STATISTICAL ANALYSIS PLAN (SAP) FOR COMP 003
THE SAFETY AND EFFICACY OF COMP360 AS AN ADJUNCTIVE THERAPY IN PARTICIPANTS WITH TREATMENT-RESISTANT DEPRESSION

DRUG:	COMP360
TITLE:	The Safety and Efficacy of COMP360 as an Adjunctive Therapy in Participants with Treatment-Resistant Depression
CLINICAL PHASE	II
SPONSOR:	COMPASS Pathfinder Limited 3rd Floor, 1 Ashley Road Altrincham, Cheshire, WA14 2DT, UK
VERSION NUMBER:	Final Version 1.0
VERSION DATE:	17 November 2021
AUTHOR	Niccolo Bassani, PhD (Principal Statistician)

CONFIDENTIALITY STATEMENT

SAP APPROVAL FORM

Protocol Number: COMP 003

Title: The Safety and Efficacy of COMP360 as an Adjunctive Therapy in Participants with Treatment-Resistant Depression

SAP Version and Date: Version 1.0 17 November 2021

This SAP was reviewed 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.

Author Details and Signature

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SAP SYNOPSIS

Protocol Number	COMP 003
Title:	The Safety and Efficacy of COMP360 as an Adjunctive Therapy in Participants with Treatment-Resistant Depression
EudraCT Number:	2018-002577-22
Investigational Product:	COMP360
ClinicalTrials.gov Identifier:	NCT04739865
Clinical Phase:	II
Rationale:	A recent open-label study of the effects of psilocybin in participants with treatment-resistant depression (TRD) showed rapid significant decrease of depressive symptoms after treatment with psilocybin coupled with psychological support. Over 40% of participants sustained response at 3 months. In this study, the aim is to explore effectiveness of 25 mg COMP360 as an adjunctive therapy in participants with TRD.
Number of Participants:	Approximately 20 participants with simultaneous study drug administration to up to six participants
Objectives:	The main purpose of this study is to investigate the efficacy of 25 mg COMP360 adjunct to serotonergic antidepressants in TRD participants via the following objectives. **Primary Objective** The primary objective of this study is to explore the efficacy of 25 mg COMP360 as an adjunct therapy to antidepressants in improving depressive symptoms. **Secondary Objectives** The secondary objective is to evaluate the safety and tolerability of COMP360 in participants with TRD based on adverse events (AEs), changes in vital signs, electrocardiograms (ECGs), clinical laboratory tests and suicidal ideation/behaviour (measured using the Columbia- Suicide Severity Rating Scale [C-SSRS]) score. **Exploratory Objectives** The exploratory objectives are to evaluate the effects of COMP360 on quality of life, wellbeing and anxiety.
Study Design and Procedures:	This is a Phase IIb, international multicentre, fixed-dose, open-label study. The study population will include adult men and women, 18 years of age or older, with TRD. Participants with TRD are defined as those who meet the Diagnostic and Statistical Manual of Mental Disorders (5th Edition; DSM-5) diagnostic criteria for single or recurrent episode of major depressive disorder (MDD) without psychotic features who have failed to respond to an adequate dose and duration of 2, 3 or 4 pharmacological treatments for the current episode. The duration of the current episode must be at least 3 months but not more than 2 years. Participants will be outpatients and will be recruited primarily through referrals from general practitioners and specialised psychiatric services.

After signing the informed consent form (ICF), participants will be assessed for their eligibility with the Mini International Neuropsychiatric Interview, Version 7.0.2 (MINI 7.0.2), the Hamilton Depression Rating Scale (17-item; HAM-D-17), the Massachusetts General Hospital-Antidepressant Treatment History Response Questionnaire (MGH-ATRQ), the C-SSRS, and McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD). At the initial Screening visit (V1), the participant will also be evaluated with the Quick Inventory of Depressive Symptomatology – Self Rated - 16 item (QIDS-SR-16). Additionally, a medical history, an ECG, blood tests, and vital signs will be obtained.

Once a participant completes all Screening (V1) assessments and all screening data is entered into the Electronic Data Capture (EDC), the Medical Monitor (MM) and Clinical Assessment Technologies Team (CAT) will review data entered and issue approval, if the participant is eligible.

The participant will meet with a therapist for 3 visits during screening. These are safety sessions and will cover what to expect during the COMP360 administration session. The therapist and the participant will review psychoeducational materials provided at the time of enrolment.

All participants will be evaluated for safety at the clinic weekly for 3 weeks prior to COMP360 administration. Any safety assessment visits during the screening period will be called V1a, V1b, V1c etc. During these visits, the C-SSRS and any changes in medications since the previous visit will be obtained in addition to other assessments at the study clinician's discretion.

At baseline [V2, day -1], the participants will undergo a baseline assessment that will consist of the HAM-D-17, Montgomery-Asberg Depression Rating Scale (MADRS), Clinical Global Impression – Severity scale (CGI-S) and Improvement scale (CGI-I), QIDS-SR-16, C-SSRS, Generalised Anxiety Disorder Scale 7-item Scale (GAD-7), EuroQoL-5 dimension-3 level (EQ-5D-3L; administered to both participant and caregiver [the latter is not mandatory]), vital signs, urinalysis, urine drug screen, and urine pregnancy test (only for women of childbearing potential). After baseline data is entered into EDC, the CAT team will complete a final review to ensure the participant's continued eligibility.

Participants cannot be progressed to V3 until this approval is received.

The COMP360 administration session (V3, day 1) will last approximately 6 h and will be supported by a trained therapist. The study drug will be administered simultaneously to up to six participants. Blood pressure will be monitored continuously during the session. The COMP360 administration session may be video recorded for training and adherence monitoring. A full description of the activities of the COMP360 administration session is found in the Therapist Manual. After the acute effects of COMP360 pass, participants will be evaluated for safety and accompanied home. On day 2 (V4), the day following COMP360 administration, participants will be seen in person for a safety check, assessment of suicidality and clinical and self-report assessments, and to discuss their experience during the COMP360 administration session. All sessions between the therapist and the participant may be audio recorded for adherence monitoring and quality assurance.

Audio and video recording of the sessions are subject to participant consent. Participants who do not consent to either or all recordings will not be excluded from the study.

	Twenty participants will receive one dose of 25 mg COMP360. Participants will be seen at the clinic for Screening (plus 3 safety visits), baseline (day -1), day 1 (dosing), day 2, week 1, week 2 and week 3. AEs, serious adverse events (SAEs) and concomitant medication and therapies will be recorded at all clinic visits. The MADRS will be done by telephone. Clinicians are advised to continue the prescription of the participant's baseline selective serotonin reuptake inhibitor (SSRI) (fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, vilazodone, vortioxetine, or escitalopram) for the duration of the follow-up period, ideally at the same dose.
Primary Endpoint:	The primary endpoint is the change in MADRS total score from baseline (day -1) to 3 weeks post COMP360 administration.
Secondary Endpoints:	The secondary endpoints are: • The proportion of participants with a response (defined as a ≥ 50% improvement in MADRS total score from baseline) at week 3 post COMP360 administration • The proportion of participants with remission (defined as a MADRS total score ≤ 10) at week 3 post COMP360 administration • Changes from baseline CGI-S at week 3 post COMP360 administration • Incidence of AEs • Change from baseline to day 2 in ECGs, and incidence of clinically important changes • Change from baseline to day 2 and to week 3 in clinical laboratory tests, and incidence of clinically important changes • Change from baseline to day 2 in vital signs • Incidence of changes from baseline in the C-SSRS at each post-baseline visit

Exploratory Endpoints:	The exploratory endpoints are:
	• Change from baseline to week 3 in total scores of:
	  • Participant EQ-5D-3L
	  • Caregiver EQ-5D-3L (this assessment is not mandatory)
	  • GAD-7
	  • QIDS-SR-16
	  • CGI-I
	  • Change from baseline to day 2 in Positive and Negative Affect Schedule (PANAS)
	  • Summary of Five Dimensional Altered States of Consciousness questionnaire (5D-ASC) on the day of the COMP360 administration session (day 1)

Estimand Framework	Due to the lack of a control group and the descriptive nature of the study, no estimand will be defined.
Sample Size Determination	No formal sample size calculations were performed for this study. Approximately 20 participants are expected to be enrolled in the study.
Analysis Sets	The Safety Analysis Set: All participants who receive study drug. The Full Analysis Set (FAS): All participants who receive study drug and have at least 1 post-dose efficacy assessment.

	The Per Protocol (PP) Population: All participants in the FAS who do not have a protocol deviation that is thought to significantly affect the integrity of the participant's efficacy data.
Hypothesis	Since there is only one treatment group, there will be no formal statistical testing of any hypothesis.
Primary Endpoint Analyses	The primary efficacy endpoint (change from baseline in MADRS total score at week 3) will be summarised using descriptive statistics for continuous measures as well as 95% confidence intervals (CIs).
Secondary Endpoint Analyses	The proportion of participants who are responders/remitters at week 3 will be summarised using counts and percentages and 95% Wald-type CIs based on the Normal distribution. CGI-S values and their changes from baseline will be summarised using descriptive statistics for continuous variables alongside 95% CIs for all timepoints up to week 3. In addition, categorical summaries will be provided for each CGI-S response option at each relevant timepoint, including 95% Wald-type CIs.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
bpm	beats per minute
CAT	Clinical Assessment Technologies
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
COMPASS	COMPASS Pathfinder Limited
CR	Code Review
CS	Clinically Significant
dp	decimal place
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
eCRF	electronic Case Report Form
eCTD	Electronic Common Technical Document
EDC	Electronic Data Capture
EOS	End of Study
ET	Early Termination
FAS	Full Analysis Set
GCP	Good Clinical Practice
HR	Heart Rate
HRQoL	Health-Related Quality of Life
ICF	Informed Consent Form
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IP	investigational product
IProg	Independent Programming
kg	kilogram
L	litres
MAP	Mean Arterial Pressure
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Regulatory Activities
min	minute(s)
mg	milligram
mITT	Modified Intent-to-Treat
MM	Medical Monitor

Abbreviation	Definition
mmHg	millimetres of mercury
MR	Manual Review
msec	millisecond(s)
NCS	Not Clinically Significant
PD	Protocol Deviation
PP	Per Protocol
PT	Preferred Term
QC	Quality Check
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SSRI	Selective Serotonin Reuptake Inhibitor
TRD	Treatment-Resistant Depression
UK	United Kingdom
WHO	World Health Organisation
Worldwide	Worldwide Clinical Trials, Inc.

LIST OF PARAMETERS

Parameter	Definition
Efficacy	
5D-ASC	5-Dimensional - Altered States of Consciousness questionnaire
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity
EQ-5D-3L	EuroQoL-5 Dimensions-3 Levels
EQ-VAS	EuroQoL Visual Analogue Scale
GAD-7	Generalised Anxiety Disorder Scale – 7 item
HAM-D-17	Hamilton Depression Rating Scale – 17 item
MADRS	Montgomery-Asberg Depression Rating Scale
MGH-ATRQ	Massachusetts General Hospital Antidepressant Treatment History Questionnaire
MINI 7.0.2	Mini International Neuropsychiatric Interview, Version 7.0.2
MSI-BPD	McLean Screening Instrument for Borderline Personality Disorder
PANAS	Positive and Negative Affect Schedule
QIDS-SR-16	Quick Inventory of Depressive Symptomatology – Self-Rated 16 item
VAS	Visual Analogue Scale
Study Disposition	
BMI	Body Mass Index
Safety	
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction

Parameter	**Definition**
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event

1 INTRODUCTION

This statistical analysis plan (SAP) is based on the final protocol (V2.2) dated 17 December 2020. The plan covers statistical analysis, tables, figures and listings of the study data to investigate the safety and efficacy of COMP360 as an adjunctive therapy in participants with treatment-resistant depression. COMP360 is COMPASS Pathfinder Limited's ('COMPASS') proprietary pharmaceutical-grade synthetic psilocybin formulation that has been optimised for stability and purity.

The SAP is prepared by Worldwide Clinical Trials, Inc (Worldwide). The statistical analyses and production of the outputs described in the SAP, as well as the quality check (QC), will be conducted by 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

The main purpose of this study is to investigate the efficacy of 25 mg COMP360 adjunct to serotonergic antidepressants in TRD participants via the following objectives.

2.1 Primary

The primary objective of this study is to explore the efficacy of 25 mg COMP360 as an adjunct therapy to antidepressants in improving depressive symptoms.

2.2 Secondary

The secondary objective is to evaluate the safety and tolerability of COMP360 in participants with TRD based on adverse events (AEs), changes in vital signs, electrocardiograms (ECGs), clinical laboratory tests and suicidal ideation/behaviour (measured using the Columbia- Suicide Severity Rating Scale [C-SSRS]) score.

2.3 Exploratory

The exploratory objectives are to evaluate the effects of COMP360 on quality of life, wellbeing and anxiety.

3 STUDY ENDPOINTS

3.1 Primary

The primary endpoint is the change in Montgomery-Asberg Depression Rating Scale (MADRS) total score from baseline (day -1) to 3 weeks post COMP360 administration.

3.2 Secondary

The secondary endpoints are:

- The proportion of participants with a response (defined as a ≥ 50% improvement in MADRS total score from baseline) at week 3 post COMP360 administration
- The proportion of participants with remission (defined as a MADRS total score ≤ 10) at week 3 post COMP360 administration
- Changes from baseline Clinical Global Impression – Severity scale (CGI-S) at week 3 post COMP360 administration
- Incidence of AEs
- Change from baseline to day 2 in ECGs, and incidence of clinically important changes
- Change from baseline to day 2 and to week 3 in clinical laboratory tests, and incidence of clinically important changes
- Change from baseline to day 2 in vital signs
- Incidence of changes from baseline in the C-SSRS at each post-baseline visit

3.3 Exploratory

The exploratory endpoints are:

- Change from baseline to week 3 in total scores of:
  - Participant EuroQoL-5 dimension-3 level (EQ-5D-3L)
  - Caregiver EQ-5D-3L (this assessment is not mandatory)
  - Generalised Anxiety Disorder 7-item Scale (GAD-7)
  - QIDS-SR-16
  - Clinical Global Impression – Improvement scale (CGI-I)
  - Change from baseline to day 2 in Positive and Negative Affect Schedule (PANAS)
  - Summary of 5-Dimensional Altered States of Consciousness questionnaire (5D-ASC) on the day of the COMP360 administration session (day 1)

4 ESTIMAND FRAMEWORK

Due to the lack of a control group and the descriptive nature of the study, no estimand will be defined.

5 STUDY DESIGN

5.1 Study Design

This is a Phase IIb, international multicentre, fixed-dose, open-label study. The study population will include adult men and women, 18 years of age or older, with TRD. Participants with TRD are defined as those who meet the Diagnostic and Statistical Manual of Mental Disorders (5th Edition; DSM-5) diagnostic criteria for single or recurrent episode of major depressive disorder (MDD) without psychotic features, who have failed to respond to an adequate dose and duration of 2, 3 or 4 pharmacological treatments for the current episode. The duration of the current episode must be at least 3 months but not more than 2 years.

Participants will be outpatients and will be recruited primarily through referrals from general practitioners and specialised psychiatric services.

After signing the informed consent form (ICF), participants will be assessed for their eligibility with the Mini International Neuropsychiatric Interview, Version 7.0.2 (MINI 7.0.2), the Hamilton Depression Rating Scale (17-item; HAM-D-17), the Massachusetts General Hospital-Antidepressant Treatment History Response Questionnaire (MGH-ATRQ), the C-SSRS, and McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD). At the initial Screening visit (V1), the participant will also be evaluated with the Quick Inventory of Depressive Symptomatology – Self Rated - 16 item (QIDS-SR-16). Additionally, a medical history, an ECG, blood tests, and vital signs will be obtained.

Once a participant completes all Screening (V1) assessments and all screening data is entered into the Electronic Data Capture (EDC), the Medical Monitor (MM) and Clinical Assessment Technologies Team (CAT) will review data entered and issue approval, if the participant is eligible.

The participant will meet with a therapist for 3 visits during screening. These are safety sessions and will cover what to expect during the COMP360 administration session. The therapist and the participant will review psychoeducational materials provided at the time of enrolment.

All participants will be evaluated for safety at the clinic weekly for 3 weeks prior to COMP360 administration. Any safety assessment visits during the screening period will be called V1a, V1b, V1c etc. During these visits, the C-SSRS and any changes in medications since the previous visit will be obtained in addition to other assessments at the study clinician's discretion.

At baseline [V2, day -1], the participants will undergo a baseline assessment that will consist of the HAM-D-17, MADRS, CGI-S and CGI-I, QIDS-SR-16, C-SSRS, GAD-7, EQ-5D-3L (administered to both participant and caregiver [the latter is not mandatory]),

vital signs, urinalysis, urine drug screen, and urine pregnancy test (only for women of childbearing potential). After baseline data is entered into EDC, the CAT team will complete a final review to ensure the participant's continued eligibility.

Participants cannot be progressed to V3 until this approval is received.

The COMP360 administration session (V3, day 1) will last approximately 6 h and will be supported by a trained therapist. The study drug will be administered simultaneously to up to six participants. Blood pressure will be monitored continuously during the session. The COMP360 administration session may be video recorded for training and adherence monitoring. A full description of the activities of the COMP360 administration session is found in the Therapist Manual. After the acute effects of COMP360 pass, participants will be evaluated for safety and accompanied home. On day 2 (V4), the day following COMP360 administration, participants will be seen in person for a safety check, assessment of suicidality and clinical and self-report assessments, and to discuss their experience during the COMP360 administration session. All sessions between the therapist and the participant may be audio recorded for adherence monitoring and quality assurance.

Audio and video recording of the sessions are subject to participant consent. Participants who do not consent to either or all recordings will not be excluded from the study.

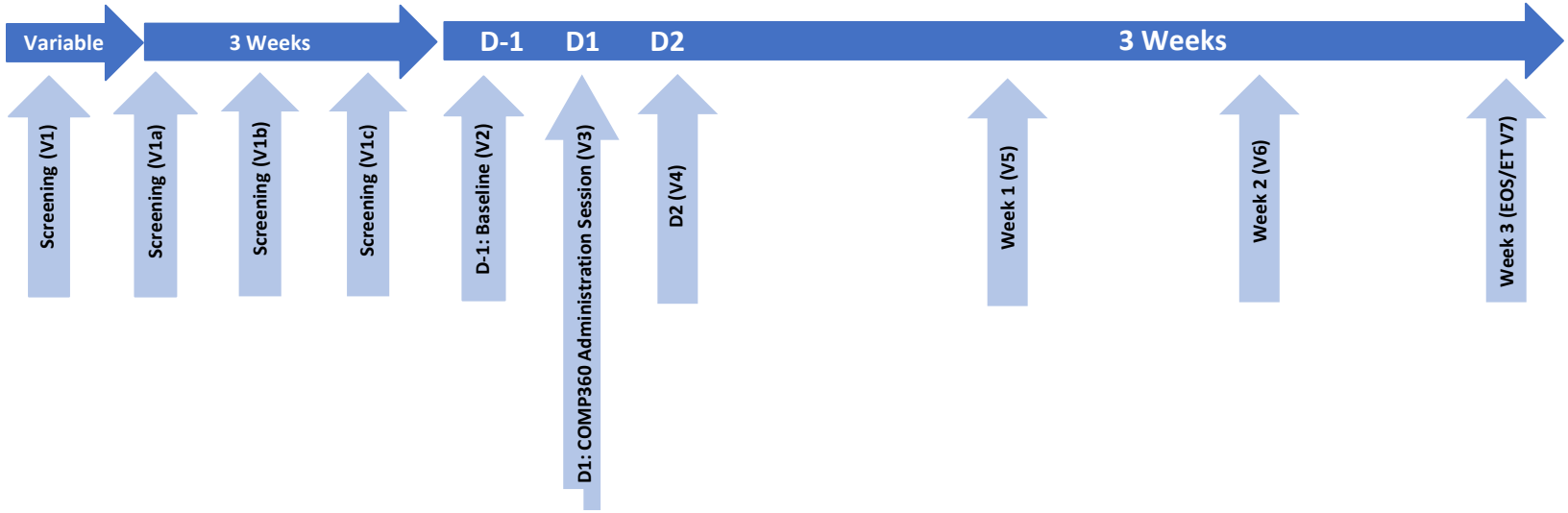
Twenty participants will receive one dose of 25 mg COMP360.

Participants will be seen at the clinic for Screening (plus 3 safety visits), baseline (day -1), day 1 (dosing), day 2, week 1, week 2 and week 3. AEs, serious adverse events (SAEs) and concomitant medication and therapies will be recorded at all clinic visits. The MADRS will be done by telephone.

Clinicians are advised to continue the prescription of the participant's baseline selective serotonin reuptake inhibitor (SSRI) (fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, vilazodone, vortioxetine, or escitalopram) for the duration of the follow-up period, ideally at the same dose.

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

5.2 Study Schematic



D=Day V=Visit EOS=End of Study ET=Early Termination

5.3 Schedule of Assessments

		3 weeks prior to Baseline			Time Post COMP360 Administration Session			
	Screening	Screening Period [1]	Baseline (Day -1)	COMP360 Administration Session (Day 1)	Day 2	Week 1 Day 8	Week 2 Day 15	Week 3 Day 22 (EOS/ET)
Visit	**1**	**1a, 1b, 1c**	**2**	**3**	**4**	**5**	**6**	**7**
Allowable Window	**-**	**Weekly**		**+ ≤ 7 days**	**None**	**±1 day**	**±1 day**	**± 1 day**
Clinical Assessments and Procedures								
Informed consent	✓							
Medical history	✓		✓					
Inclusion/Exclusion Criteria	✓		✓					
MINI 7.0.2	✓							
HAM-D-17	✓		✓					
MGH-ATRQ	✓							
C-SSRS[2]	✓	✓	✓	✓	✓	✓	✓	✓
Vital signs	✓		✓	✓	✓			
Physical examination, including weight and height	✓							
12-Lead ECG	✓				✓			
Clinical laboratory tests[3]	✓				✓			✓
Urinalysis[3]	✓		✓		✓			
Urine drug screen[3]	✓		✓					
Urine pregnancy test[4]	✓		✓					

		3 weeks prior to Baseline			Time Post COMP360 Administration Session			
	Screening	**Screening Period** [1]	**Baseline (Day -1)**	**COMP360 Administration Session (Day 1)**	**Day 2**	**Week 1 Day 8**	**Week 2 Day 15**	**Week 3 Day 22 (EOS/ET)**
Visit	**1**	**1a, 1b, 1c**	**2**	**3**	**4**	**5**	**6**	**7**
Allowable Window	**-**	**Weekly**		**+ ≤ 7 days**	**None**	**±1 day**	**±1 day**	**± 1 day**
Clinical Assessments and Procedures								
Documentation of contraceptive method to be used[5]	✓							
CGI-I					✓	✓	✓	✓
CGI-S			✓		✓	✓	✓	✓
COMP360 dose				✓				
Prior/Concomitant Medications	✓	✓	✓	✓	✓	✓	✓	✓
AE/SAEs	✓	✓	✓	✓	✓	✓	✓	✓
Participant Completed Assessments								
MSI-BPD	✓							
QIDS-SR-16	✓		✓	✓	✓	✓	✓	✓
EQ-5D-3L			✓			✓	✓	✓
GAD-7			✓		✓	✓	✓	✓
PANAS			✓		✓			
5D-ASC				✓[6]				
Remote-rater Assessment								

		3 weeks prior to Baseline			Time Post COMP360 Administration Session			
	Screening	**Screening Period** [1]	**Baseline (Day -1)**	**COMP360 Administration Session (Day 1)**	**Day 2**	**Week 1 Day 8**	**Week 2 Day 15**	**Week 3 Day 22 (EOS/ET)**
Visit	**1**	**1a, 1b, 1c**	**2**	**3**	**4**	**5**	**6**	**7**
Allowable Window	**-**	**Weekly**		**+ ≤ 7 days**	**None**	**±1 day**	**±1 day**	**± 1 day**
MADRS[7]			✓		✓	✓	✓	✓

Abbreviations: 5D-ASC = 5-Dimensional Altered States of Consciousness; AE = adverse event; CGI-I = Clinical Global Impression – Improvement; CGI-S = Clinical Global Impression – Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = End of Study; EQ-5D-3L = EuroQoL-5 dimension-3 level; ET = early termination; GAD-7 = Generalised Anxiety Disorder Scale - 7 item; HAM-D-17 = Hamilton Depression Rating Scale - 17 item; MINI 7.0.2 = Mini International Neuropsychiatric Interview, Version 7.0.2; MADRS = Montgomery-Asberg Depression Scale; MGH-ATRQ, Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; MSI-BPD = McLean Screening Instrument for Borderline Personality Disorder; PANAS = Positive and Negative Affect Schedule; QIDS-SR-16 = Quick Inventory of Depressive Symptomatology – Self Rated - 16 item; SAE = serious adverse event.

1 Screening (V1a) will be performed 3 weeks prior to the Baseline visit (V2, Day -1).
2 The "Last 12 months" version will be administered at Screening and the "Since Last Visit" version will be administered at all other visits.
3 See Section 7.2.4 of the study protocol for complete list of required tests to be performed.
4 For women of child-bearing potential only.
5 For females of childbearing potential and all males; site is to document method of contraception agreed to be used by each participant.
6 To be administered immediately after the COMP360 administration session.
7 On site clinic visits; visits allowed remotely will have the MADRS performed by telephone.

5.4 Hypotheses and Treatment Comparisons

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.

5.5 Multiplicity

Since there is no formal statistical testing and no p-values reported, no multiplicity adjustments are needed for this study.

5.6 Sample Size Considerations

No formal sample size calculations were performed for this study. Approximately 20 participants are expected to be enrolled in the study.

5.7 Randomisation

Not applicable.

6 PLANNED ANALYSES

6.1 Final Analysis

The SAP will be finalised before database lock. Final data analysis will be conducted after database lock. The tables, figures and listings planned in this document will be included in the final analysis.

6.2 Interim Analysis

No interim analyses are planned.

7 ANALYSIS SETS

Analysis Set	**Definition**
Safety Analysis Set	All participants who receive study drug.
Full Analysis Set (FAS)	All participants who receive study drug and have at least 1 post-baseline efficacy assessment.
Per Protocol (PP) Analysis Set	All participants in the FAS who do not have a protocol deviation that is thought to significantly affect the integrity of the participant's efficacy data.

The Safety Analysis Set will be used for all study participant-related and safety-related evaluations. Outputs based on this analysis set will use the actual treatment received by the study participant. The FAS will be used for all efficacy-related evaluations, with the PP Analysis Set being used for supportive efficacy-related evaluations. Outputs based on these analysis sets will use the actual treatment received by the study participant.

Protocol deviations (PDs) thought to significantly affect the integrity of the particpant's efficacy data will be identified and documented during a data review prior to database lock and confirmed at the time of database lock.

8 GENERAL CONSIDERATIONS

All TFLs will be created using SAS® version 9.4 or later[1].

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

Participant disposition, baseline/demographics and safety summaries will be presented jointly for all treatment arms whereas efficacy analysis and summaries will be split by study.

Unless otherwise specified, "baseline" is defined as the last observed value of the parameter of interest prior to dosing for each period. Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing. For numerical variables, change from baseline will be calculated as the difference between the value of interest and the corresponding baseline value.

Continuous data will be summarised descriptively using N (number of participants in the analysis set), 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 analysis set, unless otherwise specified (on some occasions, percentages may be calculated using the total number of participants with available data at a particular visit or timepoint as the denominator).

Unscheduled visits and retests (same visit number assigned) will not be displayed in by-visit summary tables and figures 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 and AEs will be coded from the actual term using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or later.

All prior and concomitant medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHO-DDE) (March 2020 Version or later).

9 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.

9.1 General

9.1.1 Change from Baseline

Definition	Derivation
Change from baseline	$= post\text{-}dose\ visit\ value - baseline\ value$
Change from baseline (%)	$=\left[\frac{post\text{-}dose\ visit\ value - baseline\ value}{baseline\ value}\right] \times 100$

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

9.1.2 Missing and Partial Dates

All rules explained below 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 or, in case of partial eCRF entries, completed as per the rules stated in Sections 9.2.5 and 9.4.2.

9.1.3 Treatment Exposure and Compliance

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

9.1.4 Inexact Values

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

9.2 Study Participants

9.2.1 Protocol Deviations

A PD is any change, divergence or departure from the protocol or investigational plan. PDs will be categorised as follows (detailed PD definitions can be found in the protocol deviation handling plan):

1. 'Important' from a reporting (TFL/CSR) perspective

2. PDs that would exclude the participant from the PP analysis set

9.2.2 Age Categories

The following age categories will be derived

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

9.2.3 Body Mass Index (BMI)

The BMI will be recalculated at screening using the formula

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

9.2.4 Length of Current Depressive Episode

The length in months of the current depressive episode will be calculated as follows:

$$12 \times \left[\frac{screening\ date - start\ date\ of\ the\ depressive\ episode}{365.25}\right]$$

The length of the current depressive episode will also be categorised as follows:

- < 1 year
- ≥ 1 year and < 2 years
- ≥ 2 years

9.2.5 Missing Major Depressive Disorder (MDD) Episode Start Dates

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

This imputation rule will only be implemented to derive the length of the current depressive episode (see Section 9.2.4), and the imputed date will not be used elsewhere (ie partial dates will be presented in the listings, in recorded).

9.2.6 Prior and Concomitant Medications

Prior medication refers to any medication that was stopped prior to the start of taking study drug/taken during the 30-day period before signing the ICF. Concomitant medication refers

to the use of any ongoing medication at the time of the start of the study/all medications taken after the ICF has been signed.

9.3 Efficacy Assessments

9.3.1 Montgomery-Asberg Depression Rating Scale Score (MADRS)

The MADRS is a clinician rated scale measuring depression severity, consisting of the following 10 items:

1. reported sadness
2. apparent sadness
3. inner tension
4. reduced sleep
5. reduced appetite
6. concentration difficulties
7. lassitude
8. inability to feel
9. pessimistic thoughts
10. suicidal thoughts.

Each item has a score ranging from 0 (normal) to 6 (severe), with higher scores denoting greater severity.

MADRS data will be obtained at baseline, day 2 (day 1 according to the study protocol, see Section 16.2 for mapping), and weeks 1, 2 and 3.

9.3.1.1 Total Score

The MADRS total score is derived by summing up the scores from the 10 items (ranging from 0 – 60).

9.3.1.2 Responder Status

A participant is defined as a MADRS responder at a post-baseline visit if they meet the following:

$$-50\% \leq change\ from\ baseline\ (\%)$$

The derivation of MADRS change from baseline (%) is defined is Section 9.1.1.

9.3.1.3 Remitter Status

A MADRS remitter is defined as a participant whose MADRS total score value is ≤ 10 at a post-baseline visit.

9.3.1.4 MADRS Partial Responder Status

A participant is defined as a MADRS partial responder at a post-baseline visit if they meet the following:

$$-25\% \leq change\ from\ baseline\ (\%) < -50\%$$

The derivation of change from baseline (%) is defined in Section 9.1.1.

9.3.2 Quick Inventory of Depressive Symptomatology (QIDS-SR-16)

The 16-item self-rated scale is designed to assess the severity of depressive symptoms. The following 9 symptom domains are used to obtain the total score:

1. The highest score on any 1 of the 4 sleep items (1-4)
2. The score on item 5
3. The highest score on any 1 of the appetite/weight items (6-9)
4. The score on item 10
5. The score on item 11
6. The score on item 12
7. The score on item 13
8. The score on item 14
9. The highest score on either of the 2 psychomotor items (15 and 16)

The total score is obtained by summing the 9 symptom scores. The total score ranges from 0 to 27 with 0 representing no depression and 27 representing severe depression.

QIDS-SR-16 will be obtained at screening, baseline and all post-baseline timepoints up to week 3.

9.3.3 European Quality of Life 5-dimension 3-level Scale (EQ-5D-3L)

The EQ-5D-3L is a multi-attribute instrument used in assessing the health-related quality of life (HRQoL) and includes two parts:

- The EQ-5D descriptive system contains five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels: 1 = no problems, 2 = some problems, 3 = severe problems. The responses to the five EQ-5D dimensions will be converted into a 5-digit number (eg 12212) called a 'health state'. The health state reflects how good or bad the health state is according to the preferences of the general population of a country/region.
- The EQ visual analogue scale (VAS) records the participant's self-rated health on a vertical VAS, where participants are asked to mark their self-rated health on a scale from 0 ('worst imaginable health state') to 100 ('best imaginable health state').

In order to convert the health state to a continuous 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 33333) will be retrieved from the EuroQoL website[2]. As suggested by EuroQoL, one collection of value sets will be used for all countries in the study, namely those for the United Kingdom. The derivation is described in a paper from Dolan et al.[3] and briefly described below.

For each dimension of the EQ-5D-3L, two variables are defined: the first one takes values of 1 (if the dimension has a value of 2), 2 (if the dimension has a value of 3) and 0 otherwise, whereas the second takes a value of 1 if the dimension has a value of 3 and 0 otherwise. In addition, an 'intercept' is defined, which can either be 0 (if all dimensions have a value of 1) or 1 otherwise, and a so-called interaction term, which can either be 0 (if no dimension has a value of 3) or 1 otherwise (at least one dimension has a value of 3). For each of these 12 variables a regression coefficient is used to derive the 'weight' associated with a given 5-digit health state. The model coefficients (taken from Table 1 of Dolan paper[3]) are reported in the table below:

Model term	**Regression Coefficient**
Intercept (any dimension > 1) – D1	0.081
Mobility (Level 2) - MO	0.069
Self-care (Level 2) - SC	0.104
Usual Activities (Level 2) - UA	0.036
Pain/Discomfort (Level 2) - PD	0.123
Anxiety/Depression (Level 2) - AD	0.071
Mobility (Level 3) – MO2	0.176
Self-care (Level 3) – SC2	0.006
Usual Activities (Level 3) – UA2	0.022
Pain/Discomfort (Level 3) – PD2	0.140
Anxiety/Depression (Level 3) – AD2	0.094
Interaction (any dimension = 3) – N3	0.269

The continuous values are then derived using the following formula:

$$EQ\text{-}5D\text{-}3L_i = 1 - D1*\beta_0 - MO*\beta_1 - SC*\beta_2 - UA*\beta_3 - PD*\beta_4 - AD*\beta_5 - MO2*\beta_6 - SC2*\beta_7 - UA2*\beta_8 - PD2*\beta_9 - AD2*\beta_{10} - N3*\beta_{11}$$

Where β_j are the coefficients regression from the above table. As an example, a health state of 12212 would have an associated continuous value derived as follows:

- The following variables have a value of 0: MO, PD, MO2, SC2, UA2, PD2, AD2, N3. Thus, the respective coefficients are irrelevant in the above formula
- The prediction formula simplifies as follows:

$$EQ\text{-}5D\text{-}3L_i = 1 - 0.081 - 1*0.104 - 1*0.036 - 1*0.071 = 0.708$$

If a component of the EQ-5D-3L was not collected, the 5-digits health state will be recorded with '-' to identify these gaps (e.g. 132-1, implying that the pain/discomfort item was not marked) and the continuous score will not be derived and set to missing for analysis purposes.

EQ-5D-3L data will be obtained at baseline, weeks 1, 2 and 3.

9.3.4 Generalised Anxiety Disorder Scale – 7 Item (GAD-7)

The Generalised Anxiety Disorder (GAD)-7 is a 7-item self-report anxiety questionnaire designed to assess the participant's health status during the previous 2 weeks. Scores of 0, 1, 2 or 3 are given for experiencing symptoms 'not at all', for 'several days', for 'more than half the days' and for 'nearly every day', respectively. The scores are then totalled and presented from 0 to 21.

GAD-7 data will be obtained at baseline, day 2, weeks 1, 2 and 3.

9.3.5 Hamilton Depression Rating Scale – 17 Item (HAM-D-17)

The Hamilton Depression Rating Scale (HAM-D) has been used in determining a participant's level of depression before, during, and after treatment. Nine items are scored on a 5-point scale ranging from 0 to 4, 7 items are scored on a 3-point scale ranging from 0 to 2, and the remaining item is scored on a 4-point scale ranging from 0 to 3. The total score is obtained as the sum of the first 17 individual items scores from this assessment (values ranging from 0 to 53) and will be used as eligibility criteria prior to treatment (minimal total symptom score $\geq$ 18).

HAM-D-17 total scores at baseline will be categorised as moderate (18-23) or severe ($\geq$24) depression.

HAM-D-17 data will be obtained at screening and baseline only.

9.3.6 The Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ)

The MGH-ATRQ is a self-rated scale used to determine treatment-resistance in MDD. The MGH-ATRQ defines 6 weeks on an adequate dose of antidepressant medication as an

adequate duration of treatment. It also provides specific operational criteria for adequate dosage for each of the most commonly used antidepressants. The ATRQ examines the efficacy using the following categorised ratings: <25% improved; 25%-49% improved; 50%-75% improved and >75% improved. A rating of 100% is completely improved and a rating of 0% is not improved at all.

MGH-ATRQ data will be obtained at screening only.

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

The MSI-BPD is a commonly used measure to assess for BPD. The scale consists of 10 items based on the DSM-5 BPD criteria; the first 8 items represent the first eight criteria in the DSM-5 for BPD diagnosis, while the last two questions assess the paranoia and dissociation criteria for BPD. Scores for the MSI-BPD range from 0 to 10, with each item rated as "1" if present and "0" if absent. A score of 7 or higher (obtained as the sum of the individual items scores) indicates a likelihood for the participant to meet criteria for BPD.

The MSI-BPD will be obtained at screening only.

9.3.8 5-Dimensional Altered States of Consciousness Questionnaire (5D-ASC)

The 5D-ASC measures the acute drug effects using 5 primary dimensions and respective subdimensions to assess alterations in mood, perception, and experience of self in relation to environment and thought disorder. The 5 dimensions include oceanic boundlessness, anxious ego dissociation, visual restructuralization, auditory alterations, and reduction of vigilance. In addition to these 5 dimensions, the 5D-ASC can be split into 11 subscales[4]: 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 were 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 (OAV and 5D-ASC) 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 [4-5]

The mapping of individual items to the 5 dimensions and to the 11 subscales is displayed in the table below (the former accounts for 93 out of 94 individual items [item 66 is excluded], whereas the latter only accounts for 42 items, as described in the paper from Studerus et al.[4]). Subscales have been ordered and displayed in accordance with the relevant dimension they are included in (apart for the last 2 dimensions for which no subscale is defined)[6].

Dimension	Items	Subscale	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	Experience of Unity	18, 34, 41, 42, 52
		Spiritual Experience	9, 81, 94
		Blissful State	12, 86, 91
		Insightfulness	50, 69, 77
Anxious Ego Dissociation	6, 8, 21, 27, 32, 38, 43, 44, 46, 47, 53, 56, 60, 64, 67, 78, 79, 80, 85, 88, 89	Disembodiment	26, 62, 63
		Impaired Control and Cognition	8, 27, 38, 47, 64, 67, 78
		Anxiety	32, 43, 44, 46, 56, 89
Visual Restructuralization	7, 14, 20, 22, 23, 28, 31, 33, 39, 54, 58, 70, 72, 75, 77, 82, 83, 90	Complex Imagery	39, 72, 82
		Elementary Imagery	14, 22, 33
		Audio-Visual Synaesthesia	20, 23, 75
		Changed Meaning of Percepts	28, 31, 54
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 subscale and dimension is obtained by averaging the score for each individual item within that subscale/dimension.

5D-ASC data will be obtained at day 1 immediately after the COMP360 administration session.

9.3.9 The Positive and Negative Affect Schedule (PANAS)

The PANAS measures the acute emotional drug effects and comprises 2 mood scales that measure positive and negative affect. Participants respond to 20 items using a 5-point scale that ranges from “very slightly or not at all (1)” to “extremely (5)”. The Positive Affect Score is obtained by summing up scores for items 1, 3, 5, 9, 10, 12, 14, 16, 17, and 19, whereas the Negative Affect Score is obtained by summing up the scores for items 2, 4, 6, 7, 8, 11, 13, 15, 18, and 20. A total higher score on the positive affect questions (ranging from 10 to 50) indicates higher levels of a Positive Affect while a lower score on the negative affect questions indicates lower levels of a Negative Affect.

PANAS data will be obtained at baseline, and day 2.

9.3.10 Clinical Global Impression – Severity (CGI-S) Scale

The CGI-S is a 7-point scale that measures the severity of symptoms in patients with mental disorders. It requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same

diagnosis. Ratings range from "normal, not at all ill" (1) to "among the most extremely ill patients" (7).

Participants scoring either 1 or 2 will be classified as responders, whereas all other options will classify a participant as 'non-responder'. If the CGI-S is missing or equal to 0 (= not assessed), then the responder status will also be set to missing.

The CGI-S will be obtained at baseline, day 2, and weeks 1, 2 and 3.

9.3.11 Clinical Global Impression – Improvement (CGI-I) Scale

The CGI-I is a 7-point scale that requires the clinician to rate how much the patient's symptoms have improved relative to a baseline state. Ratings range from "very much improved" (1) to "very much worse" (7).

Participants scoring either 1 or 2 will be classified as responders, whereas all other options will classify a participant as 'non-responder'. If the CGI-I is missing or equal to 0 (= not assessed), then the responder status will also be set to missing.

The CGI-I will be obtained at day 2, and weeks 1, 2 and 3.

9.4 Safety

9.4.1 Adverse Events

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

A treatment-related TEAE is defined as an AE reported to be possibly related or related to the study drug. If an AE has missing relationship, it will be assumed to be related to the study drug for analysis purposes. For reporting purposes, a treatment-related TEAE will be referred to as an adverse drug reaction (ADR) and a serious ADR will be referred to as a serious adverse reaction (SAR).

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

AEs will be categorised by time of onset (day 1, day 2, day 3-8, > day 8) and duration (1 day, > 1 and ≤ 2 days, > 2 and ≤ 7 days, >7 days or ongoing).

Adverse events of special interest (AESI) will be identified as follows:

AESI term	**MedDRA Preferred Terms**
Euphoric mood	Euphoric mood
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
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
Cognitive disorder	Cognitive disorder
Disturbance in attention	Disturbance in attention
Mood altered	Mood altered; Depressed mood; Affect lability; Fluctuating mood symptoms
Psychomotor skills impaired	Psychomotor skills impaired
Inappropriate affect	Inappropriate affect
Overdose	Overdose
Intentional product misuse	Intentional product misuse

In addition AESIs will include those AEs identified as AESIs by the investigator in the eCRF. In the event that the associated preferred term does not feature in the list above then they will be assigned an AESI term of "Other".

9.4.2 Missing / Partial Start / Stop Dates of AEs and Concomitant Medications

Missing and partial start and stop date 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 medication, the stop date will be imputed as the date of the participant's last clinic visit in the study.

- If only the 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 last clinic visit date, otherwise if the years differ it will be imputed as "31-Dec".

- If the month and year are known, the stop date will be imputed as the last day of that month unless the stop date corresponds to 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 instead.

Missing start date will be imputed as follows:

- If the stop date occurs on or after the dose of study drug or the event / concomitant medication is ongoing, the start date will be imputed as the date of the dose of study drug.

- If the stop date occurs before the start of study drug, the start date of the event / concomitant medication will be imputed as the participant's screening date or the stop date of the event / concomitant medication whichever the earlier.

Partial start date (year present, but month and day missing)

- If the stop date occurs on or after the dose of study drug or the event / concomitant medication 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 study drug. If the year is different from the year of dosing "01-Jan" will be used.

- If the stop date occurs before the dose of study drug, the start date of the event / concomitant medication will be imputed as the "01-Jan" of the same year.

Partial start date (month and year present, but day missing)

- If the stop date occurs on or after the dose of study drug or the event / concomitant medication 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 study drug in which case the date of dose of study drug will be used.

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

If the start time of an AE is missing it will be imputed only in the case where the start date corresponds to the date of the dose of study drug. The time will be imputed as the same time as the dose of study drug. In all other cases the time will not be imputed.

9.4.3 Vital Signs Ranges of Clinical Importance

The following ranges for the vital signs parameters will be considered clinically important:

Vital sign	Lower Limit	Upper Limit
Systolic blood pressure (mmHg)	90 mmHg	160 mmHg
Diastolic blood pressure (mmHg)	50 mmHg	100 mmHg
Pulse rate (bpm)	50 bpm	100 bpm

Vital sign	Lower Limit	Upper Limit
Respiration rate (breath / min)	11 breath/min	20 breath/min
Body temperature (°C)	-	37.5°C

9.4.4 Continuous Vital Signs Collections via Caretaker Device

During the COMP360 administration session vital signs will be continuously monitored via a device positioned on a participant fingertip that allows real-time measurements of blood pressure (systolic, diastolic, and mean arterial) and heart rate (HR).

For the purposes of this study the individual measurements will be summarised around the following specific timepoints: -0.25, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, and 8 hours post-dose. The values to be summarised for the post-dosing timepoints are values that have been measured in the minute from the timepoint itself to the next one, eg for 0.25 hours (=15 minutes) all measurements occurred between 15 and 16 minutes from the dosing will be averaged and used for summary purposes. The pre-dose timepoint -0.25 will be derived using a similar approach by taking measurements occurring between 16 and 15 minutes prior to dosing and averaging them. This measurement will only be displayed in the listings.

In order to define the elapsed hours from dosing for each measurement the difference between the timing of each given measurement and the COMP360 dose will be calculated in seconds and then converted to minutes as follows:

$$Tdiff\ (min) = Tdiff\ (sec)/60$$

Since the timing of each measurement are recorded on the device using the Eastern time zone (UTC-05:00), these will first be converted to match the time zone of each specific site (UTC+0 for site 301 and UTC-08:00 for site 302).

9.4.4.1 Clinically Relevant Categories

The following categories for the continuous vital signs parameters will be considered clinically relevant:

Parameter	Clinically Relevant Categories			
	Low	Normal	High	High CS
Systolic blood pressure (mmHg)	≤ 90	90 < SBP ≤ 160	160 < SBP ≤ 180	> 180
Diastolic blood pressure (mmHg)	≤ 50	50 < DBP ≤ 100	100 < DBP ≤ 110	> 110
Mean arterial pressure (mmHg)		≤ 135	> 135	
Heart rate (bpm)	≤ 50	50 < HR ≤ 100	100 < HR ≤ 160	>160

CS: Clinically Significant.

9.4.5 ECG Categorical Intervals

The ECG categorical intervals of interest are:

- QTcF > 450 msec
- QTcF > 480 msec
- QTcF > 500 msec
- Change from baseline in QTcF interval
  - QTcF interval increases from baseline > 30 and ≤ 60 msec
  - QTcF interval increases from baseline > 60 msec

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

The following outcomes are C-SSRS categories and have binary responses (yes / no). The categories have been re-ordered from the actual scale to facilitate the definition of composite endpoints:

Category 1	Wish to be Dead
Category 2	Non-specific Active Suicidal Thoughts
Category 3	Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Category 4	Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Category 5	Active Suicidal Ideation with Specific Plan and Intent
Category 6	Preparatory Acts or Behaviour
Category 7	Aborted Attempt
Category 8	Interrupted Attempt
Category 9	Actual Attempt (non-fatal)
Category 10	Completed Suicide

Suicidal Ideation since baseline – A "yes" answer at any time during treatment to any one of the 5 suicidal ideation questions (categories 1-5) on the C-SSRS.

Suicidal Behaviour since baseline – A "yes" answer at any time during treatment to any one of the 5 suicidal behaviour questions (categories 6-10) on the C-SSRS.

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

The C-SSRS will be obtained at every clinic visit.

10 STUDY PARTICIPANTS

10.1 Disposition of Participants

The Safety Analysis Set will be used for all disposition of participant-related evaluations, unless otherwise specified.

The number of participants screened, screen failures, and the number and percentage of participants in each analysis set will be summarised by country (including overall category) for all screened participants (*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 (*Table 14.1.1.2*). Reasons for exclusion from the PP Analysis Set will be summarised using the FAS (*Table 14.1.1.3*)

Participant disposition will be listed by discontinuations (*Listing 16.2.1.1*) and completers (*Listing 16.2.1.2*) using the Safety Analysis Set. Participation in each defined analysis set, including exclusion from the PP Analysis Set will be listed (*Listing 16.2.3*). Inclusion criteria not met/exclusion criteria met at screening and at baseline will be listed for all screened participants (*Listing 16.2.4.3 and Listing 16.2.4.4*).

10.2 Protocol Deviations

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

All PDs will be listed using the Safety Analysis Set (*Listing 16.2.2.1*). In addition, a separate listing of COVID-19 related PDs will be presented if required (*Listing 16.2.2.2*).

10.3 Demographic and Baseline Characteristics

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

Demographic and baseline characteristics (age [years; continuous and by age categories (see Section 9.2.2)], gender [male, female], race [White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other], ethnicity [Hispanic or Latino, Not Hispanic or Latino], height [cm], weight [kg], recalculated BMI [kg/m^2] (see Section 9.2.3)) will be summarised (*Table 14.1.2*).

Other baseline characteristics (number of failed treatments in the current depressive episode [2, 3, 4], HAM-D-17 total score, MGH-ATRQ [<25% improved, 25-49% improved, 50-75% improved, >75% improved], MSI-BPD total score, length of current depressive episode (see Section 9.2.4) [months] will be summarised (*Table 14.1.4*).

A listing for all demographic and baseline characteristics, and other baseline characteristics will be presented (*Listing 16.2.4.1 and Listing 16.2.9.1 – Listing 16.2.9.3*).

Other baseline measurements (urine drug screen and urine pregnancy test) will be listed only (*Listing 16.2.8.5 and Listing 16.2.8.6*).

10.4 Medical History

Medical history collected at screening and baseline will be summarised by primary system organ class (SOC) and preferred term (PT) using the Safety Analysis Set (*Table 14.1.3.1*).

All medical history data will be listed using the Safety Analysis Set (*Listing 16.2.4.2*).

10.5 Prior and Concomitant Medications

The Safety Analysis Set will be used for all prior and concomitant medication-related evaluations, unless otherwise specified.

Prior and concomitant medications will be summarised (*Table 14.1.3.2 and Table 14.1.3.3*).

Prior and concomitant medications will be listed (*Listing 16.2.4.5 and Listing 16.2.4.6*).

10.6 Treatment Exposure/Compliance and Duration

COMP360 drug administration will be listed (*Listing 16.2.5.1*).

In addition, a summary table (*Table 14.1.3.4*) and listing (*Listing 16.2.5.2*) will also be created displaying selective serotonin reuptake inhibitor (SSRI) intake after receiving the study drug, by selecting records for which CMCLAS = 'SELECTIVE SEROTONIN REUPTAKE INHIBITORS', including the drug ATC term and dosing (with eventual changes in the dosing, if applicable).

11 EFFICACY

The FAS will be used for all efficacy-related evaluations, unless otherwise specified. In addition, the PP Analysis Set will be used for supportive analyses of the primary efficacy endpoint, however, note that if there are no participants excluded from the PP Analysis Set no outputs for this population will be produced.

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

11.1 Primary Efficacy

The primary endpoint is the change from baseline in MADRS total score at week 3.

MADRS total 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 (*Table 14.2.1.1*) and the PP Analysis Set (*Table 14.2.1.2*). Both actual values and their changes from baseline will also be graphically displayed as line plots for the FAS (*Figure 14.2.1.1.1 and Figure 14.2.1.2.1*, respectively) and the PP Analysis Set (*Figure 14.2.1.1.2 and Figure 14.2.1.2.2*, respectively).

A summary of percentage change from baseline, including 95% CIs, will also be presented (*Table 14.2.1.3, Figure 14.2.1.3*).

All observed MADRS data will also be listed (*Listing 16.2.6.1*).

11.2 Secondary Efficacy

11.2.1 Proportion of MADRS response at week 3

The proportion of MADRS responders will be descriptively summarised alongside 95% asymptotic CIs for all timepoints up to week 3 (*Table 14.2.2.1*) and graphically displayed via line plots including the estimated 95% CIs (*Figure 14.2.2.1*). 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 at each timepoint will be listed (*Listing 16.2.6.1*).

11.2.2 Proportion of MADRS remission at week 3

The proportion of MADRS remitters will be descriptively summarised alongside 95% asymptotic CIs for all timepoints up to week 3 (*Table 14.2.2.2*) and graphically displayed via line plots including the estimated 95% Wald-type CIs (*Figure 14.2.2.2*).

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

11.2.3 Change from baseline to week 3 in CGI-S

CGI-S values and their changes from baseline will be descriptively summarised alongside 95% CIs for all timepoints up to week 3 for the FAS (*Table 14.2.2.3*) and graphically displayed via line plots including the 95% estimated CIs (*Figure 14.2.2.3.1* for means and *Figure 14.2.2.3.2* for mean change from baseline). In addition to continuous summaries, CGI-S values will be summarised with counts and percentages for each response option, including the number of responders (participants answering either 1 or 2) alongside 95% Wald-type CIs (*Table 14.2.2.3*).

CGI-S data will be listed (*Listing 16.2.6.2.1*).

11.3 Exploratory Efficacy

The following exploratory endpoints will be summarised similarly to the primary endpoint (ie. including summary of values and their changes from baseline, where applicable):

- Participant EQ-5D-3L total score change from baseline to weeks 1, 2 and 3 (*Table 14.2.3.1, Listing 16.2.6.3.1*)
- Caregiver EQ-5D-3L total score change from baseline to weeks 1, 2 and 3 (this assessment is not mandatory) (*Listing 16.2.6.3.1*)
- EQ-VAS change from baseline to week 1, 2 and 3 (*Table 14.2.3.2, Listing 16.2.6.3.2*)
- GAD-7 total score change from baseline to day 2 and weeks 1, 2 and 3 (*Table 14.2.3.3, Listing 16.2.6.4*)
- QIDS-SR-16 score change from baseline to day 2 and weeks 1, 2 and 3 (*Table 14.2.3.4, Listing 16.2.6.5*)
- PANAS score change from baseline to day 2 (*Table 14.2.3.6, Listing 16.2.6.6*)
- 5D-ASC at day 1 (*Table 14.2.3.7, Listing 16.2.6.7*)

The CGI-I score at day 2, and weeks 1, 2 and 3 will be summarised with counts and percentages for each response option, including the number of responders (participants that answered either 1 or 2) alongside 95% Wald-type CIs (*Table 14.2.3.5, Listing 16.2.6.2.2*).

12 SAFETY

The Safety Analysis Set will be used for all safety-related evaluations, unless specified.

12.1 Adverse Events (AEs)

An overall summary of AEs, including total number of TEAEs and treatment-emergent serious adverse events (TESAEs), ADRs and SARs, severe TEAEs, AESIs, TEAEs and TESAEs and ADRs 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 decreasing 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 ≥ 5%) (*Table 14.3.1.3*)
- Summary of Non-Serious TEAEs by Worst Severity (mild/moderate/severe) (*Table 14.3.1.4*)
- Summary of TEAEs by Strongest Relationship to Study Drug (related/not related) (*Table 14.3.1.5*)
- Summary of TEAEs by Time of Onset (see Section 9.4.1 for categories) (*Table 14.3.1.6*)
- Summary of TEAEs by Duration (see Section 9.4.1 for categories) (*Table 14.3.1.7*)
- Summary of TEAEs by Time of Onset (see Section 9.4.1 for categories) and Duration (see Section 9.4.1 for categories) (*Table 14.3.1.8*)
- Summary of Duration of TEAEs (*Table 14.3.1.9*)
- Summary of ADRs (*Table 14.3.1.10*)
- Summary of TESAEs (*Table 14.3.1.11*)
- Summary of SARs (*Table 14.3.1.12*)
- Summary of AESIs (*Table 14.3.1.13*)
- Summary of TEAEs Leading to Study Withdrawal (*Table 14.3.1.14*)
- Summary of ADRs Leading to Study Withdrawal (*Table 14.3.1.15*)

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 maximum intensity category (severe > moderate > mild) and/or maximum study drug relationship category (related > not related). If intensity 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: summaries by worst severity or strongest relationship will only report the events whose category equals the maximum category for a given participant. As an example, should a participant have 2 mild and 3 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 2 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.

AEs whose 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 reported term, SOC, PT, date and study day when AE starts/stops, duration (days), relationship, severity, action taken, outcome, seriousness 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*), ADRs (*Listing 16.2.7.3*), AESIs (*Listing 16.2.7.4*) and lead to death (*Listing 16.2.7.5*). A listing of TEAEs associated to COVID-19 (*Listing 16.2.7.6*) will be provided if there are any such events.

12.2 Laboratory Tests

The full list of parameters and their units (where applicable) is reported in the table below

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)

Category	Parameter (Unit)
	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 Occult Blood Protein Specific Gravity Urobilinogen pH

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 day 2 and week 3 (*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. Laboratory abnormalities will also be listed separately (*Listing 16.2.8.4*).

12.3 Vital Signs

The full list of parameters and their units (where applicable) is reported below:

- SBP (mmHg)

- DBP (mmHg)
- Pulse rate (bpm)
- Respiration rate (breaths / min)
- Body temperature (°C)

Descriptive statistics of the observed values and change from baseline will be presented for each parameter by visit (*Table 14.3.5.1*). The number and percentage of participants with values outside clinically important limits, as described in Section 9.4.3 will be summarised by visit (*Table 14.3.5.2*) and listed (*Listing 16.2.8.8*).

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*).

12.4 Continuous Vital Signs

HR, Mean Arterial Pressure (MAP), SBP and DBP as measured during the COMP360 dosing session on day 1 will be descriptively summarised at the following timepoints: 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8 hours post-dose (*Table 14.3.5.3*) using summary statistics for continuous measures. In addition, summaries will be provided displaying the number of participants and occurrences of any of the measured vital signs at the above timepoints falling within any of the categories described in Section 9.4.4.1 (*Table 14.3.5.4*).

Mean and 95% CIs will also be displayed in a profile plot for each parameter (*Figure 14.3.5.1*).

One listing containing all summarised values (*Listing 16.2.8.9*) and one only including individual values outside the categories described in Section 9.4.4.1 (*Listing 16.2.8.10*) will also be created.

12.5 ECGs

The full list of parameters and their units (where applicable) is reported below:

- HR (bpm)
- PR interval (msec)
- QRS interval (msec)
- QT interval (msec)
- QTcF interval (msec)
- QTcB interval (msec)

Descriptive statistics of the observed values and change from baseline will be presented for each parameter by visit (baseline and day 2) (*Table 14.3.6.1*). Shift tables in relation to

the overall interpretation (Normal, Abnormal Not Clinically Significant (NCS), and Abnormal Clinically Significant (CS)) from baseline will be presented (*Table 14.3.6.2*). The number and percentage of participants meeting the intervals as described in Section 9.4.4 will be summarised by visit (*Table 14.3.6.3*) and listed (*Listing 16.2.8.12*).

All ECG data will be listed (*Listing 16.2.8.11*).

12.6 C-SSRS

C-SSRS data will be summarised by visit (*Table 14.3.6.4*) and listed (*Listing 16.2.9.4*).

13 CHANGES FROM THE PROTOCOL-PLANNED ANALYSES

- Section 7 (Analysis Sets): FAS and Safety Analysis Set definitions were changed compared to the protocol to be aligned with the definitions provided in the pivotal COMP 001 study. The FAS has been defined as similar to a modified Intent-to-Treat (mITT), ie treated patients with at least one post-baseline efficacy assessment (the protocol definition was closer to the pure ITT definition, including all treated patients) whereas the Safety Analysis Set now only includes participants that were treated (the protocol definition included all enrolled participants).
- Section 2 (Study objectives) and Section 3 (Endpoints): Several changes were made to objectives and endpoints wording as well as other items in the protocol. These, and their rationale, are all listed in Appendix I 'Changes to COMP 003 Protocol'.

14 DATA NOT PRESENTED

All data available will be reported.

15 REFERENCES

1. SAS Institute Inc., Cary, NC, 27513, USA
2. https://euroqol.org/eq-5d-instruments/eq-5d-3l-about/valuation/
3. Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997; 35(11): 1095-1108.
4. Studerus E, Gamma A, Vollenweider FX. Psychometric evaluation of the altered states of consciousness rating scale (OAV). *PLoS One*. 2010;5: e12412.
5. Russell JA, Carroll JM. On the bipolarity of positive and negative affect. *Psychol Bull.* 1999; 125:3–30.
6. Liechti ME, Dolder PC, Schmid Y. Alterations of consciousness and mystical-type experiences after acute LSD in humans. Psychopharmacology (Berl). 2017; 234(9): 1499–1510.

16 PROGRAMMING AND DATA PRESENTATION CONVENTIONS

16.1 Treatment Labelling

COMP360 25 mg + SSRI

16.2 Visit Labelling

To ensure consistency with Clinical Data Interchange Standards Consortium (CDISC) standards, the day of drug dosing, defined as day 0 in the Protocol, will be mapped to day 1. All subsequent visits will then be consistently re-mapped (and henceforth referred to in this SAP), as follows:

Protocol Visit	**Analysis Visit**	**Output Label**
Screening – Visit 1	Screening – Visit 1	Screening
Screening Period – Visit 1a/1b/1c/…	Screening Period – Visit 1a/1b/1c/…	Visit 1a/1b/1c/…
Baseline (day -1) – Visit 2	Baseline (day -1) – Visit 2	Baseline or Day -1
Day 0 – Visit 3	Day 1 – Visit 3	Day 1[a]
Day 1 – Visit 4	Day 2 – Visit 4	Day 2
Week 1/Day 7 – Visit 5	Week 1/Day 8 – Visit 5	Week 1 or Day 8
Week 2/Day 14 – Visit 6	Week 2/Day 15 – Visit 6	Week 2 or Day 15
Week 3/Day 21 – Visit 7	Week 3/ Day 22 – Visit 7	Week 3 or Day 22

[a] Continuous vital signs are collected just prior to study drug dosing.

16.3 Baseline Definitions

Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the participant receives study drug.

Parameter	**Baseline**
Efficacy	
All	Day -1
Safety	
Clinical Laboratory	Screening
Vital Signs (discrete)	Day -1
ECGs	Screening
C-SSRS	Day -1

16.4 Study Day and Duration Derivation

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

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

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

- stop date of the event – start date of the event + 1

16.5 Decimal Places

Decimal places (dps) 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.

17 TABLES, FIGURES AND LISTINGS

The following table includes details of the tables, figures and listings to be included within each section of the eCTD. The electronic Common Technical Document (eCTD) section is shown in bold. The following validation methods maybe 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 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 – All Screened Participants	**IProg**	
14.1.1.2	Participant Disposition, Completions and Early Terminations with Reasons – Safety Analysis Set	**IProg**	
14.1.1.3	Reasons for Exclusion from the Per-Protocol Analysis Set – Full 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**	
14.1.3.4	Concomitant SSRI Treatment – Safety Analysis Set	**IProg**	14.1.3.3
14.1.4	Other Baseline Assessments – Safety Analysis Set	**IProg**	
14.2	**Efficacy Data**		
14.2.1	**Primary Efficacy Endpoint**		
14.2.1.1	Primary Endpoint – Summary of Montgomery-Asberg Depression Rating Scale (MADRS) Total Score and Change from Baseline – Full Analysis Set	**IProg**	
14.2.1.2	Primary Endpoint – Summary of Montgomery-Asberg Depression Rating Scale (MADRS) Total Score and Change from Baseline – Per-Protocol Analysis Set	**IProg**	14.2.1.1
14.2.1.3	Primary Endpoint – Summary of Percentage Change from Baseline in Montgomery-Asberg Depression Rating Scale (MADRS) Total Score – Full Analysis Set	**IProg**	
14.2.2	**Secondary Efficacy Endpoints**		
14.2.2.1	Secondary Endpoint – Proportion of Montgomery-Asberg Depression Rating Scale (MADRS) Responders Over Time – Full Analysis Set	**IProg**	
14.2.2.2	Secondary Endpoint - Proportion of Montgomery-Asberg Depression Rating Scale (MADRS) Remitters Over Time – Full Analysis Set	**IProg**	14.2.2.1
14.2.2.3	Secondary Endpoint – Summary of CGI-S and Change from Baseline – Full Analysis Set	**IProg**	
14.2.3	**Exploratory Efficacy Endpoints**		
14.2.3.1	Exploratory Endpoint – Summary of Participant EQ-5D-3L Total Score and Change from Baseline – Full Analysis Set	**IProg**	14.2.1.1

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.2.3.2	Exploratory Endpoint – Summary of EuroQoL - Visual Analogue Scale (EQ-VAS) and Change from Baseline - Full Analysis Set	**IProg**	14.2.1.1
14.2.3.3	Exploratory Endpoint – Summary of GAD-7 Total Score and Change from Baseline – Full Analysis Set	**IProg**	14.2.1.1
14.2.3.4	Exploratory Endpoint – Summary of QIDS-SR-16 Total Score Values and Change from Baseline – Full Analysis Set	**IProg**	14.2.1.1
14.2.3.5	Exploratory Endpoint – Summary of CGI-I Values– Full Analysis Set	**IProg**	
14.2.3.6	Exploratory Endpoint – Summary of PANAS Positive and Negative Affect Scores and Change from Baseline – Full Analysis Set	**IProg**	14.2.1.1
14.2.3.7	Exploratory Endpoint – Summary of 5D-ASC Questionnaire Values – 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**	
14.3.1.5	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**	
14.3.1.6	MedDRA Summary of Treatment-Emergent Adverse Events (TEAEs) by Primary System Organ Class, Preferred Term and Time of Onset – Safety Analysis Set	**IProg**	
14.3.1.7	MedDRA Summary of Treatment-Emergent Adverse Events (TEAEs) by Primary System Organ Class, Preferred Term and Duration of Adverse Event – Safety Analysis Set	**IProg**	
14.3.1.8	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**	
14.3.1.9	MedDRA Summary of Duration of Treatment-Emergent Adverse Events (TEAEs) by Primary System Organ Class and Preferred Term – Safety Analysis Set	**IProg**	
14.3.1.10	MedDRA Summary of Adverse Drug Reactions (ADRs) by Primary System Organ Class and Preferred Term – Safety Analysis Set	**IProg**	14.3.1.2

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.1.11	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
14.3.1.12	MedDRA Summary of Serious Adverse Reactions (SARs) by Primary System Organ Class and Preferred Term – Safety Analysis Set	**IProg**	14.3.1.2
14.3.1.13	MedDRA Summary of Treatment-Emergent Adverse Events of Special Interest (AESIs) by AESI Term and Preferred Term – Safety Analysis Set	**IProg**	
14.3.1.14	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
14.3.1.15	MedDRA Summary of Adverse Drug Reactions (ADRs) Leading to Study Withdrawal by Primary System Organ Class and Preferred Term – Safety Analysis Set	**IProg**	14.3.1.2
14.3.2	**Listings of Deaths, Other Serious and Significant Adverse Events**		
14.3.3	**Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events**		
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
14.3.5	**Vital Signs**		
14.3.5.1	Summary Statistics of Observed Values and Change from Baseline to Day 2 in Vital Signs – Safety Analysis Set	**IProg**	
14.3.5.2	Overall Summary of Clinically Important Vital Signs Values – Safety Analysis Set	**IProg**	
14.3.5.3	Summary Statistics of Continuous Vital Signs Monitored During the COMP360 Administration Session – Safety Analysis Set	**IProg**	
14.3.5.4	Summary of Clinically Relevant Categories of Continuous Vital Signs Monitored During the COMP360 Administration Session – 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**	
14.3.6.2	ECG Clinical Interpretation – Shift from Baseline to Day 2 – Safety Analysis Set	**IProg**	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.6.3	Summary of QTcF Intervals Categories – Safety Analysis Set	**IProg**	
14.3.6.4	Summary of C-SSRS by Visit– Safety Analysis Set	**IProg**	

Figure Number	Figure Title	Validation Method	Shell Number (if repeat)
14.2	**Efficacy Data**		
14.2.1	**Primary Efficacy Endpoint**		
14.2.1.1.1	Primary Endpoint – Montgomery-Asberg Depression Rating Scale (MADRS) Total Score - Full Analysis Set	**IProg**	
14.2.1.1.2	Primary Endpoint – Montgomery-Asberg Depression Rating Scale (MADRS) Total Score – Per-Protocol Analysis Set	**IProg**	14.2.1.1.1
14.2.1.2.1	Primary Endpoint – Change from Baseline in Montgomery-Asberg Depression Rating Scale (MADRS) Total Score - Full Analysis Set	**IProg**	
14.2.1.2.2	Primary Endpoint – Change from Baseline in Montgomery-Asberg Depression Rating Scale (MADRS) Total Score – Per-Protocol Analysis Set	**IProg**	14.2.1.2.1
14.2.1.3	Primary Endpoint – Percentage Change from Baseline in Montgomery-Asberg Depression Rating Scale (MADRS) Total Score - Full Analysis Set	**IProg**	14.2.1.2.1
14.2.2	**Secondary Efficacy Endpoints**		
14.2.2.1	Secondary Endpoint – Proportion of Montgomery-Asberg Depression Rating Scale (MADRS) Responders – Full Analysis Set	**IProg**	
14.2.2.2	Secondary Endpoint – Proportion of Montgomery-Asberg Depression Rating Scale (MADRS) Remitters – Full Analysis Set	**IProg**	14.2.2.1
14.2.2.3.1	Secondary Endpoint – CGI-S – Full Analysis Set	**IProg**	14.2.1.1.1
14.2.2.3.2	Secondary Endpoint – Change from Baseline in CGI-S – Full Analysis Set	**IProg**	14.2.1.2.1
14.3.5	**Vital Signs**		
14.3.5.1	Continuous Vital Signs Monitored During COMP360 Administration Session, Profile Plot – Safety Analysis Set	**IProg**	14.2.1.1.1

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	Protocol Deviations – Safety Analysis Set	**IProg**	
16.2.2.2	COVID-19 Related Protocol Deviations – Safety Analysis Set	**IProg**	16.2.2.1
16.2.3	**Participants Excluded from the Efficacy Analyses**		
16.2.3	Analysis Sets – Safety Analysis Set	**IProg**	
16.2.4	**Demographic Data**		
16.2.4.1	Demographics – Safety Analysis Set	**IProg**	
16.2.4.2	Medical History – Safety Analysis Set	**IProg**	
16.2.4.3	Inclusion Criteria – All Screened Participants	**IProg**	
16.2.4.4	Exclusion Criteria – All Screened Participants	**IProg**	
16.2.4.5	Prior Medications – Safety Analysis Set	**IProg**	
16.2.4.6	Concomitant Medications – Safety Analysis Set	**IProg**	
16.2.5	**Compliance and / or Drug Concentration Data**		
16.2.5.1	Study Medication Administration – Safety Analysis Set	**IProg**	
16.2.5.2	Ongoing SSRI Treatment – Safety Analysis Set	**IProg**	
16.2.6	**Individual Efficacy Response Data**		
16.2.6.1	Montgomery-Asberg Depression Rating Scale (MADRS) Score – Full Analysis Set	**IProg**	
16.2.6.2.1	Clinical Global Impression – Severity (CGI-S) – Full Analysis Set	**IProg**	
16.2.6.2.2	Clinical Global Impression – Improvement (CGI-I) – Full Analysis Set	**IProg**	
16.2.6.3.1	EuroQoL - 5 Dimensions-3 Levels (EQ-5D-3L) Descriptive System - Full Analysis Set	**IProg**	
16.2.6.3.2	EuroQoL - Visual Analogue Scale (EQ-VAS) - Full Analysis Set	**IProg**	
16.2.6.4	Generalised Anxiety Disorder Scale – 7 Item (GAD-7) – Full Analysis Set	**IProg**	
16.2.6.5	Quick Inventory of Depressive Symptomatology – Self Report – 16 items (QIDS SR-16) - Full Analysis Set	**IProg**	
16.2.6.6	The Positive and Negative Affect Schedule (PANAS) – Full Analysis Set	**IProg**	

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2.6.7	Five Dimensions Altered States of Consciousness Questionnaire (5D-ASC) – 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	Adverse Drug Reactions (ADRs) – Safety Analysis Set	**IProg**	16.2.7.1
16.2.7.4	Adverse Events of Special Interest (AESIs) – Safety Analysis Set	**IProg**	16.2.7.1
16.2.7.5	Deaths – Safety Analysis Set	**IProg**	
16.2.7.6	COVID-19 Related Treatment-Emergent Adverse Events (TEAEs) – Safety Analysis Set	**IProg**	16.2.7.1
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	Continuous Vital Signs Monitored During COMP360 Administration Session – Safety Analysis Set	**IProg**	
16.2.8.10	Clinically Important Vital Signs Values During COMP360 Administration Session – Safety Analysis Set	**IProg**	16.2.8.9
16.2.8.11	ECG Data – Safety Analysis Set	**IProg**	
16.2.8.12	Clinically Important ECG Values – Safety Analysis Set	**IProg**	
16.2.9	**Other Study Instruments**		
16.2.9.1	Hamilton Depression Rating Scale – 17-Item (HAM-D-17) - Full Analysis Set	**IProg**	
16.2.9.2.1	Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ) - Full Analysis Set	**IProg**	

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2.9.2.2	Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ) – Previous Treatments - Full Analysis Set	**IProg**	
16.2.9.3	McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD) - Full Analysis Set	**IProg**	
16.2.9.4	Columbia Suicidal Severity Rating Scale (C-SSRS) – Safety Analysis Set	**IProg**	

18 APPENDIX

18.1 Appendix I: CHANGES TO COMP 003 PROTOCOL

COMP 003 PROTOCOL
COMPARATIVE TABLE
08-March-2021

COMP 003 PROTOCOL Objective and Endpoint wording versus STATISTICAL ANALYSIS PLAN (SAP) and CLINICAL STUDY REPORT (CSR) Objective and Endpoint wording

This document will detail the minor changes between the COMP 003 protocol and the final versions of the SAP and CSR, with regards to the Objective and Endpoint wording. Note the SAP and CSR are not yet finalised during the time of writing this document as Database Lock (DBL) has not occurred. The protocol version is 2.2 (17 Dec 2020).

General Changes:

- Replacing psilocybin with COMP360 as this is COMPASS Pathfinder's' proprietary formulation name of synthetic psilocybin.
- Replacing day 1 with day 2 as this complies with the Clinical Data Interchange Standards Consortium (CDISC) requirements of there not being a day 0 in a clinical study. So, reference to day 0 and day 1 in the protocol is being replaced with day 1 and day 2.
- Replacing capitalised words with non-capitalised words for better sentence flow.
- Replacing behavior with behaviour to comply with English (UK) spelling.
- Correcting spelling errors.

Summary

Protocol Section Concerned with Wording	**SAP and CSR Amended Wording**
Section 2 STUDY OBJECTIVES The main purpose of this study is to investigate the efficacy of 25 mg psilocybin adjunct to serotonergic antidepressants in TRD participants via the following objectives.	Section 2 STUDY OBJECTIVES The main purpose of this study is to investigate the efficacy of 25 mg **COMP360** adjunct to serotonergic antidepressants in TRD participants via the following objectives.
Section 2.1 Primary (Primary Objective) The primary objective of this study is to explore the efficacy of 25 mg psilocybin as an adjunct therapy to antidepressants in improving depressive symptoms.	Section 2.1 Primary (Primary Objective) The primary objective of this study is to explore the efficacy of 25 mg **COMP360** as an adjunct therapy to antidepressants in improving depressive symptoms.

Section 2.2 Secondary (Secondary Objectives) The secondary objective is to evaluate the safety and tolerability of psilocybin in participants with TRD based on AEs, changes in vital signs, electrocardiograms (ECGs), clinical laboratory tests and suicidal ideation/behavior (measured using the Columbia- Suicide Severity Rating Scale [C-SSRS]) score.	Section 2.2 Secondary (Secondary Objectives) The secondary objective is to evaluate the safety and tolerability of **COMP360** in participants with TRD based on AEs, changes in vital signs, electrocardiograms (ECGs), clinical laboratory tests and suicidal ideation/**behaviour** (measured using the Columbia- Suicide Severity Rating Scale [C-SSRS]) score.
Section 2.3 Exploratory (Exploratory Objectives) The exploratory objectives are to evaluate the effects of psilocybin on quality of life, wellbeing and anxiety.	Section 2.3 Exploratory (Exploratory Objectives) The exploratory objectives are to evaluate the effects of **COMP360** on quality of life, wellbeing and anxiety.
Section 3.1 Primary (Primary Endpoint) The primary endpoint is the change in Montgomery-Asberg Depression Rating Scale (MADRS) total score from Baseline (Day -1) to 3 weeks post psilocybin administration.	Section 3.1 Primary (Primary Endpoint) The primary endpoint is the change in MADRS total score from **b**aseline (**d**ay -1) to 3 weeks post **COMP360** administration.

Section 3.2 Secondary (Secondary Endpoints) The secondary endpoints are: • The proportion of participants with a response (defined as a ≥ 50% improvement in MADRS total score from Baseline) at Week 3 post psilocybin administration • The proportion of participants with remission (defined as a MADRS total score ≤ 10) at Week 3 post psilocybin administration • Changes from Baseline Clinical Global Impression - Severity scale (CGI-S) at Week 3 post psilocybin administration • Incidence of AEs • Change from Baseline to Day 1 in ECGs, and incidence of clinically important changes • Change from Baseline to Day 1 and to Week 3 in clinical laboratory tests, and incidence of clinically important changes • Change from Baseline to Day 1 in vital signs • Incidence of changes from Baseline in the C-SSRS at each post-Baseline visit	(Secondary Endpoints) The secondary endpoints are: • The proportion of participants with a response (defined as a ≥ 50% improvement in MADRS total score from **b**aseline) at **w**eek 3 post **COMP360** administration • The proportion of participants with remission (defined as a MADRS total score ≤ 10) at **w**eek 3 post **COMP360** administration • Changes from **b**aseline Clinical Global Impression - Severity scale (CGI-S) at **w**eek 3 post **COMP360** administration • Incidence of AEs • Change from **b**aseline to **d**ay **2** in ECGs, and incidence of clinically important changes • Change from **b**aseline to **d**ay **2** and to **w**eek 3 in clinical laboratory tests, and incidence of clinically important changes • Change from **b**aseline to **d**ay **2** in vital signs • Incidence of changes from **b**aseline in the C-SSRS at each post-**b**aseline visit

Section 3.3 Exploratory (Exploratory Endpoints)
The exploratory endpoints are:
• Change from Baseline to Week 3 in total scores of:
  • Participant Euro QoL-5 dimension-3 level (EQ-5D-3L)
  • Caregiver EQ-5D-3L (this assessment is not mandatory)
  • Generalised Anxiety Disorder 7-item Scale (GAD-7)
  • QIDS-SR-16
  • Clinical Global Impression - Improvement scale (CGI-I)
  • Change from Baseline to Day 1 in Positive and Negative Affect Schedule (PANAS)
  • Summary of Five Dimension Altered States of Conscniousness questionnaire (5D-ASC) on the day of the psilocybin session (Day 0)
	Section 3.3 Exploratory (Exploratory Endpoints)
	The exploratory endpoints are:
	• Change from **b**aseline to **w**eek 3 in total scores of:
	  • Participant Euro QoL-5 dimension-3 level (EQ-5D-3L)
	  • Caregiver EQ-5D-3L (this assessment is not mandatory)
	  • Generalised Anxiety Disorder 7-item Scale (GAD-7)
	  • QIDS-SR-16
	  • Clinical Global Impression - Improvement scale (CGI-I)
	  • Change from **b**aseline to **d**ay **2** in Positive and Negative Affect Schedule (PANAS)
	  • Summary of Five **Dimensional** Altered States of **Consciousness** questionnaire (5D-ASC) on the day of the **COMP360 administration** session (**d**ay **1**)