputation of missing data for the BPRS+.

8.3.7 Modified Discontinuation Emergent Signs and Symptoms Scale (mDESS)

The mDESS is a 15-item, self-reported scale, listing typical symptoms that can arise from antidepressant withdrawal.[8] 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, and 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'.

mDESS data will be obtained 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.

8.3.8 Missing Data

8.3.8.1 Missing/Partial Start/Stop Dates of AEs

Missing and partial start and stop dates will be imputed for analysis purposes as detailed below.

Partial or missing stop date will be imputed as follows:

- If the stop date is completely missing and the event has resolved the stop date will be imputed as the date of the participant's last clinic visit in the study
- If only the stop date year is known, and it is equal to the year of the participant's last clinic visit in the study, the stop date will be imputed as the date of the participant's last clinic visit date, otherwise if the year differs it will be imputed as "31-Dec"
- If the stop date month and year are known, the stop date will be imputed as the last day of that month unless the stop date is in the same month as the participant's last clinic visit in which case the date of participant's last clinic visit in the study will be used

Missing start date will be imputed as follows:

- If the stop date occurs on or after the dose of COMP360 or the AE is ongoing, the start date will be imputed as the date of the dose of COMP360
- If the stop date occurs before the dose of COMP360, the start date of the AE will be imputed as the participant's Screening date or the stop date of the AE whichever the earlier

Partial start date (year present, but month and day missing) will be imputed as follows:

- If the stop date occurs on or after the dose of COMP360 or the AE is ongoing, and the year is the same as the year of dosing the start date will be imputed as the date of the dose of COMP360. If the year is different from the year of dosing "01-Jan" will be used
- If the stop date occurs before the dose of COMP360, the start date of the AE will be imputed as the "01-Jan" of the same year

Partial start date (month and year present, but day missing) will be imputed as follows:

- If the stop date occurs on or after the dose of COMP360 or the AE is ongoing, the start date will be imputed as the first day of the same month and year unless this partial start date is in same month as the dose of COMP360 in which case the date of dose of COMP360 will be used

- If the stop date occurs before the dose of COMP360, the start date will be imputed as the first day of the same month and year of the partial start date

8.3.8.2 Missing/Partial Start Times of AEs

Missing start time on day of dose will be imputed as follows:

- The time will be imputed as the same time as the dose of COMP360

Partial start time on day of dose (minute present, but hour missing) will be imputed as follow:

- The time will be imputed at the same time as the dose of COMP360

Partial start time on day of dose (hour present, but minute is missing) will be imputed as follows:

- If the hour is the same as COMP360 dose time, the start time will be imputed as the same time as the dose of COMP360

- If the hour is before or after the COMP360 dose time, the minutes will be imputed as 00

Missing start time on any day after dose will be imputed as follows:

- The start time will be imputed as 00:00

Partial start time on any day after dose (minute present, but hour missing) will be imputed as follows:

- The hour will be imputed as 00

Partial start time on day after dose (hour present, but minute missing) will be imputed as follows:

- The minute will be imputed as 00

8.3.8.3 Missing/Partial Stop Times of AEs

For AEs occurring within 24 hours of COMP360 administration and ending either on day of COMP360 dose or the day after:

- The missing AE stop times will be imputed as 23:59

- In the case of partial times, if the hour is missing it will be imputed as 23, and if the minute is missing it will be imputed as 59

8.4 Efficacy Assessments

Unless otherwise stated, if any of items contributing to an instrument total score are missing then the total score will not be calculated.

8.4.1 Clinician-Administered PTSD Scale for DSM-5 (CAPS-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, 3=severe/markedly elevated, 4=extreme/ incapacitating.[9]

8.4.1.1 CAPS-5 Total Symptom Severity Score

The CAPS-5 total symptom severity score is calculated by summing the severity scores for items 1-20 (ie the sum of criteria B, C, D, and E) as defined in Table 10, where the range of the total score is 0-80 and a higher score indicates greater symptom severity.

Table 10: CAPS-5 Item Mapping to Criterion

Criterion	Symptom Number	Symptom
B – Intrusion symptoms	1 (B1)	Intrusive memories
	2 (B2)	Distressing dreams
	3 (B3)	Dissociative reactions
	4 (B4)	Cued psychological distress
	5 (B5)	Cued physiological reactions
C – Avoidance symptoms	6 (C1)	Avoidance of memories, thoughts, feelings
	7 (C2)	Avoidance of external reminders
D – Cognitions and mood symptoms	8 (D1)	Inability to recall important aspects of event
	9 (D2)	Exaggerated negative beliefs or expectations
	10 (D3)	Distorted cognitions leading to blame
	11 (D4)	Persistent negative emotional state
	12 (D5)	Diminished interest or participation in activities
	13 (D6)	Detachment or estrangement from others
	14 (D7)	Persistent inability to experience positive emotions
E – Arousal and reactivity symptoms	15 (E1)	Irritable behavior and angry outbursts
	16 (E2)	Reckless or self-destructive behavior
	17 (E3)	Hypervigilance

	18 (E4) 19 (E5) 20 (E6)	Exaggerated startle response Problems with concentration Sleep disturbance

8.4.1.2 CAPS-5 PTSD Subtypes

The CAPS-5 is also used to identify the following PTSD subtypes, using the 'PTSD diagnosis' section of the CAPS-5 summary sheet:

- PTSD with dissociative symptoms
- PTSD with delayed onset (≥ 6 months)

8.4.1.3 CAPS-5 Index Event

The participant's index event is identified by the participant and will serve as the basis for symptom enquiry on the CAPS-5. This is captured in the 'index event' box on criterion A.

The CAPS-5 'last month' version will be used at Baseline for diagnostic purposes. The 'last month' version of the assessment will also be used at Week 4 and Week 12 (Visits 7 and 10, respectively) to monitor participants symptoms improvement after treatment.

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

The PCL-5 is a 20-item self-reported scale, used for provisional PTSD diagnosis, screening, and symptoms monitoring purposes. Participants will complete the assessment scoring the severity of their symptoms on a 5-points Likert scale where 0 = not at all and 4 = extremely.[10]

A total symptom severity score (range 0-80) can be obtained by summing the scores for each of the 20 items. The symptom cluster severity score can be obtained by summing the scores for the items within a cluster, as defined in Table 11.

Table 11: PCL-5 Item Mapping to Cluster

Criterion	Symptom Number
B	1, 2, 3, 4, 5
C	6, 7
D	8, 9, 10, 11, 12, 13, 14
E	15, 16, 17, 18, 19, 20

The PCL-5 'Screening' version will be used at Screening (Visit 1). The 'past day' version will be used at Day 2 (Visit 2) and the 'past week' version of the assessment will be used at Baseline and at Weeks 1, 2, 4, 6, 9, and 12 (Visits 3, 5, 6, 7, 8, 9, and 10, respectively).

8.4.3 Sheehan Disability Scale (SDS)

The SDS is a brief, five-item self-report inventory assesses functional impairment in work/school (score ranges from 0 to 10), social life (score ranges from 0 to 10), and family

life (score ranges from 0 to 10).[11] The sum of the above three domain scores lead to a SDS total score ranging from 0 to 30 with 0 representing no impairment and 30 representing severe impairment. The past week version of the SDS will be performed.

For the main derivation, if the participant selects 'I have not worked/studied at all during the past week for reasons unrelated to the disorder', and has not answered the work/school item, the total score will be prorated by multiplying the scores of questions 2 (social life) and 3 (family life) by 1.5.

In addition to the main derivation, a sensitivity derivation will be calculated as follow: if a participant ticks the 'I have not worked/studied at all during the past week for reasons unrelated to the disorder' box and has not answered the work/school item, then no SDS total score will be derived.

The SDS data will be obtained at Baseline, Week 4, and Week 12 (Visits 2, 7, and 10, respectively).

8.4.4 EQ-5D-5L

The EQ-5D-5L was introduced by the EuroQoL Group in 2009 and is a multi-attribute instrument used in assessing the health-related quality of life**Error! Reference source not found.**.[12,13]

The EQ-5D-5L descriptive system contains five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels: 1 = no problems, 2 = slight problems, 3 = moderate problems, 4 = severe problems, and 5 = extreme problems. The responses to the five dimensions will be converted into a five-digit number (eg 23245) that describes the participant's 'health state'. This reflects how good or bad the health state is according to the preferences of the general population of a country/region.

In order to convert the health state to a continuous health index value, value sets (ie weights ranging from 1 for a health state of 11111 to negative values for health states reflective of a poor condition such as 55555) will be utilised.

A position statement from NICE suggests to not use the EQ-5D-5L value set for England published by Devlin et al. 2018.[14] The recommendation is to utilise the Van Hout cross-walk in order to obtain values for the EQ-5D-5L by mapping to the available EQ-5D-3L value sets.[15] SAS code is available to carry out the cross-walk method on the United Kingdom value set on the EQ-5D website.[16]

If a component of the EQ-5D-5L was not collected, the five-digit health state will be recorded with '-' to identify these missing values (eg 132-1, implying that the pain/discomfort item was missing) and the continuous health index value will not be derived and set to missing for analysis purposes.

The EQ-5D-5L data will be obtained at Baseline, Week 4, and Week 12 (Visits 2, 7, and 10, respectively).

8.4.5 Perceived Ability to Cope with Trauma (PACT) 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]

Participants will complete the assessment scoring their ability to complete each item following a potentially traumatic event if they needed to on a 7-point Likert scale where 1 = not at all able, and 7 = extremely able. The subscale scores are derived by taking the mean of the items in Table 12.

Table 12: PACT Item Mapping to Subscales

Subscale	Items
Forward Focus	1, 2, 3, 4, 5, 8, 9, 13, 15, 16, 17, 18
Trauma Focus	6, 7, 10, 11, 12, 14, 19, 20

Additionally, an overall flexibility score can be derived as follows:

$$(FF + TF) - |FF - TF|$$

Where FF is the forward focus subscale score, TF is the trauma focus subscale score, and $|FF - TF|$ is the absolute difference of the scores.

8.4.6 Resilience Adult Scale (RAS)

The RAS was developed to capture a set of fundamental protective factors based on resilience research. It includes 33 items, assessed on a 7-point Likert scale where 1 is low and 7 is high, split into 6 subscales.[18]

The RAS data will be obtained at Baseline, Week 4, and Week 12 (Visits 2, 7, and 10, respectively).

8.4.7 Five-Dimensional Altered States of Consciousness (5D-ASC)

The 5D-ASC measures the acute drug effects using five primary dimensions and respective subdimensions to assess alterations in mood, perception, and experience of self in relation to environment and thought disorder. The five dimensions include oceanic boundlessness, anxious ego dissolution, visual restructuralization, auditory alterations, and reduction of vigilance. In addition to these five dimensions, the 5D-ASC can be split into 11 subscales, as described by Studerus et al.[20]: experience of unity, spiritual experience, blissful state, insightfulness, disembodiment, impaired control and cognition, anxiety, complex imagery, elementary imagery, audio-visual synaesthesia and changed meaning of percepts.

Participants are instructed to respond to the described experiences by placing vertical marks on a horizontal VAS 100 millimetres long. The VAS of the altered states of

consciousness rating scales are anchored as "No, not more than usual" on the left and as "Yes, much more than usual" on the right. The items are scored by measuring the millimetres from the low end of the scale to the participant's mark (integers from 0–100). Because the low end of the scale indicates a neutral response, the response format of these items can be considered as strictly unipolar according to the response format typology of Russell and Carroll.[21]

The mapping of individual items to the five dimensions is displayed in Table 13 below (the former accounts for 93 out of 94 individual items [item 66 is excluded].)[22]

Table 13: 5D-ASC Dimensions

Dimension	Items
Oceanic Boundlessness	1, 3, 9, 12, 16, 18, 26, 34, 35, 36, 40, 41, 42, 45, 50, 52, 57, 62, 63, 69, 71, 73, 81, 86, 87, 91, 94
Anxious Ego Dissolution	6, 8, 21, 27, 32, 38, 43, 44, 46, 47, 53, 56, 60, 64, 67, 78, 79, 80, 85, 88, 89
Visual Restructuralization	7, 14, 20, 22, 23, 28, 31, 33, 39, 54, 58, 70, 72, 75, 77, 82, 83, 90
Auditory Alterations	4, 5, 11, 13, 19, 25, 30, 48, 49, 55, 65, 74, 76, 92, 93
Reduction of Vigilance	2, 10, 15, 17, 24, 29, 37, 51, 59, 61, 68, 84

The overall score for each dimension is obtained by averaging the score for each individual item within that dimension.

The 5D-ASC data will be obtained at the end of the COMP360 administration session on Day 1 (Visit 3).

8.4.8 Emotional Breakthrough Inventory (EBI)

The EBI is an eight-item brief measure intended to index the degree to which an individual experiences their emotion during the COMP360 administration session. Each item is a VAS, with units from 0 to 100. A total score is obtained by averaging the following six items: Item 1: I faced emotionally difficult feelings that I usually push aside; Item 2: I experienced a resolution of a personal conflict/trauma; Item 3: I felt able to explore challenging emotions and memories; Item 5: I had an emotional breakthrough; Item 6: I was able to get a sense of closure on an emotional problem; Item 8: I achieved an emotional release followed by a sense of relief.[23] The other two items (Item 4: I was resisting and avoiding challenging feelings throughout, without a breakthrough; and Item 7: I felt emotionally stuck throughout, without a breakthrough) will be listed only.

The EBI data will be obtained the day after COMP360 administration on Day 2 (Visit 4).

9 STUDY PARTICIPANTS

9.1 Disposition of Participants

The summaries will be presented overall.

The number of participants screened, screen failures, and the number and percentage of participants in each analysis set will be summarised by country and overall, for the Screening Analysis Set (*Table 14.1.1.1*). The number and percentage of participants who completed the study and number and percentage of participants who discontinued from the study, with reasons for discontinuation, will be summarised using the Safety Analysis Set (*Table 14.1.1.2*). The reasons for screen failures will also be tabulated (*Table 14.1.1.3*).

Participant disposition will be listed by study discontinuations (*Listing 16.2.1.1*) and completers (*Listing 16.2.1.2*) using the Safety Analysis Set. Participation in each defined analysis set will be listed using the Screening Analysis Set (*Listing 16.2.3*). Inclusion criteria not met/exclusion criteria met at Screening and at Baseline will be listed using the Screening Analysis Set (*Listing 16.2.4.4* and *Listing 16.2.4.5*).

9.2 Protocol Deviations

The frequency and percentage of participants in each important protocol deviation category will be summarised and presented overall using the Safety Analysis Set (*Table 14.1.1.4*).

All important protocol deviations will be listed using the Safety Analysis Set *(Listing 16.2.2.1)*.

9.3 Demographic and Baseline Characteristics

The Safety Analysis Set will be used for all demographic and baseline characteristics-related evaluations, unless otherwise specified. The summaries will be presented overall.

Demographic and baseline characteristics (age [years; continuous and by age categories (see Section 8.2.2)], sex [male, female], ethnicity [Hispanic or Latino, Not Hispanic or Latino], race [White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other], lifetime prior psilocybin experience [yes, no], height [cm], weight [kg], BMI [kg/m^2; continuous and by BMI categories (see Section 8.2.3)]) will be summarised (*Table 14.1.2*).

Other baseline characteristics (duration of PTSD in months, CAPS-5 total symptom severity score, PTSD subtype [dissociative symptoms, delayed onset (see Section 8.4.1.2)], index event as collected on the CAPS-5 (see Section 8.4.1.3), and 'how long ago did worst event happen' as collected on the LEC-5) will be summarised (*Table 14.1.3.8*).

The MINI version 7.0.2 will be summarised (*Table 14.1.3.9*) – note this summary will only display whether participants meet the criteria for specific modules as displayed on the questionnaire cover pages.

The MSI-BPD, LEC-5, and CTQ will be listed (*Listing 16.2.9.4, Listing 16.2.9.5, and Listing 16.2.9.6*).

Listings of the demographic baseline characteristics, other baseline characteristics, and the MINI version 7.0.2 will be presented (*Listing 16.2.4.1, Listing 16.2.4.2,* and *Listing 16.2.9.1*).

Other Baseline measurements (Urine Drug Screen and Pregnancy Test) will be listed only (*Listing 16.2.8.5 and Listing 16.2.8.6*). The pregnancy test listing will include results from both the urine test and, where this was done, of the serum test.

9.4 Medical History

Medical history collected at Screening will be summarised by primary system organ class (SOC) sorted by alphabetical order and by total descending frequency for preferred term (PT), and presented overall using the Safety Analysis Set (*Table 14.1.3.1*). This includes both the number and percentage of participants with a given medical history item as well as the number of occurrences of such item. In case of a tie for the number of participants with a given PT, PTs will be sorted also by the number of occurrences of that PT.

All medical history data will be listed using the Safety Analysis Set (*Listing 16.2.4.3*).

9.5 Prior and Concomitant Medications

The Safety Analysis Set will be used for all prior and concomitant medication-related evaluations, unless otherwise specified. The summaries will be presented overall. They will be sorted by alphabetical order for anatomical therapeutic chemical (ATC) level and descending frequency for PT.

Prior and concomitant medications will be summarised (*Table 14.1.3.2* and *Table 14.1.3.3*) and listed (*Listing 16.2.4.6* and *Listing 16.2.4.7*).

9.6 Prior and Concomitant Non-Drug Therapies

The Safety Analysis Set will be used for all prior and concomitant non-drug therapies (eg cognitive psychotherapy, group psychotherapy) evaluations. They will be sorted by alphabetical order for SOC and by total descending frequency for PT.

Prior and concomitant non-drug therapies will be summarised (*Table 14.1.3.4* and *Table 14.1.3.5*) and listed (*Listing 16.2.4.8* and *Listing 16.2.4.9*).

9.6.1 Prior Non-Drug Therapies for PTSD

Prior non-drug therapies for PTSD will be summarised (*Table 14.1.3.6*) and listed (*Listing 16.2.4.10*).

9.6.2 Concomitant Non-Drug Therapies for PTSD

Concomitant non-drug therapies for PTSD will be summarised (*Table 14.1.3.7*) and listed (*Listing 16.2.4.11*).

9.7 Treatment Exposure/Compliance and Duration

COMP360 administration will be listed (*Listing 16.2.5*).

10 SAFETY

10.1 Adverse Events (AEs)

An overall summary of AEs, including total number of TEAEs and treatment-emergent serious adverse events (TESAEs), severe TEAEs, AESIs, TEAEs and TESAEs leading to study discontinuation, and TEAEs leading to death will be presented (*Table 14.3.1.1*).

The following summary tables will be summarised by SOC and PT, and sorted by alphabetical order for SOC and by total descending frequency for PT, including both the number of participants with a given event and the number of events.

- Summary of TEAEs (*Table 14.3.1.2*)
- Summary of non-serious TEAEs ≥ 5% (PT for any treatment group ≥ 5%) (*Table 14.3.1.3)*
- Summary of TEAEs by worst severity (mild/moderate/severe) (*Table 14.3.1.4*)
- Summary of TEAEs by strongest relationship to COMP360 (related/not related) (*Table 14.3.1.5*)
- Summary of TEAEs by time of onset (see Section 8.3.1 for categories) and duration (see Section 8.3.1 for categories) (*Table 14.3.1.6*)
- Summary of TESAEs (*Table 14.3.1.7*)
- Summary of TESAEs by time of onset (see Section 8.3.1 for categories) and duration (see Section 8.3.1 for categories) (*Table 14.3.1.8*)
- Summary of AESIs (*Table 14.3.1.9*)
- Summary of AESIs by time of onset (see Section 8.3.1 for categories) and duration (see Section 8.3.1 for categories) (*Table 14.3.1.10*)
- Summary of TEAEs leading to study withdrawal (*Table 14.3.1.11*)
- Summary of pre-treatment AEs (*Table 14.3.1.14*)

For each of the summaries done at the participant level, multiple occurrences of the same event within a participant will be counted once in the summaries by SOC and PT; multiple occurrences of the same event within a participant will be counted once in the worst severity category (severe > moderate > mild) and/or strongest study drug relationship category (related > not related). For relationship category, related also includes "possibly related" events. If severity or relationship is found to be missing, the most severe occurrence will be imputed for that particular summary.

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 worse severity category and strongest relationship category they were classed as. As an example, should a participant have two mild and three severe AEs, only these latter will be reported in the 'Severe' line of the table for the overall and appropriate SOC/PT summaries, whereas the two mild events will not be considered; similarly, if a participant has only mild events all of them will be reported in the appropriate 'Mild' lines of the display.

Summaries of the subset of (i) TEAES, and (ii) AESIs occurring within 24 hours of the COMP360 administration by SOC, PT, and start/stop time category since administration (see Section 8.3.1 for categories) will be produced (*Table 14.3.1.12* for TEAEs, and *Table 14.3.1.13* for AESIs).

AEs for which the end date is not available because the data is genuinely missing will be considered as ongoing for analysis purposes.

All AEs for each participant, including multiple occurrences of the same event, will be presented in full in a comprehensive listing including participant number, treatment, reported term, SOC, PT, date/time and study day when AE starts/stops, , duration (days), relationship to COMP360, severity, action taken, outcome, seriousness, whether concomitant medication started due to AE and whether the AE leads to study withdrawal (*Listing 16.2.7.1*). Listings will also be provided for participants who experience TESAEs (*Listing 16.2.7.2*), AESIs (*Listing 16.2.7.3*), AEs that led to death (*Listing 16.2.7.4*), and pre-treatment AEs (*Listing 16.2.7.5*).

10.2 Laboratory Tests

Descriptive statistics of the observed values and change from baseline (continuous data) will be presented for each haematology (*Table 14.3.4.1*) and chemistry (*Table 14.3.4.2*) parameter by visit.

Shift tables will display numbers of participants with normal range shifts at baseline versus post-treatment at Day 2, Week 4, and Week 12 (*Table 14.3.4.3* and *Table 14.3.4.4* for haematology and chemistry, respectively).

Listings for haematology, chemistry, and urinalysis data (*Listing 16.2.8.1*, *Listing 16.2.8.2,* and *Listing 16.2.8.3*) will also flag values that are outside normal reference ranges or markedly abnormal findings. Clinically significant laboratory data will also be listed separately (*Listing 16.2.8.4*).

10.3 Vital Signs

Descriptive statistics of the observed values and change from baseline on non-administration and administration visits will be presented for each parameter by visit and by timepoint on COMP360 administration day (*Table 14.3.5.1, Figure 14.3.5.1* [for day of dosing only]). Individual participant plots will also be produced for the observed and change from baseline values for each parameter by timepoint on COMP360 administration

day only (*Figure 14.3.5.2*). The number and percentage of participants with values outside clinically important limits, as described in Section 8.3.3.1 will be summarised by visit and timepoint on COMP360 administration day (*Table 14.3.5.2*).

All vital signs data will be listed, which will also include flagged values that are outside normal reference ranges or markedly abnormal findings (*Listing 16.2.8.7*). Clinically important vital signs values will also be listed separately (*Listing 16.2.8.8)*.

10.4 ECGs

Descriptive statistics of the observed values and change from baseline will be presented for each parameter by visit (*Table 14.3.6.1*).

Shift tables in relation to the overall interpretation (normal, abnormal not clinically significant (NCS), and abnormal clinically significant (CS) at baseline versus post-COMP360 administration at Day 2 will be presented (*Table 14.3.6.2)*.

The number and percentage of participants meeting the QTc intervals as described in Section 8.3.4.1 will be summarised by visit (*Table 14.3.6.3*).

All ECG data will be listed (*Listing 16.2.8.9*). Clinically important ECG values will also be listed separately (*Listing 16.2.8.10*)

10.5 C-SSRS

C-SSRS data will be summarised by visit (*Table 14.3.6.4*) and listed (*Listing 16.2.9.2*).

10.6 BPRS+

BPRS+ total score data will be summarised by visit (*Table 14.3.6.5*) and BPRS+ symptom score data will be summarised categorically by visit (*Table 14.3.6.6*). BPRS+ data will also be listed (*Listing 16.2.9.3*).

11 EFFICACY

The FAS will be used for all efficacy-related evaluations.

The summaries and analyses will be presented overall.

Since there is only one treatment group, there will be no formal statistical testing of any hypothesis. In some cases, 95% confidence intervals (CIs) will be reported but these are to be interpreted as exploratory.

11.1 Secondary Efficacy Endpoint(s)

The secondary endpoints are:

- Change in CAPS-5 total symptom severity score and criteria scores from baseline
- Change in PCL-5 total symptom severity score and cluster severity scores from baseline
- Change in SDS total score from baseline
- Change in EQ-5D-5L index score from baseline
- Proportion of participants with response (defined as a $\geq$ 15 point improvement on the CAPS-5 total score from baseline)
- Proportion of participants with remission (defined as CAPS-5 total score $\leq$ 20)

11.1.1 Main Analysis

Total/total severity/index score values and their changes from baseline at each post-baseline timepoint will be descriptively summarised using statistics for continuous variables including 95% CIs for the FAS. Both actual values and their change from baseline will also be graphically displayed as line plots for the FAS. All observed scale data will also be listed. These summaries, figures and listings will be presented for the scales below:

- CAPS-5 (*Table 14.2.2.1* , *Figure 14.2.2.1, Listing 16.2.6.1*)
- PCL-5 (*Table 14.2.2.2* , *Figure 14.2.2.2, Listing 16.2.6.2*)
- SDS (*Table 14.2.2.3* , *Figure 14.2.2.3, Listing 16.2.6.3*)
- EQ-5D-5L (*Table 14.2.2.4* , *Figure 14.2.2.4, Listing 16.2.6.4*)

The proportion of CAPS-5 responders (defined as a $\geq$ 15 point improvement on the CAPS-5 total score from Baseline) and CAPS-5 remitters (defined as CAPS-5 total score $\leq$ 20), will be descriptively summarised alongside 95% asymptotic CIs at each post-baseline timepoint (*Table 14.2.2.5* for response and *Table 14.2.2.6* for remission) and graphically

displayed via bar charts including the estimated 95% Wald-type CIs (*Figure 14.2.2.5* for response and *Figure 14.2.2.6* for remission). At each timepoint separate proportions will be calculated using both the total number of participants in the FAS (N) and the total number of participants with available data at a particular visit as the denominator (n*).

CIs will be Wald-type asymptotic intervals based on the Normal approximation to the binomial distribution, obtained in SAS as follows:

```
ods output BinomialCLs = <output-dataset>;
proc freq data = <input-dataset>;
  by avisitn;
  tables aval / binomial (level = 2 cl = wald);
run;
```

Participant's status as a responder/remitter at each timepoint will be listed (*Listing 16.2.6.1*).

Participant's status as a remitter at each timepoint will be listed (*Listing 16.2.6.1*).

11.2 Additional Efficacy Endpoint(s)

The change from baseline in PACT scores (Forward Focus subscale, Trauma Focus subscale, and overall flexibility score) will be summarised, graphically displayed, and listed similarly to the secondary endpoints (*Table 14.2.3.1, Figure 14.2.3.1* and, *Listing 16.2.6.5*).

The 5D-ASC dimensions and EBI total score will be summarised (*Table 14.2.3.2* and *Table 14.2.3.3*, respectively) and listed (*Listing 16.2.6.7* and *Listing 16.2.6.8*, respectively).

The RAS total score will be listed (*Listing 16.2.6.6*).

12 CHANGES FROM THE PROTOCOL-PLANNED ANALYSES

Below is a list of changes from the protocol-planned analyses:

- Section 6 (Analysis Sets): The definition of FAS was updated to include those participants who do not have a post-baseline assessment

- Section 8.3.1 (Adverse Events): The AESI terms and MedDRA terms in AESI Table 5 have been updated from those included in the protocol to account for additional PTs of interest and updated MedDRA dictionary versions

13 DATA NOT PRESENTED

Data from the semi-structured qualitative interview, Cue app, fMRI, and blood biomarker components of the study will not be analysed for the CSR (clinical study report) so are not included in the scope of this SAP.

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15 PROGRAMMING AND DATA PRESENTATION CONVENTIONS

15.1 Treatment Labelling

Table 14: Treatment Group Labels

COMP360 25 mg

15.2 Visit Labelling

Table 15: Analysis Visits and Output Labels

Analysis Visit	Output Label
Screening – Visit 1	Screening
Screening Period – Visit 1a/1b/1c/…	Screening a/ Screening b/Screening c/…
Baseline (Day -1) – Visit 2	Baseline or Day -1
Administration Session (Day 1) – Visit 3	Day 1
Day 2 – Visit 4	Day 2
Week 1 – Visit 5	Week 1
Week 2 – Visit 6	Week 2
Week 4 – Visit 7	Week 4
Week 6 – Visit 8	Week 6
Week 9 – Visit 9	Week 9
Week 12 (ET) – Visit 10	Week 12

15.3 Timepoint Labelling

Table 16: Timepoint Labels

Analysis Visit	Timepoint	Output Label
Day 1	15 minutes pre-COMP360	pre-dose
	1 hour post-COMP360	1 hour
	3 hours post-COMP360	3 hours
	6 hours post-COMP360	6 hours

15.4 Baseline Definitions

Table 17: Baseline Definitions

Parameter	Baseline
Safety	
All	Day -1
Vital Signs	Day 1 (pre-COMP360 administration)
Efficacy	
All	Day -1

15.5 Study Day and Duration Derivation

Study day, defined as the number of days from the dose of COMP360, will be derived as follows:

- date of event – date of dose of COMP360 + 1, for events on or after dose
- date of event – date of dose of COMP360, for events before dose

Duration of AEs (in days) will be calculated as follows:

- [stop date of the event – start date of the event + 1] or
- [(stop datetime of the AE-start datetime of the AE)/(60×60×24)]

In cases where the time component of either the start or the stop date is missing the following approach will be taken:

- If the AE start time is missing and the AE occurred after Day 1, the duration will be calculated assuming the event at started at 00:00:00 AM of that day, otherwise if the AE occurred on Day 1 the duration will be derived using the datetime of dosing as starting point.
- If the AE stop time is missing the duration will be calculated assuming the event stopped at 23:59:59 (11:59:59 PM) of that day.

15.6 Decimal Places

Decimal places (dps) for derived data described in Section 8 will be determined by the scale of measurement unless otherwise stated. No dps will be displayed if the smallest calculated value is ≥ 100; 1 dp will be displayed when the smallest value is within the interval (10, 100), with 10 being inclusive; 2 dps will be displayed when the smallest value is within (1, 10), with 1 being inclusive; and so on for even smaller scales of measurement.

Derived data where it is known in advance the result will be an integer for example day, month, year, number of days and total scores (for rating scales) will be presented with zero dps.

Means, medians, and percentiles will be displayed to one more dp than the data, dispersion statistics (eg SD) will have two more dps, and the minimum and maximum will be displayed to the same number of dps as reported in the raw data. Percentages will be displayed with one dp. No percentage will be displayed for zero-frequency scenarios.

16 TABLES, FIGURES AND LISTINGS

The following tables include details of the tables, figures and listings to be created.

The following validation methods may be used:

- Independent programming of numbers and manual review of format (Iprog)
- Independent programming by statistician of numbers and manual review of format (Stat Iprog)
- Manual review (MR)
- Code review (CR)

Table 18: List of Tables, Figures and Listings

Table Number	Table Title	Validation Method	Shell Number (if Repeat)
14.1	**Demographic Data**		
14.1.1	**Disposition**		
14.1.1.1	Participant Disposition by Country – Screening Analysis Set	IProg	
14.1.1.2	Participant Disposition, Completions, and Early Terminations with Reasons – Safety Analysis Set	IProg	
14.1.1.3	Screen Failures with Reasons – Screening Analysis Set	IProg	
14.1.1.4	Important Protocol Deviations – Safety Analysis Set	IProg	
14.1.2	**Demographics**		
14.1.2	Demographics – Safety Analysis Set	IProg	
14.1.3	**Baseline Characteristics**		
14.1.3.1	Medical History – Safety Analysis Set	IProg	
14.1.3.2	Prior Medications – Safety Analysis Set	IProg	
14.1.3.3	Concomitant Medications – Safety Analysis Set	IProg	14.1.3.2
14.1.3.4	Prior Non-Drug Therapies – Safety Analysis Set	IProg	14.1.3.1
14.1.3.5	Concomitant Non-Drug Therapies – Safety Analysis Set	IProg	14.1.3.1
14.1.3.6	Prior Non-Drug Therapies for PTSD – Safety Analysis Set	IProg	14.1.3.1
14.1.3.7	Concomitant Non-Drug Therapies for PTSD – Safety Analysis Set	IProg	14.1.3.1
14.1.3.8	Other Baseline Characteristics – Safety Analysis Set	IProg	
14.1.3.9	Mini International Neuropsychiatric Interview (MINI, Version 7.0.2) – Safety Analysis Set	IProg	
14.1.3.10	Life Event Checklist for DSM-5 (LEC-5) – Safety Analysis Set	IProg	
14.2	**Efficacy Data**		
14.2.2	**Secondary Efficacy Endpoints**		
14.2.2.1	Secondary Endpoint – Summary of Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) and Change from Baseline– Full Analysis Set	IProg	

Table Number	Table Title	Validation Method	Shell Number (if Repeat)
14.2.2.2	Secondary Endpoint – Summary of PTSD Checklist for DSM-5 (PCL-5) and Change from Baseline – Full Analysis Set	IProg	14.2.2.1
14.2.2.3	Secondary Endpoint – Summary of Sheehan Disability Scale (SDS) Total Score and Change from Baseline – Full Analysis Set	IProg	14.2.2.1
14.2.2.4	Secondary Endpoint – Summary of EQ-5D-5L Index Score and Change from Baseline – Full Analysis Set	IProg	14.2.2.1
14.2.2.5	Secondary Endpoint – Proportion of Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) Responders Over Time – Full Analysis Set	Stat IProg	
14.2.2.6	Secondary Endpoint – Proportion of Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) Remitters Over Time – Full Analysis Set	Stat IProg	14.2.2.6
14.2.3	**Additional Efficacy Endpoints**		
14.2.3.1	Additional Endpoint – Summary of Perceived Ability to Cope with Trauma (PACT) Scale Scores and Change from Baseline – Full Analysis Set	IProg	14.2.2.1
14.2.3.2	Additional Endpoint – Summary of Five-Dimensional Altered State of Consciousness (5D-ASC) – Full Analysis Set	IProg	
14.2.3.3	Additional Endpoint – Summary of Emotional Breakthrough Inventory (EBI) – Full Analysis Set	IProg	
14.3	**Safety Data**		
14.3.1	**Displays of Adverse Events**		
14.3.1.1	Summary of Treatment-Emergent Adverse Events (TEAEs) – Safety Analysis Set	IProg	
14.3.1.2	MedDRA Summary of Treatment-Emergent Adverse Events (TEAEs) by Primary System Organ Class and Preferred Term – Safety Analysis Set	IProg	
14.3.1.3	MedDRA Summary of Non-Serious Treatment-Emergent Adverse Events (TEAEs) with >= 5% Incidence by Primary System Organ Class and Preferred Term – Safety Analysis Set	IProg	14.3.1.2
14.3.1.4	MedDRA Summary of Treatment-Emergent Adverse Events (TEAEs) by Primary System Organ Class, Preferred Term and Worst Severity – Safety Analysis Set	IProg	14.3.1.2
14.3.1.5	MedDRA Summary of Treatment-Emergent Adverse Events (TEAEs) by Primary System Organ Class, Preferred Term and Strongest Relationship to Study Drug – Safety Analysis Set	IProg	

Table Number	Table Title	Validation Method	Shell Number (if Repeat)
14.3.1.6	MedDRA Summary of Treatment-Emergent Adverse Events (TEAEs) by Primary System Organ Class, Preferred Term, Time of Onset and Duration of Adverse Event – Safety Analysis Set	IProg	
14.3.1.7	MedDRA Summary of Treatment-Emergent Serious Adverse Events (TESAEs) by Primary System Organ Class and Preferred Term – Safety Analysis Set	IProg	14.3.1.2
14.3.1.8	MedDRA Summary of Treatment-Emergent Serious Adverse Events (TESAEs) by Primary System Organ Class, Preferred Term, Time of Onset and Duration of Adverse Event – Safety Analysis Set	IProg	14.3.1.6
14.3.1.9	MedDRA Summary of Treatment-Emergent Adverse Events of Special Interest (AESIs) by AESI Term and Preferred Term – Safety Analysis Set	IProg	14.3.1.2
14.3.1.10	MedDRA Summary of Treatment-Emergent Adverse Events of Special Interest (AESIs) by AESI Term, Preferred Term, Time of Onset and Duration of Adverse Event – Safety Analysis Set	IProg	14.3.1.6
14.3.1.11	MedDRA Summary of Treatment-Emergent Adverse Events (TEAEs) Leading to Study Withdrawal by Primary System Organ Class and Preferred Term – Safety Analysis Set	IProg	14.3.1.2
14.3.1.12	MedDRA Summary of Treatment-Emergent Adverse Events (TEAEs) Occurring Within 24 Hours of Study Drug Administration by Primary System Organ Class, Preferred Term, and Start/Stop Time Since Study Drug Administration – Safety Analysis Set	IProg	
14.3.1.13	MedDRA Summary of Treatment-Emergent Adverse Events of Special Interest (AESIs) Occurring Within 24 Hours of Study Drug Administration by AESI Term, Preferred Term, and Start/Stop Time Since Study Drug Administration – Safety Analysis Set	IProg	14.3.1.12
14.3.1.14	MedDRA Summary of Pre-Treatment Adverse Events (Aes) by Primary System Organ Class, and Preferred Term – Screening Analysis Set	IProg	14.3.1.2
14.3.4	**Laboratory Values**		
14.3.4.1	Summary Statistics of Observed Values and Change from Baseline in Haematology – Safety Analysis Set	IProg	
14.3.4.2	Summary Statistics of Observed Values and Change from Baseline in Chemistry – Safety Analysis Set	IProg	14.3.4.1
14.3.4.3	Normal Range Shifts from Baseline in Haematology Values – Safety Analysis Set	IProg	
14.3.4.4	Normal Range Shifts from Baseline in Chemistry Values – Safety Analysis Set	IProg	14.3.4.3

Table Number	Table Title	Validation Method	Shell Number (if Repeat)
14.3.5	**Vital Signs**	IProg	
14.3.5.1	Summary Statistics of Observed Values and Change from Baseline in Vital Signs by Visit and Timepoint – Safety Analysis Set	IProg	
14.3.5.2	Overall Summary of Clinically Important Vital Signs Values – Safety Analysis Set	IProg	
14.3.6	**Other Safety**		
14.3.6.1	Summary Statistics of Observed Values and Changes from Baseline to Day 2 in ECG Variables – Safety Analysis Set	IProg	14.3.4.1
14.3.6.2	ECG Clinical Interpretation – Shift from Baseline to Day 2 – Safety Analysis Set	IProg	
14.3.6.3	Summary of QTc Interval Categories – Safety Analysis Set	IProg	
14.3.6.4	Summary of C-SSRS by Visit– Safety Analysis Set	IProg	
14.3.6.5	Summary of BPRS+ Total Score by Visit – Safety Analysis Set	IProg	
14.3.6.6	Summary of BPRS+ Symptom Score by Visit – Safety Analysis Set	IProg	

Figure Number	Figure Title	Validation Method	Shell Number (if Repeat)
14.2	**Efficacy Endpoints**		
14.2.2	**Secondary Endpoints**		
14.2.2.1	Secondary Endpoint – Summary of Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) and Change from Baseline– Full Analysis Set	IProg	
14.2.2.2	Secondary Endpoint – Summary of PTSD Checklist for DSM-5 (PCL-5) and Change from Baseline – Full Analysis Set	IProg	14.2.2.2

Figure Number	Figure Title	Validation Method	Shell Number (if Repeat)
14.2.2.3	Secondary Endpoint – Summary of Sheehan Disability Scale (SDS) Total Score and Change from Baseline – Full Analysis Set	IProg	14.2.2.2
14.2.2.4	Secondary Endpoint – Summary of EQ-5D-5L Index Score and Change from Baseline – Full Analysis Set	IProg	14.2.2.2
14.2.2.5	Secondary Endpoint – Proportion of Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) Responders – Full Analysis Set	Stat IProg	14.2.2.2
14.2.2.6	Secondary Endpoint – Proportion of Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) Remitters – Full Analysis Set	Stat IProg	14.2.2.2
14.2.3	**Additional Endpoints**		14.2.2.2
14.2.3.1	Additional Endpoint – Summary of Perceived Ability to Cope with Trauma (PACT) Scales Scores and Change from Baseline – Full Analysis Set	IProg	14.2.2.2
14.3.5	**Safety Endpoints**		
14.3.5.1	Summary of Administration Day Vital Signs – Safety Analysis Set	IProg	
14.3.5.2	Individual Participant Plots of Administration Day Vital Signs – Safety Analysis Set	IProg	

Listing Number	Listing Title	Validation Method	Shell Number (if Repeat)
16.2	**Participant Data Listings**		
16.2.1	**Discontinued Participants**		
16.2.1.1	Details of Study Discontinuations – Safety Analysis Set	IProg	
16.2.1.2	Details of Study Completers – Safety Analysis Set	IProg	
16.2.2	**Protocol Deviations**		
16.2.2.1	Important Protocol Deviations – Safety Analysis Set	IProg	
16.2.3	**Participation in each Defined Analysis Set**		

Listing Number	Listing Title	Validation Method	Shell Number (if Repeat)
16.2.3	Analysis Sets – Screening Analysis Set	IProg	
16.2.4	**Demographic Data**		
16.2.4.1	Demographics – Safety Analysis Set	IProg	
16.2.4.2	Other Baseline Characteristics – Safety Analysis Set	IProg	
16.2.4.3	Medical History – Safety Analysis Set	IProg	
16.2.4.4	Inclusion Criteria – Screening Analysis Set	IProg	
16.2.4.5	Exclusion Criteria – Screening Analysis Set	IProg	
16.2.4.6	Prior Medications – Safety Analysis Set	IProg	
16.2.4.7	Concomitant Medications – Safety Analysis Set	IProg	
16.2.4.8	Prior Non-Drug therapies – Safety Analysis Set	IProg	
16.2.4.9	Concomitant Non-Drug Therapies – Safety Analysis Set	IProg	
16.2.4.10	Prior Non-Drug Therapies for PTSD – Safety Analysis Set	IProg	
16.2.4.11	Concomitant Non-Drug Therapies for PTSD – Safety Analysis Set	IProg	
16.2.5	**Compliance And/Or Drug Concentration Data**		
16.2.5	Study Drug Administration – Safety Analysis Set	IProg	
16.2.6	**Individual Efficacy Response Data**		
16.2.6.1	Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) – Full Analysis Set	IProg	
16.2.6.2	PTSD Checklist for DSM-5 (PCL-5) – Full Analysis Set	IProg	
16.2.6.3	Sheehan Disability Scale (SDS) – Full Analysis Set	IProg	
16.2.6.4	EQ-5D-5L – Full Analysis Set	IProg	
14.2.6.5	Perceived Ability to Cope with Trauma (PACT) Scale – Full Analysis Set	IProg	
14.2.6.6	Resilience Adult Scale (RAS) – Full Analysis Set	IProg	
16.2.6.7	Five-Dimensional Altered State of Consciousness (5D-ASC) – Full Analysis Set	IProg	
16.2.6.8	Emotional Breakthrough Inventory (EBI) – Full Analysis Set	IProg	
16.2.7	**Adverse Event Listings**		
16.2.7.1	Treatment-Emergent Adverse Events (TEAEs) – Safety Analysis Set	IProg	
16.2.7.2	Treatment-Emergent Serious Adverse Events (TESAEs) – Safety Analysis Set	IProg	
16.2.7.3	Treatment-Emergent Adverse Events of Special Interest (AESIs) – Safety Analysis Set	IProg	

Listing Number	Listing Title	Validation Method	Shell Number (if Repeat)
16.2.7.4	Deaths – Safety Analysis Set	IProg	
16.2.7.5	Pre-Treatment Adverse Events – Screening Analysis Set	IProg	
16.2.8	**Individual Laboratory Measurements and Other Safety**		
16.2.8.1	Haematology – Safety Analysis Set	IProg	
16.2.8.2	Chemistry – Safety Analysis Set	IProg	16.2.8.1
16.2.8.3	Urinalysis – Safety Analysis Set	IProg	16.2.8.1
16.2.8.4	Clinically Significant Laboratory Values – Safety Analysis Set	IProg	
16.2.8.5	Urine Drug Screen – Safety Analysis Set	IProg	
16.2.8.6	Pregnancy Test – Safety Analysis Set	IProg	
16.2.8.7	Vital Signs Data – Safety Analysis Set	IProg	
16.2.8.8	Clinically Important Vital Signs Values – Safety Analysis Set	IProg	16.2.8.4
16.2.8.9	ECG Data – Safety Analysis Set	IProg	
16.2.8.10	Clinically Important ECG Values – Safety Analysis Set	IProg	
16.2.9	**Other Study Instruments**		
16.2.9.1	Mini International Neuropsychiatric Interview (MINI, Version 7.0.2) - Safety Analysis Set	IProg	
16.2.9.2	Columbia Suicidal Severity Rating Scale (C-SSRS) – Safety Analysis Set	IProg	
16.2.9.3	Brief Psychiatric Rating Scale – Positive Symptom subscale (BPRS+) – Safety Analysis Set	IProg	
16.2.9.4	McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD) – Safety Analysis Set	IProg	
16.2.9.5	Life Event Checklist for DSM-5 (LEC-5) – Safety Analysis Set	IProg	
16.2.9.6	Childhood Trauma Questionnaire (CTQ) – Safety Analysis Set	IProg	

Statistical Analysis Plan
Post Database Lock Addendum

Title: *The Safety and Tolerability of COMP360 in Participants with Post-Traumatic Stress Disorder*

Protocol Number: *COMP 201*

Protocol Version: *UK Version 5.0 / 09 June 2023*
US Version 5.0 / 09 June 2023

SAP Version: *1.0, 05-March-2024*

Addendum Version: 1.0

Addendum issue Date: 06-June-2024

Previous Addenda

Not Applicable

1. BACKGROUND

This document details changes and / or additions to the planned statistical analyses for Compass Pathfinder Limited protocol COMP 201 study previously described in version 1.0 of the Statistical Analysis Plan (SAP) dated 05-March-2024.

These amendments were made post database lock but since the study was open label there was no unblinding step.

Rationale for Addendum:

1. To include instructions on how to derive the CAPS-5 cluster severity scores to be able to summarise, graphically display, and list these scores.
2. To include a summary of concomitant medications relative to COMP360 dose (i.e. medications that were taken pre-dose, post-dose, and overall).
3. To include individual participant plots of the CAPS-5 total scores.
4. To include details of scatter plots with Spearman's rank correlation coefficients to be produced for each dimension of the 5D-ASC on the x-axis and change from baseline in CAPS-5 total score on the y-axis.
5. To clarify in Section 11.2 that only individual item scores for the Resilience Adult Scale (RAS) are to be listed.
6. To remove Table 14.1.3.10 'Life Event Checklist for DSM-5 (LEC-5) – Safety Analysis Set' in Section 16 as this summary is redundant as this information is incorporated into Table 14.1.3.8 'Other Baseline Characteristics – Safety Analysis Set'.
7. To include a summary table and listing to report results for the Modified Discontinuation Emergent Signs and Symptoms Scale (mDESS).

2. CHANGES TO EXISTING SAP

2.1 Change 1

2.1.1 Original text: Section 9.6 Prior and Concomitant Medications

Prior and concomitant medications will be summarised (*Table 14.1.3.2* and *Table 14.1.3.3*) and listed (*Listing 16.2.4.6* and *Listing 16.2.4.7*).

2.1.2 Revised Text

Prior medications will be summarised (*Table 14.1.3.2*) and listed (*Listing 16.2.4.6*).

Concomitant mediations will be summarised by medications that were taken pre-dose, post-dose (including the medications that were started pre-dose but increased in dose post-dose), and overall (*Table 14.1.3.3*).

Concomitant medications will be listed (and *Listing 16.2.4.7*), and a separate listing will be produced containing only the medications that were started post-dose, including the medications that were started pre-dose but increased in dose post-dose (and *Listing 16.2.4.12*).

2.2 Change 2

2.2.1 **Original text: Section 11.2 Additional Efficacy Endpoint(s)**

The RAS total score will be listed (*Listing 16.2.6.6*).

2.2.2 **Revised Text**

The RAS item scores will be listed (*Listing 16.2.6.6*).

2.3 Change 3

2.3.1 **Original text: Section 16 TABLES, FIGURES AND LISTINGS**

14.1.3.10	Life Event Checklist for DSM-5 (LEC-5) – Safety Analysis Set	IProg

2.3.2 **Revised Text**

~~14.1.3.10~~	~~Life Event Checklist for DSM-5 (LEC-5) – Safety Analysis Set~~	~~IProg~~

3. ADDITIONS TO EXISTING SAP

3.1 Addition 1

3.1.1 New text: Section 8.4.1.4 CAPS-5 Clusters

The CAPS-5 cluster severity scores are calculated by summing the individual item severity scores for the symptoms contained in each DSM-5 diagnostic criterion for PTSD as shown in Table 10. The sum of the symptoms in cluster B correspond to the intrusion symptoms criterion , the sum of cluster C symptoms correspond to the avoidance symptoms criterion, the sum of cluster D corresponds to the negative alterations in cognitions and mood criterion, and the sum of cluster E corresponds to the arousal and reactivity criterion.

3.2 Addition 2

3.2.1 New text: Section 10.7 mDESS

The total number of items on the mDESS, endorsed by the participant as being: (i) 'new symptom(s)'; (ii) 'old symptom(s) but worse'; and (iii) 'new symptom(s)' and 'old symptom(s) but worse', will be summarised by visit (*Table 14.3.6.7*).

mDESS data will be listed (*Listing 16.2.9.7*).

3.3 Addition 3

3.3.1 New text: Section 11.1.1 Main Analysis

Individual participant plots will be produced for the observed and change from baseline values for the CAPS-5 total score by timepoint (*Figure 14.2.2.7*).

3.4 Addition 4

3.4.1 New text: Section 11.2 Additional Efficacy Endpoint(s)

Scatterplots will also be created, for each dimension of the 5D-ASC on the x-axis and the change from baseline in CAPS-5 total score on the y-axis. A regression line overlaying the scatterplot will be included along with Spearman's rank correlation coefficient, added in the plot area (*Figures 14.2.3.3 and 14.2.3.4*) for CAPS-5 change from baseline at Week 4 and Week 12 respectively.

Sample SAS code to estimate the Spearman correlation coefficient is provided below:

```
ods output FisherSpearmanCorr = corr;
proc corr data = <input-dataset> fisher spearman;
  var <caps-cfb> <5d-asc>;
run;
```

The CAPS-5 cluster scores and their changes from baseline will be summarised, graphically displayed, and listed (*Table 14.2.3.4, Figure 14.2.3.2, Listing 16.2.6.1*).

Table Number	Table Title	Validation Method

14.2.3.4	Additional Endpoint – Summary of Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) Cluster Scores and Change from Baseline – Full Analysis Set	IProg
14.3.6.7	Summary of mDESS Symptom Scores by Visit – Safety Analysis Set	IProg

3.5 New text: Section 16 TABLES, FIGURES AND LISTINGS

Figure Number	Figure Title	Validation Method
14.2.2.7	Secondary Endpoint – Individual Participant Plot of Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) – Full Analysis Set	IProg
14.2.3.2	Additional Endpoint – Summary of Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) Cluster Scores and Change from Baseline – Full Analysis Set	IProg
14.2.3.3	Additional Endpoint - Scatterplot of Change from Baseline in CAPS-5 at Week 4 vs 5D-ASC Dimensions – Full Analysis Set	Stat IProg
14.2.3.4	Additional Endpoint - Scatterplot of Change from Baseline in CAPS-5 at Week 12 vs 5D-ASC Dimensions – Full Analysis Set	Stat IProg

Listing Number	Listing Title	Validation Method
16.2.4.12	Post-COMP360 Administration Concomitant Medications – Safety Analysis Set	IProg
16.2.9.7	Modified Discontinuation Emergent Signs and Symptoms scale (mDESS) – Safety Analysis Set	IProg

Approval for implementation of

Statistical Analysis Plan Post Database Lock Addendum

REVIEW / APPROVAL SIGNATURES

Plan Author [redacted] *Senior Principal Statistician, Biostatistics* Signature: [redacted]	**Plan Reviewer, Worldwide** [redacted] *Statistician, Biostatistics* Signature: [redacted]
Plan Approver, Sponsor Statistician [redacted] *Senior Director, Statistics and Data Management* Signature: [redacted]	**Plan Approver, Sponsor Statistician** [redacted] *Statistician* Signature: [redacted]