Statistical Analysis Plan

Protocol Title: A Randomised Double-Blinded Placebo-Controlled Trial to Assess the Efficacy and Safety of Scopolamine Compared to Placebo in Individuals with Bipolar Disorder who are Experiencing a Depressive Episode (SCOPE-BD)

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1 *Revision History*

Revision	Description
1	First Release

2 *Abbreviations and Definitions*

Abbreviation	Full Form
AUDIT	Alcohol Use Disorder Identification Test
CANTAB	Cambridge Neuropsychological Test Automated Battery
CGI-S	Clinical Global Impression-Severity
CRF	Case Report Form
CSR	Clinical Study Report
GAF	Global Assessment of Functioning
HDRS	Hamilton Depression Rating Scale score
ICH	International Conference on Harmonisation
IV	Intravenous
MADRS	Montgomery and Asberg Depression Scale
MedDRA	Medical Dictionary for Regulatory Activities
NEO PI-FFI	NEO Personality Inventory-Five Factor Inventory
POMS	Profile of Mood States
PRISE	Patient Rated Inventory of Side Effects
SAP	Statistical Analysis Plan
SCID	Structured Clinical Interview for DSM
SCOPE-BD	Scopolamine Compared to Placebo in Individuals with Bipolar Disorder who are Experiencing a Depressive Episode
SOC	System Organ Class
VAS	Visual Analogue Scale
YMRS	Young Mania Rating Scale

3 *Preface*

Bipolar disorder is a chronic disabling psychiatric disorder characterized by recurrent episodes of mania or hypomania and depression. Current pharmacological treatments for bipolar disorder and in particular for the management of depressive episodes in bipolar disorder remain sub-optimal, with pharmacological strategies employed to date often only partially effective.

Putative effect of scopolamine is suggested from animal studies and clinical trials in humans, with a suggestion that the effect was most evident with intravenous (IV) administration of scopolamine. However, studies of IV scopolamine as a treatment agent for depressive episodes to date have had limited numbers of participants and have included heterogeneous populations. This study will be the first to exclusively examine depressive episodes in bipolar disorder to ascertain if a rapid antidepressant effect is demonstrated.

This is the rationale behind the Safety of Scopolamine Compared to Placebo in Individuals with Bipolar Disorder who are Experiencing a Depressive Episode (SCOPE-BD) Trial.

4 *Purpose of SAP*

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for the SCOPE-BD Trial. This is a Phase IIb, randomised, double-blinded, placebo-controlled trial of IV Scopolamine in the treatment of reducing severity of depression in individuals with bipolar disorder who are experiencing a depressive episode of at least moderate severity.

The structure and content of this SAP provides sufficient detail to meet all the requirements in accordance with the International Conference on Harmonisation guidance of Statistical Principles in Clinical Trials (ICH E9). All work planned and reported for this SAP will follow internationally accepted guidelines. The following documents were reviewed in the preparation of this SAP:

- Clinical Research Protocol 2017-003112-39 Version 3, 18-Dec-2020.
- Case Report Forms (CRFs).
- ICH E9 and E3

The reader of this SAP is encouraged to also read the clinical protocols for details on the conduct of this study, and the operational aspects of clinical assessments and timing for completing a patient in this study.

5 *Study Objectives and Endpoints*

5.1 Study objectives

To assess the efficacy and safety of IV Scopolamine compared to Placebo in Individuals with Bipolar Disorder who are experiencing a depressive episode.

5.1.1 Primary Objective

The primary objective is to investigate the efficacy and safety of IV Scopolamine, compared to placebo, in reducing severity of depression in individuals with bipolar disorder who are experiencing a depressive episode of at least moderate severity.

5.1.2 Secondary objectives

- To investigate if IV Scopolamine compared to placebo improves mood, cognition and functioning as measured on a number of objective and subjective psychometric instruments in individuals with bipolar disorder experiencing a depressive episode of at least moderate severity.

- To investigate the safety and tolerability of repeated (x3) IV Scopolamine versus placebo in individuals with bipolar disorder experiencing a depressive episode of at least moderate severity.

5.2 Study endpoints

5.2.1 Primary endpoint

The primary endpoint will be the change in severity of objective depressive symptoms as measured by change in Hamilton Depression Rating Scale score (HDRS) score from pre-randomisation (pre-IV infusion at Visit 3) compared to Visit 6.

5.2.2 Secondary endpoints

1. Remission of depressive episode after the last IV treatment (measured objectively at Visit 6), and is defined as occurring when an individual has:

(i) a HDRS score <= 7

(ii) a Montgomery and Asberg Depression Scale (MADRS) score <6

2. Remission of depressive episode at follow-up (measured objectively at Visit 7)

(i) a HDRS score <=7

(ii) a MADRS score <6

3. Response to a depressive episode after the last IV treatment (measured at Visit 6) is defined as:

(i) a 50% reduction in MADRS score at Visit 6 compared to Visit 3

4. Response to a depressive episode at follow-up (measured objectively at Visit 7)

(i) a 50% reduction in MADRS score at Visit 6 compared to Visit 3

5. Improvement in mood symptoms measured with the HDRS and MADRS at visits 5, 6 and 7 compared to Visit 3.

6. Improvement in objectively measured overall functioning, measured with the Global Assessment of Functioning (GAF) at Visit 5, 6 and at follow-up at Visit 7 compared to Visit 3

7. Improvement in objectively rated illness severity, measured with the CGI-S at visits 4, 5, 6 and 7 compared to Visit 3 and CGI-I at visits 4, 5, 6 and 7 compared to Visit 3.

8. Changing subjective measured depressive symptoms with the Profile of Mood States (POMS) and Visual Analogue Scale (VAS).

(i) a reduction in POMS score post-infusion compared to pre-infusion at visits 2, 3, 4 and 5 across the six different factors of the POMS (tension, depression, anger, fatigue, vigour and confusion).

(ii) a reduction in VAS scores post-infusion compared to pre-infusion at visits 2, 3, 4 and 5 across 8 items (happy, restless, sad, anxious, anger, drowsiness and alertness).

9. A change in subjectively measured depressive symptoms at Visit 6 compared to Visit 3 as measured with the POMS and VAS.

10. A reduction in subjectively measured depressive symptoms at follow-up (Visit 7) compared to Visit 3 as measured with the POMS and VAS.

11. Psychiatric inpatient admission of a participant due to depressive episodes between Visit 2 and Visit 7.

12. Antidepressants medication use or change by a participant due to depressive episodes over the duration of the study (Visit 2 to Visit 7):

(i) Introduction of a new antidepressant (yes / no)

(ii) Increase in dose of an existing antidepressant (yes / no)

13. Change in motor processing, visual and spatial memory (3 categorical variables) at Visit 6 compared to Visit 2 based on the Cambridge Neuropsychological Test Automated Battery (CANTAB) battery of tests.

14. Occurrence of a hypo (manic) episodes at visits 3, 4, 5, 6 or 7, as defined by a score of >6 on the Young Mania Rating Scale (YMRS).

15. Occurrence of other adverse effects as observed on monitoring of vital signs, reported by participants or measured utilising the Patient Rated Inventory of Side Effects (PRISE) questionnaire

5.3 Derived variables

None of the variables related to the primary and secondary endpoints are calculated using additional variables from the data recorded in the CRF, with the exception of change scores that will be calculated as indicated in the previous 2 sections.

6 *Study Methods*

6.1 General Study design and Plan

This is a single-site, randomised, double-blind, placebo-controlled, parallel, phase IIb clinical trial. Participants will receive IV Scopolamine or placebo in addition to their current treatment regimen. At Visit 2, all participants will receive placebo run-in (100mls of Saline IV). Within 7 days of Visit 2, participants will be assessed against the placebo run-in criteria and if these criteria are met they will be randomised (visit 3) to receive either placebo or 4 µg/kg Scopolamine IV in 100mls of Saline over 15 minutes at Visit 3 (Day 0), Visit 4 (days 2-6) and Visit 5 (days 6-10).

A flow-chart and schedule of assessments are included for greater clarity.

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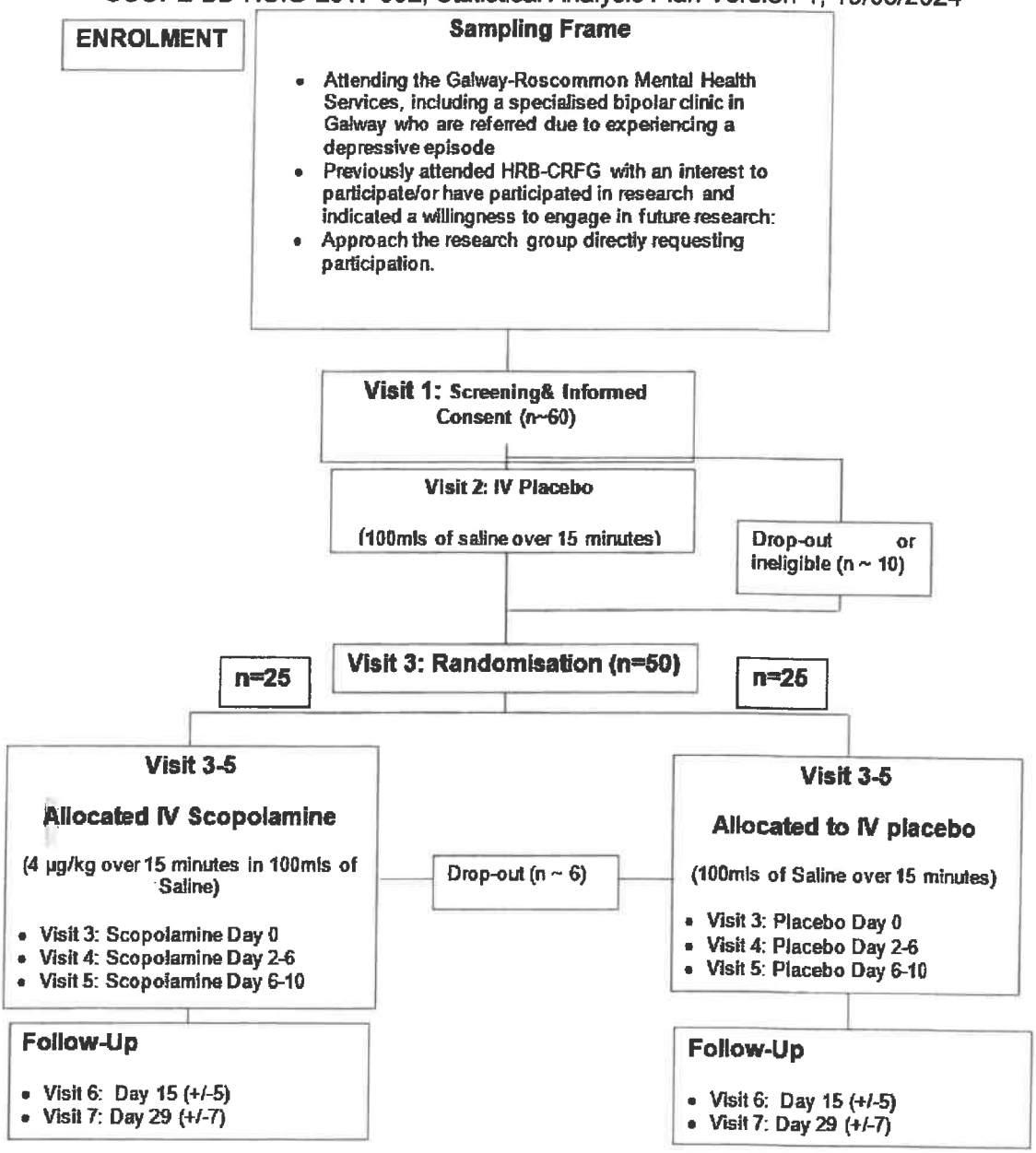

Note timeline between visits:
Visit 1 and 2: ≤14 days. Can also occur on the same day and thus data does from screening visit does not need to be replicated at Visit 2
Visit 2 and 3: ≥2 days and ≤7 days
Visit 3 and Visit 4 and Visit 5 and Visit 6: ≥2 days
Visit 6 and Visit 7: ≥3 days

Procedures	Visit 1 Screening	Visit 2 PLACEBO IV Infusion			Visit 3 Randomisation Day 0 Scopolamine or Placebo IV Infusion			Visit 4 Day 4 (± 2 Days) Scopolamine or Placebo IV Infusion			Visit 5 Day 8 (± 2 Days) Scopolamine or Placebo IV Infusion			Visit 6 Day 15 (± 5 Days) Follow-Up	Visit 7 Day 29 (± 7 Days) Follow-Up
		Pre	During	Post	Pre	During	Post	Pre	During	Post	Pre	During	Post		
Signed informed consent	X														
Inclusion/Exclusion	X	X			X***										
Randomisation					X										
IWRS					X			X			X				
Demography	X														
MEHI	X														
Medical/Surgical History/History BPD	X														
Current Medication	X	X			X			X			X			X	X
Vital Signs – HR, BP & RR	X	X		X	X		X	X		X	X		X		
SCID-RV	X														
HDRS	X	X			X			X			X			X	X
YMRS	X	X			X			X			X			X	X
AUDIT	X														
Pregnancy Discussion	X	X			X			X			X				
Contraception Advice	X	X			X			X			X				
Serum Pregnancy Test^		X													
Pregnancy urine dipstick^		X			X			X			X				
U&Es, LFTs, TFTs °	X	X													
Fagerstrom		X													
CGI-S		X			X			X			X			X	X
CGI-I					X			X			X			X	X
VAS		X		X	X		X	X		X	X		X		
MADRS		X			X			X			X			X	X
GAF					X						X			X	X
ECG		X													
Height (cm) & Weight (kg)		X													
IV Cannulation		X			X			X			X				
Infusion administration			X			X			λ			λ			
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cannulation Site Check		X		X	X		X	X		X	X		X		
POMS (Optional)		X		X	X		X	X		X	X		X	X	X
CANTAB ** (Optional)				X			X							X	
WAIS * (Optional)				X*			X*			X*			X*	X*	X*
NEO-PI-FFI * (Optional)				X*			X*			X*			X*	X*	X*
PRISE (Optional) Subjective Assessment				X			X			X			X		X

Randomisation will only occur at Visit 3 after HDRS is demonstrated to be ≥ 8 and YMRS < 6. These measures will be conducted pre-randomisation (and consequently also pre-infusion).
Pre-infusion vital signs should be taken post cannulation. Post-infusion vital signs within 15 minutes of infusion stopping and 50 to 90 minutes post-infusion.
Visit 6 and 7 can be conducted by telephone in limited circumstances if a participant has withdrawn or is unwilling/unable to attend clinic at the scheduled time.
* Can be undertaken at any of the marked visit
** These include Paired Associates Learning (PAL), Spatial recognition, Delayed Match to Sample, ID-ED Shift, motor screening and Eyes of the Mind tests.
***Only inclusion criterion 7 and exclusion criteria 21 and 22 are required to be met for randomisation at Visit 3 only
Λ Pregnancy test (serum pregnancy test and pregnancy urine dipstick), when required, for female participants only. Serum result confirmed prior to Visit 3.
° Blood tests for U&Es (Urine and Electrolytes), LFTs (Liver Function Tests) and TFTs (Thyroid Function Tests) should be confirmed within acceptable ranges in the previous 4 months of the Screening (Visit 1). Can be performed if required at Visit 1 or 2 (results must be confirmed as acceptable prior to infusion).

AUDIT = Alcohol Use Disorder Identification Test; **BP** = Blood Pressure; **CANTAB** = Cambridge Neuropsychological Test Automated Battery, **CGI-I** = Clinical Global Impression – Improvement, **CGI-S**= Clinical Global Impression- Severity, **ECG**= Electrocardiograph; **Fagerstrom:** Test for Nicotine Dependence, **GAF** = Global Assessment of Functioning; **HDRS** = Hamilton Depression Rating Scale; **HR** = Heart Rate; **IV** = Intravenous; **IWRS** = Interactive Web Response System; **MADRS** = Montgomery and Asberg Depression Rating Scale; **MEHI** = Modified Edinburgh Handedness Inventory; **NEO PI-FFI** = NEO Personality Inventory-Five Factor Inventory; **POMS** = Profile of Mood States; **PRISE**= Patient Rated Inventory of Side Effects; **RR** = Respiratory Rate; **SCID-RV** = Structured Clinical Interview for DSM; **VAS** = Visual Analogue Scale; **YMRS** = Young Mania Rating Scale; **WAIS** = Wechsler Adult Intelligence Scale.

Note timeline between visits:
Visit 1 and 2: ≤14 days. Can also occur on the same day and thus data does from screening visit does not need to be replicated at Visit 2.
Visit 2 and 3: ≥2 days and ≤7 days
Visit 3 and Visit 4 and Visit 5 and Visit 6: ≥2 days
Visit 6 and Visit 7: ≥3 days

6.2 General Study Population

Participants will be (male and female) adults who have bipolar disorder (bipolar disorder 1 or 2) and are experiencing a depressive episode of at least moderate severity as measured by a HDRS of ≥ 14 at Visit 2.

Participants will be attending the Galway-Roscommon Mental Health Services, including a specialised bipolar clinic in Galway and referred due to experiencing a depressive episode by their treating clinical team; or patients who have previously attended University of Galway / HRB-CRFG with an interest to participate/or have participated in research and have indicated a willingness to engage in future research; or patients who approach the research group directly requesting participation.

Once participants have consented to the trial they will be reviewed against the inclusion and exclusion criteria at the screening visit (Visit 1).

6.3 Randomisation and Blinding

Participants will be randomly assigned to receive either scopolamine or placebo in a 1:1 ratio. Randomly permuted blocks of sizes 4 and 6 will be used to ensure similar numbers of participants in each arm of the trial.

Randomisation will be stratified by the HDRS score at trial entry (a score of <23 indicating a mild-moderate depressive episode and a score ≥23 indicating a severe depressive episode) to ensure greater balance between arms in the final trial sample and increase the efficiency of our treatment effect estimates.

A validated randomisation system will be used at Visit 3, (after HDRS and YMRS are completed) to randomise patients to either arm. This centralised system will ensure allocation concealment; preventing blinded trial staff from knowing which treatment group will be allocated. Blocks of randomly varying length will also reduce the predictability of the allocation sequence.

This trial will be conducted in a double-blind fashion with placebo control identical to Scopolamine solution to avoid bias in the assessment of outcomes. Site Investigators, site personnel, participants, and outcome assessors will be blinded to treatment allocation.

7 *Sample Size*

The primary outcome in this study is the Hamilton Depression Rating Scale score (HDRS). It is judged that a decrease of 50% or more in the HDRS score between randomisation and Visit 6 will be sufficient to consider a patient to have experienced a response. We anticipate that the average HDRS score in the proposed population pre-randomisation will be 24 units and that this outcome variable will be approximately normal. Based on results from the literature, it is estimated that a range of plausible values for the standard deviation is between 5 to 13 units.

Using this information, a sample of 44 participants (22 in each group) will have 85% power to detect a difference of 12 units between the treatment and control arms, i.e. an expected HDRS mean score of 12 in the treatment group vs. an expected HDRS mean score of 24 in the control group after Visit 6. The sample size is based on a 2-sample t-test (two-sided) with a standard deviation of 13 units (conservative approach) and a significant level of 0.05. Allocating 25 participants to each arm will ensure power >=85% when loss to follow-up is <12% (6 participants missing at Visit 6 follow up).

8 *Timing of analyses*

8.1 Interim analyses

There are no planned interim analyses for this study with the exception of the following: A Data Safety and Management Board (DSMB) will be established to perform on-going safety surveillance and to review interim analyses on the safety data. All analyses for the DSMB will be conducted by the independent statistician who is a member of the DSMB.

8.2 Final analyses

All final analyses identified in the protocol and in this SAP will be performed after the last patient has completed the study. If a participant withdraws before completing the study, the reason for withdrawal will be documented and reported.

Before carrying out the analyses, the data manager's team at CRFG is responsible for the database cleaning process to ensure the integrity of the analyses. The database will be locked prior to the initiation of the analysis.

Any post-hoc exploratory analyses completed to support planned study analyses, which were not identified in this SAP, will be documented and reported in appendices to the Clinical Study Report (CSR).

9 *Analysis populations*

Screening Population: all subjects who provide informed consent and provide demographic and/or baseline screening assessments, regardless of the subject's treatment status in the study.

Intent-to-treat Population: all patients who randomised to treatment.

Effectiveness and safety outcomes will be analysed on an intention-to-treat basis for all participants randomised and with available follow-up data as per their randomised allocation. Safety outcomes will be evaluated on all participants who received at least 1 dose of treatment after randomisation (**Safety set**).

A **per-protocol** dataset is not well-defined under multiple treatments, here it could reasonably be defined as those participants who either received at least 1, at least 2

or all 3 IV treatments after randomisation. Sensitivity analyses will thus be performed on the primary outcome to assess efficacy of the treatment compared to placebo by incorporating the original allocation of participants and their level of adherence to treatment. This will involve examining the short term-effect of treatment in a longitudinal model and the overall effect of number of IV treatments received at follow-up visits after the final IV treatment.

10 *General issues for Statistical Analysis*

10.1 Software used for the analysis

All the statistical analyses will be carried out in R statistical software (version 3.6.0 or higher) unless otherwise noted by the statisticians assigned to this study. Primary and secondary analysis will be reviewed by an independent statistician, and all the code generated will be kept by the study statistician.

10.2 Methods for Withdrawals, Missing Data, and Outliers

Any missing data which occurs will be summarised and reasons given. As per the statistical analysis specification, an inverse probability weighting will be performed in the primary outcome analysis (weights based on the inverse probability of a patient's data being missing given their pre-randomisation measurements). This will ensure the estimate and inference is more representative of all patients randomised.

10.3 Data Transformations

No transformations have been identified for the analysis of the primary and secondary endpoints.

10.4 Multicentre Studies

This is a single-site study.

10.5 Multiple Testing

The power of this trial is based on a single analysis that focus only on the primary endpoint. The remaining secondary analyses will be considered exploratory and hypothesis generation and therefore no methods will be used to preserve the overall significance level (as in multiple testing procedures).

10.6 Planned Subgroups, Interactions, and Covariates

No subgroup or interaction analyses are planned.

11 *Study Subjects*

11.1 Subject Disposition

Different variables from the CRF will be considered to determine the number of patients who reached the various stages of the study. Summaries will be presented as the number and percentage of patients who are initially screened (Visit 1), enrolled for the run-in period, attend for initial treatment visit (Visit 3), satisfy the run-in criteria, receive initial treatment (IV at Visit 3) and attend for the subsequent treatment visits (Visits 4 & 5) and follow-up visits in the study.

11.2 Protocol Deviations

Protocol deviations include:

- There are any issues with the informed consent (consent not obtained or obtained after study procedures started).
- The inclusion /exclusion criteria are not followed correctly.

In the unlikely case that any deviations occur, a brief explanation will be presented in the clinical study report.

11.3 Inclusion and Exclusion Criteria

The number and percentage will be presented for subjects meeting each of the Inclusion and Exclusion Criteria in the trial sample, post run-in phase. It is expected that the overall percentage will be 100% for inclusion and exclusion criteria, except when waivers are granted or when data review indicates that inclusion or exclusion criteria have been violated.

12 *Demographic and Baseline variables*

12.1 Demographics

The following will be considered demographic variables: Age, Gender, Race and handedness. Handedness will be accurately measured utilising the Modified Edinburgh Handedness Inventory (MEHI). Mean, standard deviation, median, max and min will be reported for continuous variables, and counts and percentages will be reported for categorical variables. These variables will be summarised by treatment group.

12.2 Prior and Concurrent medications

Concomitant medications are recorded in the Concomitant Medications Form of the CRF. For each one of the generic names, summaries will be provided for the number of times the medication was reported at baseline (counts and percentages), the number of times the medication was added during the treatment period (counts and percentages).

12.3 Baseline and Screening Conditions

All outcome variables (primary and secondary) at baseline, and additional baseline variables including smoking, alcohol and drug usage, medical/surgical history, clinical history of bipolar disorder, NEO-PI diagnosis and WAIS scores (Verbal/Performance/Total) will be summarised for each treatment group using descriptive statistics.

12.4 Treatment Compliance

Treatment will be summarised by reporting the number and percentage of participants who attend and receive IV (placebo or Scopolamine) for each treatment Visit 3, 4 and 5. The numbers and percentages of eligible trial participants will also be summarised by total number of IV treatments received (0, 1, 2 or 3 IV treatments). This total IV treatments received variable will be used in efficacy analysis to explore the impact of receiving IV treatments, in addition to being randomised to them.

13 *Efficacy Analyses*

13.1 Primary Efficacy Analysis

For the primary effectiveness analysis of the primary outcome, it is expected that pre-randomisation measurements of the HDRS score will be correlated with the scores obtained at Visit 6 of treatment. The mean scores at Visit 6 will be compared across the study arms using an ANCOVA model. The response variable will be the change in HDRS score from Visit 3 to HDRS at Visit 6 including the HDRS score at Visit 3 as a covariate in the model.

The addition of stratifying variables and other variables as covariates will be considered as appropriate. This analysis will increase the power to detect significant differences between the groups.

Inverse probability weighting will be applied to the primary outcome analysis. These weights will be derived based on the inverse of the probability of a patient's data being missing given their pre-randomisation measurements. This will ensure the estimate and inference is more representative of all patients randomised, reducing bias in the estimation of the treatment effect due to participants lost to follow-up and missing data.

Inference regarding the treatment effectiveness will focus on the point estimate, confidence interval and p-value for hypothesis confirmation.

13.2 Secondary Efficacy Analyses

Secondary outcomes will be analysed as appropriate (according to the distribution of each outcome), comparing the difference between groups at the specified follow-up visit and relative to baseline value (where specified/measured). Baseline variables predictive of each outcome (the measure at baseline where available), and stratifying

variables will be included in ANCOVA or generalised linear models of outcome variables.

For secondary outcomes, the focus will be on the point estimates and confidence intervals for hypothesis generation.

Additional analysis of the primary outcome will compare the time course of HDRS under placebo and treatment using a mixed-effects model including fixed-effects terms for time since randomisation/study visit, trial arm and their interactions, and a random effect to account for correlation of multiple observations per participant.

13.3 Other Efficacy Analysis

Sensitivity analyses will be performed on the primary outcome to assess efficacy of getting the treatment (rather than being offered/randomised to treatment) compared to placebo by incorporating the original allocation of participants and their level of adherence to treatment. This will involve examining the short term-effect of treatment in a longitudinal model and the overall effect of number of IV treatments received at follow-up visits after the final IV treatment.

14 *Safety Analyses*

The results of clinical monitoring including blood pressure or heart rate changes, and AEs secondary to phlebotomy or cannulation will be examined between the groups. Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of treatment-emergent adverse events will be summarized by system organ class (SOC) and preferred term.

Safety data will be presented primarily in a descriptive fashion. The small sample size and likely low adverse event rates will mean any inference is likely underpowered to detect a range of meaningful differences.

Blinded data will be presented to the DSMB for safety evaluation to coincide with scheduled DSMB meetings.

14.1 Drug Exposure

The analysis of drug exposure will include:

- Counts and percentages of participants achieving full dose by visit and treatment group.
- Summaries of the duration of infusion by visit and treatment group.
- Summaries of the overall duration of infusion by treatment group.

A discussion on how drug exposure may be related to the appearance of expected events during the 90 minutes post-infusion will also be provided.

14.2 Adverse Events

The analysis of adverse events will include:

• A summary of the number of patients experiencing any adverse event, counts and percentages per group.

• Summaries of the number of patients experiencing each of the adverse events. Summaries will also be reported by severity using the preferred term. Note that if a patient has different severity grades for the same adverse event the highest severity grade will be considered.

• Summaries of patients with AEs related to the treatment by preferred term will be given.

• Summaries of the number of patients experiencing each of the adverse events and the action taken will be given. Summaries will also be reported by severity using the preferred term.

These will be summarised overall, by visit and by treatment group.

14.3 Deaths, withdrawal, Serious Adverse Events and other Significant Adverse Events

The analysis of Serious Adverse Events (SAE) will include:

• An overview of the number of SAEs recorded in the study. Specifically, the number of patients experiencing at least one SAE and whether the patient was withdrawn as a result of the SAE. The information will be summarised using counts and percentages.

• Summaries of the number of patients experiencing serious adverse events, by preferred term (counts and percentages).

These will be summarised overall, by visit and by treatment group.

14.3.1 Withdrawal due to Adverse Events

Withdrawals will be summarised as the number and percentage of patients who were withdrawn from the study including reason for withdrawal as given in the Off Study Form.

14.3.2 Deaths

In the unlikely event of any deaths, these will be summarised as the number and percentage of patients who died within the study period by treatment arm.

14.3.3 Other AE Assessments

No additional Adverse Event Assessments were completed, and no additional analysis is planned.

14.4 Pregnancies

Pregnancy data will be shown in a data listing. No special analysis will be performed on the pregnancy data. Patients are to be discontinued from the study if they become pregnant.

14.5 Clinical Laboratory Evaluations

Urea and Electrolytes (U&Es), Liver Function Tests (LFTs) and Thyroid Function Tests (TFTs) will be measured from bloods prior to screening and analysed as follows:

- Summaries of the results (mean, sd, median, min and max)

- The number and percentage of patients with values below, within, or above normal ranges and any action taken.

Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges. Any out-of-range values that are identified by the investigator as being clinically significant will also be shown in a data listing.

These will be summarised overall, by visit and by treatment group.

14.6 Haemodynamics (Vital Signs)

The analysis of Vital signs will include the measurements specified in the corresponding CRF form. These measurements are: blood pressure (BP), heart rate (HR) (beats per minute (bpm)), and respiratory rate (RR) (respirations per minute).

For each of these measurements, the analysis will include:

- Summaries of the results by visit: at Screening and Visit 2, and at treatment visits (Visits 3, 4 and 5) pre- and post-infusion (mean, sd, median, min and max).

- Summaries of the with pre- and post-infusion differences at each treatment visit (Visit 3, 4 and 5) (mean, sd, median, min and max).

- The number and percentage of patients with values below, within, or above normal ranges and any action taken.

These will be summarised overall, by visit and by treatment group.

14.7 ECGs

An ECG will be performed at Visit 2. Summaries at this visit will be provided and abnormal findings will be reported.

15 *Other Planned Analysis*

No other analysis planned

16 *Reporting conventions*

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

17 *References*

See protocol for relevant medical references

18 *Listing of Tables, Listings and Figures*

All listings, tables and figures will be generated based on the analysis described in this SAP.