STATISTICAL ANALYSIS PLAN

SEP361-201

A 4-WEEK, RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, PLACEBO-CONTROLLED, FLEXIBLY-DOSED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF SEP-363856 IN ACUTELY PSYCHOTIC ADULT SUBJECTS WITH SCHIZOPHRENIA

AUTHOR:

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan Final V1.0 (dated 28Aug2018) for protocol SEP361-201.

	Name	Signature	Date
Author:			
Position:	Statistician		
Company:			
Approved By:			
Position:			
Company:			

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date
Approved By:			
Position:			
Company:			
	Name	**Signature**	**Date**
Approved By:			
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LIST OF ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BLQ	Below the Lower Limit of Quantification
C-SSRS	Columbia Suicide Severity Rating Scale
CBB	Cogstate Brief Battery
CGI-S	Clinical Global Impression – Severity of Illness
CI	Confidence Interval
CRF	Case Report Form
CSP	Clinical Study Protocol
DMC	Data Monitoring Committee
DSM-5	Diagnostic and Statistical Manual of Mental Disorder, 5th Edition
ECG	Electrocardiogram
HLT	High Level Term
HR	Heart Rate
IPD	Important Protocol Deviations
mITT	Modified Intent-to-Treat
LOCF	Last Observation Carried Forward
LS	Least Squares
MAR	Missing At Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
PANSS	Positive and Negative Syndrome Scale
PMM	Pattern Mixture Model
PP	Per Protocol
PT	Preferred Term

Abbreviation	Explanation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SE	Standard Error
SI	International System of Units
SOC	System Organ Class
ULQ	Above the Upper Limit of Quantification
UPSM	Uncorrelated PANSS Score Matrix
VAS	Visual Analogue Scale

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for protocol SEP361-201. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version 3.01 (17-Aug-2017). Hereafter, this protocol version is referred to as the Clinical Study Protocol (CSP).

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

To evaluate the efficacy of flexibly dosed SEP-363856 (50 or 75 mg/day) compared with placebo in acutely psychotic adult subjects with schizophrenia as measured by the Positive and Negative Syndrome Scale (PANSS).

2.2. SECONDARY OBJECTIVES

To evaluate the efficacy of flexibly-dosed SEP-363856 (50 or 75 mg/day) compared with placebo in acutely psychotic adult subjects with schizophrenia as measured by:

- Clinical Global Impression-Severity (CGI-S)
- PANSS subscale scores (positive, negative, and general psychopathology)
- Brief Negative Symptom Scale (BNSS)
- Montgomery-Asberg Depression Rating Scale (MADRS)

To evaluate the safety and tolerability of flexibly-dosed SEP-363856 (50 or 75 mg/day) using:

- physical examinations (PE)
- 12-lead electrocardiograms (ECG)
- vital signs
- adverse event (AE) reports
- clinical laboratory results
- body weight and body mass index (BMI)

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

2.3. OTHER OBJECTIVES

- To assess whether SEP-363856 is associated with extrapyramidal symptoms as measured by the Barnes Akathisia Rating Scale (BARS), the Abnormal Involuntary Movement Scale (AIMS), and the Simpson-Angus Scale (SAS).
- To characterize the effects of SEP-363856 as measured by the Drug Effects Questionnaire (DEQ).
- To explore the subjective effects of SEP-363856 on sleep as measured by the Pittsburgh Sleep Quality Index (PSQI).
- To assess the effects of SEP-363856 on cognition based on the CogState Brief Battery (CBB).
- To perform population pharmacokinetic (POPPK) analysis using plasma SEP-363856 concentrations.
- To characterize the relationship between PANSS total score and plasma SEP-363856 exposure using population PK/pharmacodynamics (PD) methods.
- To explore the impact of cytochrome (CYP) P450 CYP2D6 metabolizer status on SEP-363856 plasma exposure.

3. STUDY DESIGN

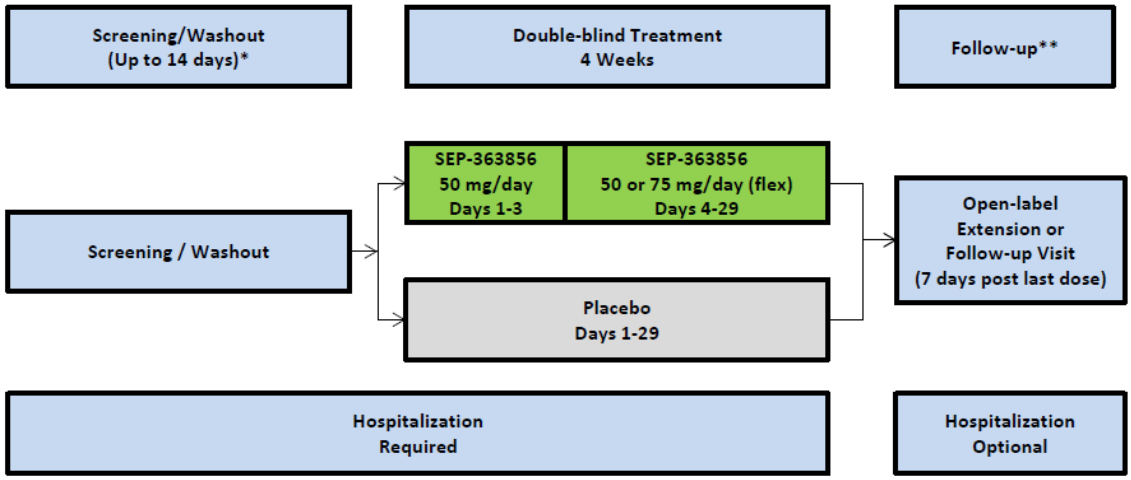
3.1. GENERAL DESCRIPTION

This is a multicenter, randomized, double-blind, parallel-group, flexibly-dosed, study evaluating the efficacy and safety of SEP-363856 in acutely psychotic adult subjects with schizophrenia using SEP-363856 (50 or 75 mg/day [i.e., once daily]) versus placebo over a 4-week treatment period.

This study is projected to randomize at least 240 subjects to 2 treatment groups (SEP-363856 or placebo) in a 1:1 ratio. Treatment assignment will be balanced within each clinical site.

The study will consist of 3 periods: Screening/Washout (up to 14 days), Treatment (4 weeks in-patient), and a Follow-up visit (7 days after last study drug dose for subjects who discontinue prior to Visit 7 or who complete the study but do not elect to enrol in the open-label extension study [SEP361-202]) as shown in Figure 1.

Figure 1: Study Schematic



* Screening/washout period will be up to 14 days.

** Follow-up visit 7 ± 2 days after last dose only for subjects not continuing in to open-label extension study SEP361-202. Hospitalization will be allowed for up to an additional 7 days to stabilize the subject, if necessary.

3.2. SCHEDULE OF EVENTS

Schedule of events can be found in section 11 of the CSP.

Table 1. Schedule of Assessments

Study Visit Number **Study Visit Week**	**Visit 1** **Screening**[a]	**Visit 2** **Baseline**	**Visit 3** **Day 4**	**Visit 4** **Week 1**	**Visit 5** **Week 2**	**Visit 6** **Week 3**	**Visit 7** **Week 4** **or ET**[b]	**Visit 8** **Week 5**
Study Visit Day	**-14 to -1**	**1**	**4**	**8**	**15**	**22**	**29**	**7 ± 2days after Last Dose**
Study Visit Type	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient follow-up**[c]
Obtain informed consent	X							
Review inclusion/exclusion criteria	X	X						
Review randomization criteria		X						
Prior/concomitant medication review	X	X	X	X	X	X	X	X
Randomize (IXRS) to treatment		X						
Administration of study drug[d]		X	X	X	X	X		
Study drug accountability			X	X	X	X	X	
Clinical and Laboratory Evaluations								
Demography	X							
Medical history	X							
Psychiatric history/mental status	X							
SCID-CT[e]	X							
Physical and neurological examination	X						X	
Height	X							
Vital signs[f]	X	X	X	X	X	X	X	
Weight (including BMI)[g]	X	X			X		X	
Waist circumference		X					X	

Study Visit Number **Study Visit Week**	**Visit 1** **Screening**[a]	**Visit 2** **Baseline**	**Visit 3** **Day 4**	**Visit 4** **Week 1**	**Visit 5** **Week 2**	**Visit 6** **Week 3**	**Visit 7** **Week 4** **or ET**[b]	**Visit 8** **Week 5**
Study Visit Day	**-14 to -1**	**1**	**4**	**8**	**15**	**22**	**29**	**7 ± 2days after Last Dose**
Study Visit Type	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient follow-up**[c]
Electrocardiogram (ECG)	X	X					X	
Hematology, chemistry, and urinalysis	X	X					X	
Serum prolactin	X	X					X	
Glycosylated hemoglobin (HbA_{1c})	X						X	
Glucose and Lipid panelh	X	X					X	
Serum follicle stimulating hormone (FSH)i	X							
Serum human chorionic gonadotropin (β-hCG)	X							
Blood sample for pharmacogenomics (CYPP450 2D6)		X						
Blood sample for Population PKj		X					X	
Urine drug screenk	X	X					X	
Urine β-hCGl		X					X	
Positive and Negative Syndrome Scale (PANSS)	X	X	X	X	X	X	X	
Clinical Global Impression – Severity (CGI-S)	X	X	X	X	X	X	X	
Brief Negative Symptom Scale (BNSS)	X	X	X	X	X	X	X	
Montgomery-Asberg Depression Rating Scale (MADRS)		X	X	X	X	X	X	
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X	X	X	X	X	X	X

Study Visit Number Study Visit Week	Visit 1 Screening[a]	Visit 2 Baseline	Visit 3 Day 4	Visit 4 Week 1	Visit 5 Week 2	Visit 6 Week 3	Visit 7 Week 4 or ET[b]	Visit 8 Week 5
Study Visit Day	**-14 to -1**	**1**	**4**	**8**	**15**	**22**	**29**	**7 ± 2days after Last Dose**
Study Visit Type	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient**	**Inpatient follow-up[c]**
Barnes Akathisia Rating Scale (BARS)m	X	X	X	X	X	X	X	
Abnormal Involuntary Movement Scale (AIMS)m	X	X	X	X	X	X	X	
Simpson-Angus Scale (SAS)m	X	X	X	X	X	X	X	
Drug Effects Questionnaire (DEQ)		X					X	
Pittsburg Sleep Quality Index (PSQI)		X					X	
CogState Brief Battery (CBB)		X					X	
Pretreatment event monitoring	X							
Adverse events (AE) monitoring		X	X	X	X	X	X	X
Duplicate Subject Checkn	X						X	X

Abbreviations: AE = adverse event; BARS = Barnes Akathisia Rating Scale; β-hCG = human chorionic gonadotropin; BMI = Body Mass Index; BNNS = Brief Negative Symptom Scale; C-SSRS = Columbia Suicide Severity Rating Scale; ET = early termination; FSH = Follicle stimulating hormone; IXRS = interactive response technology; MADRS = Montgomery-Asberg Depression Rating Scale; SAS = Simpson-Angus Scale; PANSS = Positive and Negative Syndrome Scale; PSQI = Pittsburg Sleep Quality Index; PK = pharmacokinetic; SCID-CT = Structured Clinical Interview for DSM-5, Clinical Trials Version.

[a] Subjects who screen fail may be re-screened up to two times, if judged appropriate by the Investigator.

[b] If a subject discontinues from the study, all Visit 7 procedures should be performed at the ET visit, within 48 hours of last study dose. All procedures and assessments scheduled for Visit 7 (Week 4) will be utilized as the Baseline procedures and assessments for the open-label extension study (SEP361-202).

[c] All subjects will have an inpatient/outpatient safety follow-up prior to discharge (7 [± 2]) days after their last dose of study drug.

[d] All study drug will be taken once daily in the evening by mouth.

[e] The SCID-CT will be used to support the DSM-5 diagnosis and must be administered by a qualified rater listed on Form 1572 with at least 2 years' experience with the population under study.

[f] Vital signs will include supine and standing measurements of blood pressure; and heart rate, respiratory rate, and oral body temperature.

[g] BMI will be calculated and recorded in the eCRF at the clinical site at Screening for other visits, BMI will be calculated during statistical analysis.

[h] Subjects must be fasted (no food or drink except water at least 8 hours prior to specified blood tests). Blood samples should be drawn in the morning followed by a snack or meal.
[i] Blood samples for follicle stimulating hormone (FSH) will be collected if menopause is suspected.
[j] Blood samples for determination of plasma SEP-363856 and SEP-363854 concentrations will be collected predose (prior to administration of the first dose) on Day 1; one postdose sample will be collected on Day 29. The time and date of the 3 previous doses of study drug, time, and date of sampling must be recorded. Time and date of food intake must be recorded on Day 29 when blood samples are collected for determination of SEP-363856 and SEP-363854 concentrations.
[k] If a subject is issued a day pass, an unscheduled urine drug screen will be performed upon returning to the site. Urine drug screen may be ordered at other visits as deemed clinically appropriate. These results should be discussed with the Medical Monitor.
[l] Any positive urine β-hCG test should be confirmed by a serum β-hCG test.
[m] Unscheduled BARS, AIMS, and SAS scales should be administered if a subject develops extrapyramidal symptoms (EPS) requiring treatment. See Section 10.3.
[n] Following the last contact with a subject, the duplicate enrollment system should be updated, as appropriate (US sites only).
Note: With the exception of SCID-CT and DEQ, all rating assessments will be performed by the rater using a tablet. In the event that a tablet is not available, the rating assessments will be performed by the rater using a paper version of the assessment.

3.3. Determination of Sample Size

A sample size of 100 subjects per treatment group (SEP-363856 and placebo) will provide 80% power to detect a treatment effect size of 0.4 in change from baseline in PANSS total score at Week 4 for SEP-363856 versus placebo, using a two independent sample t-test method with 2-sided significance level of 0.05. A clinically meaningful effect size of 0.4 was estimated based on review of published studies of other antipsychotics for the short-term treatment of schizophrenia. It is anticipated that 17% of all randomized subjects will discontinue early from the study. An upward adjustment of the sample size is thus used to compensate for missing data from subjects who are randomized and discontinue from the study. The total sample size will be 240 randomized subjects (or 120 subjects per treatment group).

3.4. Method of Assigning Subjects to Treatment Groups

The randomization schedule is based on permuted blocks and is generated by a non-study biostatistician.

Site dynamic block randomization is used to assign subjects to treatments. Subjects are randomized to treatment arms based on a block of randomization codes that have been assigned to the subject's site. When the first subject for a site is randomized, one entire block is bound to that site. The next subject randomized in that site will use the next randomization code in that bound block. A subject from another site will be randomized to a treatment group from the block of codes assigned to their site. A subject being randomized after a block is used up will cause another block to be bound to the site depending on how many blocks should be maintained at all times. Further details on treatment assignment are provided in the Randomization Specifications Document.

Once a subject is deemed eligible to be randomized at Day 1 (Visit 2), an IXRS (the Oracle Interactive Response Technology system) will perform treatment assignment. Subjects will be randomized to one of the following treatment groups in a 1:1 ratio and balanced within each clinical site:

- SEP-363856 (50 or 75 mg/day flexible dosing for 4 weeks)
- Placebo (once daily for 4 weeks)

Once a randomization number has been assigned, it cannot be reused.

3.5. Blinding

Subjects, Investigator staff, persons performing the assessments, clinical operations personnel, data analysts, and personnel at central laboratories (including imaging) will remain blind to the identity of the treatment from the time of randomization until database lock and unblinding, using the following methods; (1) randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the exception of bioanalytical personnel involved in the analysis of PK samples; (2) the identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration and appearance.

Actual subject identity for plasma concentrations of SEP-363856 and SEP-363854 will not be disclosed before the database lock and the unblinding of the double-blind treatment phase.

In the case of medical emergency, where knowledge of study drug by the Investigator or an authorized delegate is essential for immediate medical management, a 24-hour code-break service will be available via the IXRS. The date and reason for unblinding are to be documented in the source documents. Any subject for whom the treatment assignment was unblinded is to be discontinued from further study participation, other than the follow-up visit.

3.6. Changes in conduct of the study

The first subject entered the study under protocol version 2.00 (23 June 2016), following the implementation of Amendment 1.00 (23 June 2016) and non-substantial Amendments 1 (8 September 2016) and 2 (7 October 2016). The protocol versions and amendments listed below were implemented after the screening and randomization of the first subject.

- Protocol version 3.00 (22-Mar-2017); Amendment 2.00 (22-Mar-2017)
- Protocol version 3.01 (17-Aug-2017); Non-substantial Amendment 1.00 (17-Aug-2017)

3.7. Changes to Analysis from Protocol

- The protocol specified ANCOVA analysis on the Week 4 LOCF endpoint of Cogstate Brief Battery (CBB) composite score. This analysis will not be performed because a Week 4 LOCF endpoint will not be calculated for the CBB composite score. CBB is only scheduled to be measured at baseline and at Week 4.
- The protocol specified that the total score will be used as a summary measure of the subject's ratings on the Simpson-Angus Rating Scale (SAS). Rather than the total score, the mean score will be used, which is calculated as the average of the 10 item scores.
- The per protocol population definition is updated to exclude subjects who received benzodiazepines or hypnotics within 8 hours of the Visit 2 or Visit 7/ET PANSS assessment.

4. Planned Analyses

The following analyses will be performed for this study:

- Final analysis

4.1. DATA MONITORING COMMITTEE (DMC)

There will be no planned DMC for this study.

4.2. INTERIM ANALYSIS

No interim analysis is planned for this study.

4.3. FINAL ANALYSIS

The final, planned analysis identified in this SAP will be performed by QuintilesIMS Biostatistics following Sunovion authorization of this SAP, Sunovion authorization of analysis populations, database lock, and unblinding of treatment.

5. ANALYSIS POPULATIONS

Agreement and authorization of subjects included/excluded from each analysis population will be conducted prior to database lock and the unblinding of the study.

5.1. MODIFIED INTENT-TO-TREAT [MITT] POPULATION

The Modified Intent-to-Treat (mITT) population is defined as all subjects who were randomized, received at least one dose of study medication, and had a baseline and at least one post-baseline efficacy measurement in PANSS or CGI-S. Subjects will be included in the mITT population regardless of any protocol deviation.

The mITT population will be the primary population for the efficacy analyses. Subjects will be analyzed based on the treatment to which they are randomized.

5.2. PER PROTOCOL [PP] POPULATION

The per protocol (PP) population comprises all mITT subjects who:

- Received assigned study medication as randomized;
- Have 14 days or more overall exposure to study medication;
- Have 75%-125% compliance, both limit values inclusive;

- Did not receive benzodiazepines or hypnotics within 8 hours of the Visit 2 or Visit 7/ET PANSS assessment
- Have no important protocol deviations (IPDs), determined by blinded data reviews prior to database lock.

Subjects who received benzodiazepines or hypnotics within 8 hours of the Visit 2 or Visit 7/ET PANSS assessment will be identified by clinical review of the concomitant medications data, date and time of PANSS assessments, and the psychotropic medications within 8 hours of an efficacy assessment data.

Selected efficacy endpoints will be analyzed using the PP population. Subjects will be analyzed based on the treatment to which they are randomized.

5.3. SAFETY POPULATION

The safety population includes subjects who were randomized and received at least one dose of study medication.

Safety population will be the primary population for the safety analyses. Subjects will be analyzed based on the actual treatment received. This will generally be the same as the randomized treatment group, unless the subject takes incorrect therapy during the entire study.

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

Study day will be calculated from the reference start date, and will be used to show start/stop day of assessments and events.

Reference start date is defined as the date of the first dose of study medication (Day 1).

- If the date of the event is on or after the reference start date then:

o Study day = (date of event – reference start date) + 1.

- If the date of the event is prior to the reference start date then:

o Study day = (date of event – reference start date).

In the situation where the event date is partial or missing, study day, and any corresponding durations will appear missing in the listings. Partial dates will be however presented as is in the listings.

6.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to the first dose of study medication (including unscheduled assessments).

Whenever available, the time information should be accounted for in the derivation of baseline values. In the case where time isn't available and the date of last non-missing measurement and the date of first dose of study medication coincide, that measurement will be considered baseline.

6.3. DERIVED TIME POINTS

The last post-baseline measurement collected during the study will be carried forward and will be defined as the last observation carried forward (LOCF) endpoint, using the post-baseline value up to and including the Week 4 visit data.

The LOCF endpoint will be derived for the following outcome measures: PANSS total score, CGI-S score, PANSS subscale scores, PANSS five-factor model factor scores, PANSS seven-factor model factor scores, BNSS total score, BNSS subtotal score, MADRS total score, AIMS total score, AIMS global severity score (item 8), BARS total score, BARS individual item scores, SAS mean score, and the C-SSRS suicidal ideation score. In addition, the LOCF endpoint will be derived for vital signs, body weight, and BMI data.

Both scheduled and unscheduled assessments as well as the early termination assessments that are collected post baseline will contribute to the derivation of the LOCF endpoint.

6.4. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the scheduled visits will be presented.

Unscheduled measurements will not be included in by-visit summaries. Unscheduled measurements collected prior to the first dose of study medication will contribute to the derivation of the baseline value. Unscheduled measurements collected post baseline will contribute to the derivation of the LOCF endpoint value, potentially clinically significant (PCS) value, and best/ worst case value where required (e.g. shift tables).

Early termination data collected post baseline will be assigned to the next planned visit for that assessment. This mapping will be done for all data points used in the efficacy and safety analyses.

In the case of a retest (same visit number assigned), the latest available measurement for that visit will be used for by-visit summaries.

Listings will include scheduled, unscheduled, retest and early termination data.

6.5. WINDOWING CONVENTIONS

All data will be analyzed according to the schedule outlined in the CSP and according to the visit denoted on the case report form (CRF). No visit windowing will be performed during the analysis for this study.

6.6. STATISTICAL TESTS

All statistical inference, unless otherwise stated, will be performed with two-sided tests at the significance level of 0.05, and two-sided 95% confidence intervals (CIs) will be calculated whenever appropriate.

6.7. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

- Value at visit X – baseline value

Percentage change from baseline in PANSS total score will be calculated as:

- (Value at visit X – baseline value)*100 / (baseline value – 30)

6.8. SOFTWARE VERSION

All data analyses will be conducted using SAS version 9.4 or later.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES TO BE INCLUDED IN ANALYSES

The following covariates are used in the analyses. For details of their inclusion in the models, see specific analysis sections.

- Pooled study center
- Baseline value of the variable to be analyzed

7.2. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple sites in 5 countries.

When specified, statistical analyses will be adjusted for pooled study centers. Centers will be pooled by country.

7.3. MISSING DATA

Missing efficacy data will be handled as described in section 16.1.2 of this statistical analysis plan.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

There is only one primary efficacy comparison of change from baseline in PANSS total score at Week 4. Therefore no adjustment for multiplicity is planned in this study. For all other analyses, nominal p-values will be presented; no multiplicity adjustment will be performed.

7.5. EXAMINATION OF SUBGROUPS

Subgroup analyses will be conducted as stated in the respective efficacy and safety analysis sections. It should be noted that the study was not powered to detect treatment differences within subgroups.

The following subgroups will be assessed:

- Geographic region

o US
o Non-US

- Country

o US
o Hungary
o Romania
o Russia
o Ukraine

- Sex

o Female
o Male

- Age group (years)

o <25
o >=25

- Race

- White
- Black
- Other

- Number of prior hospitalizations for treatment of schizophrenia

- 0
- 1
- 2

- Duration of schizophrenia (years)

- < 5
- >= 5

8. OUTPUT PRESENTATIONS

APPENDIX 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by QuintilesIMS Biostatistics.

9. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study.

Subject disposition will be summarized by the randomized treatment group (where applicable) and overall for all subjects. The number and percentage of subjects who were screened, screen-failed, randomized, received study medication, and completed or discontinued early from the double-blind treatment phase (including reasons for discontinuation) will be presented. In addition, the number and percentage of subjects who will rollover to the open-label extension study (SEP361-202) in each treatment group and overall will be presented.

With respect to the above, the following definitions apply:

- Screened Subjects: All subjects who provided informed consent for this study.
- Enrolled Subjects: Screened subjects who passed screening.
- Randomized Subjects: Enrolled subjects who were randomized to study treatments.

10. IMPORTANT PROTOCOL DEVIATIONS

Important protocol deviations (IPDs) will be identified and documented based on blinded reviews of data listings. The IPD categories may include, but may not be limited to:

- Did not satisfy important inclusion, exclusion, and/or randomization criteria
- Received any disallowed concomitant medication
- Overall double-blind compliance rate < 75% or > 125%

Further details on the identification of IPDs are provided in the Important Protocol Deviation Review Specifications document.

IPDs will be identified for all randomized subjects and presented in data listings. The number and percentage of subjects within each IPD category will be summarized for the mITT population.

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the mITT population, safety population, and PP population. For mITT population and PP population, the data will be presented by randomized treatment groups. For safety population, the data will be presented by the actual treatments received. Demographic data will also be summarized for all screened subjects by randomization status (i.e. randomized vs. not randomized). No statistical testing will be carried out for demographic or other baseline characteristics. The following demographic and other baseline characteristics will be reported for this study:

- Age (years), calculated relative to date of informed consent; as a continuous variable and categorically

o <18
o 18 to <25
o 25 to <=40
o >40

- Sex

- Race

o American Indian or Alaska Native
o Asian
o Black or African American
o Native Hawaiian or Other Pacific Islander
o White
o Multiracial
o Other

- Ethnicity

o Hispanic or Latino
o Not Hispanic or Latino

- Country

- Geographic region
- Weight (kg)
- Height (cm)
- Waist circumference (cm)
- BMI (kg/m^2), as a continuous variable and categorically:

o Underweight: <18.5
o Normal: 18.5 to <25.0
o Overweight: 25.0 to <30.0
o Obese: >=30.0

- Baseline PANSS total score and subscale scores, as continuous variables and categorically:

o < Overall median value at baseline
o >= Overall median value at baseline
o Positive subscale score < Negative Subscale score
o Positive subscale score >= Negative Subscale score

- Baseline CGI-S score, as a continuous variable and categorically:

o < 4
o >= 4 to <= 5
o > 5

The following psychiatric history data will be summarized for the mITT population, safety population, and PP population in a separate table:

- Time since initial onset of schizophrenia, in years, calculated relative to date of informed consent; both as a continuous variable and categorically

o < 5
o >= 5 to < 10
o >= 10 to < 20
o >= 20

- Time since onset of current acute exacerbation of psychotic symptoms, in days, calculated relative to date of informed consent
- DSM-5 schizophrenia subtype diagnosis
- Other current psychiatric diagnoses
- Number (0, 1, 2, 3 or more) of prior hospitalizations for treatment of an acute exacerbation of schizophrenia

11.1. DERIVATIONS

- BMI (kg/m^2) = weight (kg)/ height $(m)^2$

12. MEDICAL AND SURGICAL HISTORY

Medical and surgical history information, including both past and concomitant medical conditions and major surgical history, as collected on the Medical History CRF form, will be coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 18.1 or higher, and presented for the safety population by System Organ Class (SOC) and Preferred Term (PT).

13. MEDICATIONS

Medications will be presented for the safety population and coded using the WHO drug dictionary, Version 01MAR2016E or higher.

Whenever available, the time information should be accounted for in the derivation of prior, concomitant, and post-treatment medications. See APPENDIX 2 for the handling of partial dates for medications. In the case where it is not possible to define a medication as prior, concomitant, or post-treatment, the medication will be classified by the worst case; i.e. concomitant.

- Prior medications are medications which stopped prior to the first dose of study medication.
- Concomitant medications are medications which started at the same time of or after the first dose of study medication and at the same time of or before the last dose of study medication; or started prior to and ended at the same time of or after the first dose of study medication; or started at the same time of or prior to the last dose of study medication and marked as ongoing.
- Post-treatment medications are medications which started after the last dose of study medication.

Prior and concomitant medication use will be summarized by Anatomical Therapeutic Chemical (ATC) Level 3 classification and preferred name using frequencies and percentages. Prior, concomitant, and post-treatment medications will be provided in data listings.

14. STUDY MEDICATION EXPOSURE

Duration of exposure to study medication will be summarized for the safety population.

Duration of exposure (in days) will be summarized both as a continuous variable for the double-blind treatment period and categorically:

- Number and percentage of subjects with drug exposure ≥ 1, ≥ 3, ≥ 7, ≥ 14, ≥ 21, and ≥ 28 days;

- Number and percentage of subjects with drug exposure for 1 - 2, 3 - 6, 7 - 13, 14 - 20, 21 - 27, and ≥ 28 days

The modal daily dose (i.e. the dose level that a subject was on for the most number of days during the study) will be summarized categorically by treatment group:

- 50 mg/day
- 75 mg/day
- Tie

The number of days that a subject was on the 50 mg/day dose level and on the 75 mg/day dose level will also be summarized, both as a continuous variable and categorically:

- 1 – 2 days
- 3 – 6 days
- 7 – 13 days
- 14 – 20 days
- 21 – 27 days
- ≥ 28 days

The dose adjustment decision at each visit will be summarized in a shift table.

14.1. DERIVATIONS

Duration of exposure (days) = last dose date - first dose date + 1.

15. STUDY MEDICATION COMPLIANCE

Compliance to study medication will be summarized for the safety population.

Percent compliance will be calculated by visit and overall for the double-blind treatment period. Non-compliance is defined as less than 75% or more than 125% non-missing compliance for the double-blind period. Subjects with missing compliance will not be classified as non-compliant. Compliance will be summarized both as a continuous variable and categorically:

- Number and percentage of subjects with compliance < 75%, 75% - 125%, > 125%, and missing

15.1. DERIVATIONS

Compliance with study medication will both be calculated for each period defined by study visits (i.e. per-visit compliance) and overall.

Per-visit compliance for the period defined by visit (V-1) and visit V will be calculated as:

$$\frac{\text{\# Capsules dispensed at Visit (V-1) - \# Capsules returned at Visit V - \# Capsules reported lost during this period}}{\text{\# Capsules should be taken per day} \times (\text{Date of Visit V - Date of Visit (V-1)})} \times 100\%$$

If any of the following numbers are missing, per-visit compliance will not be calculated for the period impacted: number capsules dispensed at Visit (V-1), number capsules returned at Visit V, and number capsules reported lost during this period.

If a subject discontinued from the study in between Visit (V-1) and Visit V, then the above formula will be modified to:

$$\frac{\text{\# Capsules dispensed at Visit (V-1) - \# Capsules returned at Visit ET - \# Capsules reported lost during this period}}{\text{\# Capsules should be taken per day} \times (\text{Date of Visit ET - Date of Visit (V-1)})} \times 100\%$$

The per-visit compliance calculated above will contribute to the summary of per-visit compliance for the period defined by visit (V-1) and visit V.

Overall compliance will be calculated as:

$$\frac{\text{Total \# capsules dispensed - Total \# capsules returned - Total \# capsules reported lost}}{\text{\# Capsules should be taken per day} \times \text{Duration of Exposure}} \times 100\%$$

Duration of exposure is calculated as specified in section 14.1.

If any of the following numbers are missing at one or more visits, overall compliance will not be calculated: number capsules dispensed, number capsules returned, number capsules reported lost.

For subjects whose Visit 2 and Visit 3 drug accountability records are folded into one record, the by-visit compliance will be set to missing for these 2 visits.

16. EFFICACY OUTCOMES

In addition to the analyses described in sections 16.1, 16.2 and 16.3, all efficacy variables will be summarized descriptively by treatment group and visit for the mITT population. For PANSS total score and CGI-S score, the data will also be summarized descriptively for each subgroup.

16.1. PRIMARY EFFICACY

The analyses of the primary efficacy variable will be performed on the mITT population, unless otherwise specified.

16.1.1. PRIMARY EFFICACY VARIABLE & DERIVATION

The primary efficacy variable is the change from baseline in PANSS total score at Week 4.

PANSS is used to measure the psychopathology in adults with psychotic disorders, comprising 30 items and 3 subscales. The positive subscale assesses hallucinations, delusions and related symptoms (7 items), the negative subscale assesses emotional withdrawal, lack of motivation and related symptoms (7 items), and the general psychopathology subscale assesses other symptoms such as anxiety, somatic

concern and disorientation (16 items). An anchored Likert scale from 1 to 7 (1 = absent, 7 = extreme, with values of 2 and above indicating the presence of progressively more severe symptoms) is used to score each item. Individual items are summed to derive the following scores:

- Total score = sum of all 30 items. Total score ranges from 30 to 210.
- Subscale scores = sum of items within each of the following subscales:
  - Positive subscale: delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, hostility. This subscale score ranges from 7 to 49.
  - Negative subscale: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking. This subscale score ranges from 7 to 49.
  - General psychopathology subscale: somatic concern, anxiety, guilt feelings, tensions, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, active social avoidance. This subscale score ranges from 16 to 112.
- Five-factor model scores – sum of items within each of the following factors (Marder, Davis, Chouinard. 1997):
  - Negative symptoms: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, lack of spontaneity and flow of conversation, motor retardation, active social avoidance
  - Positive symptoms: delusions, hallucinatory behavior, grandiosity, suspiciousness/persecution, stereotyped thinking, somatic concern, unusual thought content, lack of judgment and insight
  - Disorganized thought: conceptual disorganization, difficulty in abstract thinking, mannerisms and posturing, poor attention, disturbance of volition, preoccupation, disorientation
  - Uncontrolled hostility/excitement: excitement, hostility, uncooperativeness, poor impulse control
  - Anxiety/depression: anxiety, guilt feelings, tension, depression
- Seven-factor model scores

The PANSS item scores of each subject at each visit will be transformed using the uncorrelated PANSS score matrix (UPSM), to obtain the scores of 7 transformed PANSS factors (Hopkins et al. 2018):

- POS: Positive
- DIS: Disorganized
- NAA: Negative apathy/avolition
- NDE: Negative deficit of expression
- HOS: Hostility
- ANX: Anxiety
- DEP: Depression

The transformation will be done as follows:

$$[\text{PANSS Data}]_{(N\times 30)} * [\text{UPSM}]_{(30\times 7)} = [\text{Transformed PANSS Factor Data}]_{(N\times 7)}$$

where

$[\text{PANSS Data}]_{(N\times 30)}$ is a matrix with N PANSS assessments and 30 columns containing the scores of 30 PANSS items ordered in the same way as shown in UPSM.

$[\text{UPSM}]_{(30\times 7)}$ is a matrix with 30 rows (one for each PANSS item) and 7 columns (one for each of the 7 transformed PANSS factors)

$[\text{Transformed PANSS Factor Data}]_{(N\times 7)}$ is the transformed matrix with N sets of scores for the 7 transformed PANSS factors

Table 2. Uncorrelated PANSS Score Matrix (UPSM) for Generating Transformed PANSS Factor Scores

PANSS	POS	DIS	NEG	HOS	DEP/ ANX	POS	DIS	NAA	NDE	HOS	ANX	DEP	ITEM
PANSS01	1	0	0	0	0	0.579	-0.155	-0.083	0.007	-0.059	-0.074	0.002	P01 DELUSIONS
PANSS06	1	0	0	0	0	0.354	-0.063	0.048	0.001	0.019	-0.016	0.006	P06 SUSPICIOUSNESS/PERSECUTION
PANSS03	1	0	0	0	0	0.207	-0.018	-0.025	-0.013	-0.030	0.000	0.029	P03 HALLUCINATORY BEHAVIOR
PANSS23	1	0	0	0	0	0.143	0.094	-0.033	-0.037	-0.068	-0.021	-0.018	G09 UNUSUAL THOUGHT CONTENT
PANSS26	1	0	0	0	0	0.014	0.155	-0.031	-0.033	0.026	-0.058	-0.063	G12 LACK OF JUDGEMENT AND INSIGHT
PANSS14	1	0	0	0	0	-0.011	0.146	-0.028	0.002	-0.006	-0.012	0.004	N07 STEREOTYPED THINKING
PANSS05	1	0	0	0	0	-0.034	-0.030	-0.004	-0.023	-0.007	-0.031	0.031	P05 GRANDIOSITY
PANSS15	1	0	0	0	0	-0.036	0.055	-0.038	0.011	-0.031	0.044	0.106	G01 SOMATIC CONCERN
PANSS29	0	1	0	0	0	-0.052	0.291	0.003	-0.032	-0.044	-0.005	0.057	G15 PREOCCUPATION
PANSS25	0	1	0	0	0	-0.104	0.281	-0.048	0.003	0.004	-0.023	0.040	G11 POOR ATTENTION
PANSS02	0	1	0	0	0	0.029	0.198	-0.026	-0.023	-0.037	-0.001	-0.036	P02 CONCEPTUAL DISORGANIZATION
PANSS27	0	1	0	0	0	-0.057	0.187	-0.014	0.058	-0.015	-0.037	0.046	G13 DISTURBANCE OF VOLITION
PANSS12	0	1	0	0	0	0.004	0.106	0.026	-0.030	-0.013	0.010	-0.069	N05 DIFFICULTY IN ABSTRACT THINKING
PANSS19	0	1	0	0	0	-0.046	0.049	-0.032	0.103	-0.014	0.029	-0.044	G05 MANNERISMS AND POSTURING
PANSS24	0	1	0	0	0	-0.038	-0.032	-0.026	-0.018	-0.027	-0.021	-0.018	G10 DISORIENTATION
PANSS11	0	0	1	0	0	-0.094	-0.086	0.461	-0.029	-0.019	-0.019	-0.013	N04 PASSIVE/APATHETIC SOCIAL WITHDRAWAL
PANSS09	0	0	1	0	0	-0.032	-0.024	0.332	-0.023	-0.051	-0.015	0.011	N02 EMOTIONAL WITHDRAWAL
PANSS30	0	0	1	0	0	-0.011	-0.001	0.286	-0.061	0.018	-0.030	0.037	G16 ACTIVE SOCIAL AVOIDANCE
PANSS21	0	0	1	0	0	-0.035	-0.037	-0.078	0.441	-0.007	-0.019	0.046	G07 MOTOR RETARDATION
PANSS13	0	0	1	0	0	0.004	0.005	0.001	0.258	-0.009	0.019	-0.104	N06 LACK OF SPONTANEITY AND FLOW OF CONVERSATION
PANSS08	0	0	1	0	0	-0.005	-0.029	0.057	0.247	-0.039	0.019	-0.009	N01 BLUNTED AFFECT
PANSS10	0	0	1	0	0	-0.074	-0.040	-0.010	0.016	0.025	-0.018	-0.017	N03 POOR RAPPORT
PANSS07	0	0	0	1	0	-0.038	-0.177	-0.030	0.031	0.503	-0.100	0.057	P07 HOSTILITY
PANSS22	0	0	0	1	0	-0.080	0.033	-0.009	-0.020	0.286	-0.057	-0.053	G08 UNCOOPERATIVENESS
PANSS28	0	0	0	1	0	-0.075	0.017	-0.027	-0.003	0.255	-0.020	-0.008	G14 POOR IMPULSE CONTROL
PANSS04	0	0	0	1	0	-0.034	0.012	0.001	-0.072	0.138	0.111	-0.105	P04 EXCITEMENT
PANSS18	0	0	0	0	1	-0.093	-0.033	-0.013	0.023	-0.029	0.512	-0.031	G04 TENSION
PANSS16	0	0	0	0	1	-0.033	-0.082	-0.033	-0.053	-0.039	0.458	0.120	G02 ANXIETY
PANSS20	0	0	0	0	1	-0.034	-0.069	-0.041	0.038	0.004	-0.064	0.451	G06 DEPRESSION
PANSS17	0	0	0	0	1	-0.037	0.000	-0.002	-0.041	-0.027	-0.025	0.246	G03 GUILT FEELINGS

The coefficients of UPSM (a matrix of 30 rows of PANSS items × 7 columns of transformed PANSS factors) will be used to transform individual PANSS assessments (items scores at each visit) to reduce the 30 items into 7 factors for each PANSS assessment. Each column of the score matrix (POS, DIS, NAA, NDE, HOS, ANX, DEP) represents a transformed PANSS factor.

For the above total, subscale, or factor scores, if any item contributing to its calculation is missing then the score will be set to missing.

16.1.2. Missing Data Methods for Primary Efficacy Variable

The PANSS total score will be set to missing if any one item is missing. The primary efficacy variable, change from baseline in PANSS total score at Week 4, will be set to missing if PANSS total score at Week 4 is missing. The same applies to all other visits.

The primary analysis of the primary efficacy variable will use a mixed model for repeated measures (MMRM) based on observed data (with early termination data mapped as described in section 6.4). Missing data will not be imputed.

The ANCOVA analysis of the primary efficacy variable will utilize the Week 4 LOCF endpoint, which is imputed as described in section 6.3.

16.1.3. Primary Analysis of Primary Efficacy Variable

The primary objective of this study is to test whether the mean changes from baseline in PANSS total score at Week 4 in the SEP-363856 (50 or 75 mg/day) group and the placebo group are equal.

Let μ_{SEP} and μ_{PBO} represent the mean changes from baseline at Week 4 in PANSS total score for the SEP-363856 (50 or 75 mg/day) and placebo groups, respectively. The following hypothesis will be tested:

H_0: $\mu_{SEP} = \mu_{PBO}$ versus H_1: $\mu_{SEP} \neq \mu_{PBO}$

The primary efficacy analysis will be performed on the mITT population.

Change from baseline in PANSS total score at Week 4 will be analyzed using an MMRM model, with fixed factors for pooled study center, visit (Day 4, Weeks 1, 2, 3, and 4; as a categorical variable), treatment, and treatment-by-visit interaction, and with baseline PANSS total score as a covariate. An unstructured covariance matrix will be used to model the within-subject correlation. The Kenward-Roger approximation will be used to calculate the denominator degrees of freedom. Pooled centers will be generated by country.

In case the model above fails to converge, a spatial exponential covariance structure and a spatial power covariance structure will be assumed sequentially. The first covariance structure to yield convergence will be used in the analysis.

Within group effect size at each time point will be calculated as the least squares (LS) mean of each treatment group divided by the model estimate of standard deviation, obtained as the square root of the corresponding diagonal element of the residual covariance matrix (R matrix from PROC MIXED). Between group effect size at each time point will be calculated as the LS mean difference divided by the model estimate of standard deviation, obtained as described above.

16.1.4. SENSITIVITY ANALYSIS OF PRIMARY EFFICACY VARIABLE

16.1.4.1. Graphical examination

Patterns of missing data in the primary endpoint will be assessed through graphical tools based on the reason and timing of study withdrawal by subjects.

Graphs of change from baseline in PANSS total score by visit will be plotted by reasons of early discontinuation (adverse event, lack of efficacy, progressive disease, withdrawal by subject, protocol deviation, noncompliance with study medication, death, pregnancy, other reasons) and for completers, separately for each treatment group. Similar reasons may be combined, depending on the number of subjects under each reason.

Graphs of change from baseline in PANSS total score by visit will also be plotted by time of termination (Day 4 terminators, Week 1 terminators, Week 2 terminators, Week 3 terminators, Week 4 terminators) and for completers, separately for each treatment group.

- Day 4 terminators: subjects who discontinued before or on Visit 3.
- Week 1 terminators: subjects who discontinued after Visit 3 but before or on Visit 4
- Week 2 terminators: subjects who discontinued after Visit 4 but before or on Visit 5.
- Week 3 terminators: subjects who discontinued after Visit 5 but before or on Visit 6.
- Week 4 terminators: subjects who discontinued after Visit 6 but before Visit 7.

16.1.4.2. Pattern-mixture model with placebo-based multiple imputation

The MMRM model used in the primary analysis makes the assumption that data are missing at random (MAR). However the missing data mechanism may or may not be at random. Sensitivity to the missing data assumptions will be tested by using the pattern-mixture model with placebo-based multiple imputation method (Ratitch, O'Kelly, Tosiello. 2013), exploring the robustness of the MMRM results of the primary efficacy analysis. In this analysis, missing values in the SEP-363856 (50 or 75 mg/day) treatment group will be imputed based on data of the placebo group, assuming that, after withdrawal, subjects from the SEP-363856 (50 or 75 mg/day) group will exhibit the same future evolution of schizophrenia as subjects from the placebo group, and that subjects who discontinue from the placebo group will exhibit the same future evolution of schizophrenia as subjects in the placebo group remaining in the study. This approach does not assume a sustained benefit of experimental treatment after discontinuation.

Two separate imputation procedures are used to impute missing values. Firstly, the Markov chain Monte Carlo (MCMC) method is used to perform partial imputation to obtain datasets with monotone missing patterns. Then a sequential regression multiple imputation method is used to impute the monotone missing values.

Under the assumption that the PANSS total scores have a multivariate normal distribution, the MCMC method is used to impute only intermittent missing values (using the SAS MI procedure with MCMC statement), by using a data augmentation algorithm, with each iteration n consisting of an imputation step and a posterior step. The imputation step uses a random draw of $\theta^{(n)}$, parameter of the joint imputation model, to sample missing values from a conditional distribution $P(Y_{mis}|x, y_{obs}, \theta^{(n)})$, obtaining $y_{mis}^{(n)}$, the subset of missing values that need to be filled in to achieve monotone missingness. The posterior step simulates a new draw of the parameter $\theta^{(n+1)}$ from the posterior distribution given the current monotone missing data $P(\theta|x, y_{obs}, y_{mis}^{(n)})$ with a non-informative Jeffreys prior. These steps are repeated to obtain 500 datasets with monotone missingness. The random seed number is specified in the sample code.

The remaining monotone missing data will be imputed using sequential regression multiple imputation, where a separate regression model is estimated for imputation of each variable (i.e., PANSS total score at each time point). Imputation of values in the placebo group will assume MAR. Imputation of values in the SEP-363856 (50 or 75 mg/day) group will be done as if the subject had been a member of the placebo group. Missing values in the SEP-363856 (50 or 75 mg/day) group will be imputed using the imputation model of the placebo group, i.e., conditional on subject values observed at time points prior to discontinuation relative to the mean of the model for the placebo group. Each sequential regression model (i.e., for imputation of values at a given time point) will include explanatory variables for pooled study center and all previous (Baseline, Day 4, Week 1, 2, and 3) values of PANSS total score. Missing values at a given time point in placebo and SEP-363856 (50 or 75 mg/day) arms will be imputed from the same imputation model, conditional on subject values observed or imputed at previous time points. The SAS MI procedure with the MONOTONE REG statement is used to specify that the regression method will be used for the imputation. The random seed numbers are specified in the sample code.

No rounding restriction will be applied to imputed PANSS total scores. The imputed PANSS total scores must be within the range of 30 to 210.

Each of the 500 imputed datasets will be analyzed using the same MMRM model as the primary efficacy analysis. Results from the analysis of each imputed dataset, i.e. the LS means of each treatment group, the LS mean treatment difference, and their standard errors, will be combined using Rubin's imputation rules (using the SAS MIANALYZE procedure) to produce pooled LS mean estimates, their standard errors and 95% CI, and a pooled p-value for the test of null hypothesis of no treatment effect.

16.1.4.3. Tipping point analysis

Sensitivity to departures from the MAR assumption will also be investigated using a tipping point analysis. In this analysis, departures from MAR in the SEP-363856 (50 or 75 mg/day) group will be assessed assuming that subjects who discontinue the study have, on average, efficacy outcomes after discontinuation that are worse by some amount δ compared to other similar subjects with observed data at the same time point (i.e., compared to a value which would have been assumed under a MAR model).

A series of analyses will be performed with increasing values of δ until the analysis conclusion of a statistically significant treatment effect no longer holds. The value of δ that overturns the primary results will represent a tipping point. An interpretation of clinical plausibility of the assumption underlying the tipping point will be provided.

Change from baseline in PANSS total score will be analyzed based on data observed while the subject remains on study as well as data imputed using multiple imputation methodology for the time points at which no value is observed. Intermittent (non-monotone) missing data will be imputed first based on the MAR assumption and a multivariate joint Gaussian imputation model using the MCMC method within each treatment arm, as described above for the pattern-mixture model with placebo-based multiple imputation.

The remaining monotone missing data will be imputed using sequential regression multiple imputation, where a separate regression model is estimated for imputation of each variable (i.e., PANSS total score at each time point). Each regression model will include explanatory variables for treatment, pooled study center and all previous (Baseline, Day 4, Week 1, 2, and 3) values of PANSS total score. After the MAR-based imputations have been generated for PANSS total score at each time point, the change from baseline values based on the imputed PANSS total scores in the SEP-363856 (50 or 75 mg/day) group will be penalized by a value of δ. This approach assumes that the marginal mean of unobserved subject measurements is worse by δ at each time point after discontinuation compared to the marginal mean of subjects with observed data at the same

time point.

No rounding restriction will be applied to imputed continuous values. The imputed PANSS total scores must be within the range of 30 to 210.

Five hundred (500) imputed datasets will be generated. The random seed numbers for the partial imputation step and the sequential regression imputation step are specified in the sample code.

Each of the 500 imputed and δ-adjusted datasets will be analyzed using the same MMRM model as the primary efficacy analysis. Results from the analysis of each imputed dataset, i.e. the LS mean treatment difference and its standard error, will be combined using Rubin's imputation rules (using the SAS MIANALYZE procedure) to produce a pooled LS mean estimate of treatment difference, its standard error and 95% CI, and a pooled p-value for the test of null hypothesis of no treatment effect.

Analyses will be conducted with different values of δ at each visit, which represents a percentage of the LS mean treatment difference at that visit, starting at 10% with 10% increments, until either the tipping point is identified or the 100% penalty is applied.

16.1.4.4. Analysis of covariance

As another supportive analysis of the primary efficacy analysis, an analysis of covariance (ANCOVA) will be performed on the change from baseline in PANSS total score at each scheduled post-baseline visit and the Week 4 LOCF endpoint, with treatment and pooled study center as categorical factors, and baseline PANSS total score as a covariate. Between-group difference for baseline PANSS total score will be based on an ANCOVA model adjusting for pooled center.

Within group effect size will be calculated as the least squares (LS) mean of each treatment group divided by the standard deviation, obtained as the standard error of the LS mean multiplied by the square root of the treatment group sample size. Between group effect size will be calculated as the LS mean difference divided by the pooled standard deviation, obtained as the standard error of the LS mean difference divided by the square root of the sum of inverse treatment group sample sizes.

16.1.4.5. Complete case analysis

The complete case analysis will be performed on the subset of subjects in the mITT population who completed the double-blind treatment period and have Week 4 PANSS total score data available.

The MMRM analysis used in the primary efficacy analysis will be repeated on the above subjects.

16.1.4.6. Analysis on the per protocol population

Sensitivity to the analysis population will be tested by repeating the MMRM analysis used in the primary efficacy analysis on the PP population.

16.1.5. SUBGROUP ANALYSIS OF PRIMARY EFFICACY VARIABLE

For each of the subgroup factors listed in section 7.5, change from baseline in PANSS total score will be analyzed using the MMRM method. For the subgroup factors other than country, the MMRM model will include fixed effects for treatment, subgroup, visit, pooled center, baseline PANSS total score, and treatment-by-subgroup, treatment-by-visit, subgroup-by-visit, and treatment-by-subgroup-by-visit interactions. For the

subgroup factor of geographic region, the pooled centers will be nested within region.

For the subgroup factor of country, the MMRM model will include fixed effects for treatment, country, visit, baseline PANSS total score, and treatment-by-country, treatment-by-visit, country-by-visit, and treatment-by-country-by-visit interactions.

The estimates obtained from the MMRM models will be presented separately for each subgroup. The p-value for the treatment-by-subgroup interaction at Week 4 will be presented. Its statistical significance will be assessed at the 0.10 level for homogeneity of the treatment effect across the different categories of a subgroup factor. In case a significant interaction effect is detected, estimates by subgroup will be examined to determine the nature of the interaction (qualitative or quantitative).

16.2. SECONDARY EFFICACY

The analyses of the secondary efficacy variables will be performed on the mITT population.

16.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

16.2.1.1. Change from baseline in CGI-S score at Week 4

The CGI-S is a clinician-rated assessment of the subject's current illness state on a 7-point scale, where a higher score is associated with a greater illness severity. The CGI-S score takes one of the following values: 1 (normal, not at all ill), 2 (borderline mentally ill), 3 (mildly ill), 4 (moderately ill), 5 (markedly ill), 6 (severely ill), 7 (among the most extremely ill patients).

16.2.1.2. Change from baseline in PANSS subscale scores at Week 4

See section 16.1.1 for the derivation of PANSS subscale scores.

16.2.1.3. Change from baseline in PANSS five-factor model scores at Week 4

See section 16.1.1 for the derivation of PANSS five-factor model scores.

16.2.1.4. Change from baseline in PANSS seven-factor model scores at Week 4

See section 16.1.1 for the derivation of PANSS seven-factor model scores.

16.2.1.5. Change from baseline in MADRS total score at Week 4

The MADRS is a clinician-rated assessment of the subject's level of depression. The measure contains 10 items that measure apparent and reported sadness, inner tension, reduced sleep and appetite, difficulty concentrating, lassitude, inability to feel, and pessimistic and suicidal thoughts. Each item is scored in a range of 0 to 6 points, with higher scores indicating increased depressive symptoms. MADRS total score will be calculated by the sum of all 10 item scores.

16.2.1.6. Change from baseline in BNSS total scores at Week 4

The BNSS is a rating scale to measure the current level of severity of negative symptoms in schizophrenia and schizoaffective disorder. The measure is comprised of 13 individual items organized in 6 subscales (blunted affect (items 9, 10, 11), alogia (items 12, 13), avolition (items 7, 8), anhedonia (items 1, 2, 3), asociality (items 5, 6), and distress (item 4)). The 13 individual items provide a composite total score (ranging from 0 to 78). Each of the items are scored on a Likert-type 7-point scale from 0 - 6, where values of 0 indicates symptom is absent and a value of 6 means the symptom is a severe form. In addition BNSS subscale scores will be calculated by summing the item scores under each subscale.

16.2.1.7. Proportion of subjects who achieve a PANSS response

PANSS response is defined as having at least 20% improvement in PANSS total score from baseline to the Week 4 LOCF endpoint. See section 16.1.1 for the derivation of PANSS total score. The percent change in PANSS total score from baseline will be calculated by:

$$\frac{\text{PANSS total score at the Week 4 LOCF endpoint - PANSS total score at baseline}}{\text{PANSS total score at baseline - 30}} \times 100\%$$

For each subject, the responder indicator will be set to 1 if the percent change as calculated above is <= -20%. The indicator will be set to 0 if the percentage is > -20%. The indicator will be set to missing if the percentage is missing.

PANSS response rate will also be calculated for each scheduled visit (i.e. Day 4, Week 1, Week 2, Week 3, and Week 4) using a similar method as above.

16.2.2. Missing Data Methods for Secondary Efficacy Variable(s)

For rating scales with more than one item, such as PANSS subscales, PANSS five-factor model, PANSS seven-factor model, BNSS, and MADRS, if any item score contributing to the total/ subscale/ factor score is missing, then the total/ subscale/ factor score will be set to missing. The change from baseline scores will also be set to missing accordingly. In addition, for BNSS, if any individual item is given a score of “9” (i.e. not rated), the BNSS total score and subscale score will be set to missing.

The MMRM analysis of the continuous secondary efficacy variables will be based on observed data (with early termination data mapped as described in section 6.4). Missing data will not be imputed. PANSS responder calculation will be based on the PANSS total score at the Week 4 LOCF endpoint. The ANCOVA analyses of the continuous secondary efficacy variables will utilize the change from baseline at the Week 4 LOCF endpoints.

16.2.3. Analysis of Secondary Efficacy Variables

16.2.3.1. Analysis of change from baseline in CGI-S score at Week 4

Change from baseline in CGI-S score at Week 4 will be analyzed using an MMRM model similar to the model used in the primary analysis of the primary efficacy variable (see section 16.1.3), with baseline CGI-S score as a covariate.

Sensitivity analyses of this variable will be performed similarly to those outlined in section 16.1.4. For CGI-S,

the complete case analysis will be performed on the subset of subjects in the mITT population who completed the double-blind treatment period and have Week 4 CGI-S score data available.

Subgroup analysis of this variable will be performed similarly to those described in section 16.1.5.

16.2.3.2. Analysis of other continuous secondary efficacy variables

The secondary efficacy variables of change from baseline at Week 4 in PANSS subscale scores, factor scores of the PANSS five-factor model, factor scores of the PANSS seven-factor model, BNSS total score, and MADRS total score will be analyzed using MMRM similarly to the primary analysis of the primary efficacy variable (see section 16.1.3), with the respective baseline scores as a covariate.

In addition, ANCOVA analysis on the change from baseline scores will be performed, similarly to the ANCOVA analysis described in section 16.1.4.4.

A sensitivity analysis for BNSS will be performed where a BNSS subtotal score will be calculated by summing the scores of items 1-6 and 8-13. Item 7 (Avolition: Behavior) is excluded due to a large number of subjects being given a score of '9' for this item when '9' is not a valid rating. Among the 12 items contributing to BNSS subtotal score, if any item is rated as '9', the subtotal score will be set to missing. The same analyses performed on BNSS total score will be repeated on BNSS subtotal score.

16.2.3.3. Analysis of PANSS responders

The secondary efficacy variable of PANSS response will be analyzed using logistic regression with geographic region and treatment as categorical factors, and baseline PANSS total score as a covariate. The analysis will be performed for the Week 4 LOCF endpoint as well as for each of the scheduled visits.

Odds ratio and its 95% CI as estimated by the model will be presented. In addition, the number-needed-to-treat (NNT) will be calculated for the SEP-363856 (50 or 75 mg/day) group as:

$$\text{NNT} = \frac{1}{\text{Absolute Risk Reduction}} = \frac{1}{\text{PANSS Response Rate}_{\text{SEP-363856}} - \text{PANSS Response Rate}_{\text{Placebo}}}$$

The 95% CI of NNT will be obtained by taking the reciprocal of the 95% CI bounds of the Absolute Risk Reduction when both lower and upper confidence limits are positive. The NNT and its 95% CI will be provided as integers; any fractional values will be rounded up to the nearest integer (the lower confidence limit will be rounded down and the upper confidence limit will be rounded up).

16.2.3.4. Subjects with given PANSS percent changes from baseline

The proportion of subjects achieving a given PANSS percent change from baseline or lower at the Week 4 LOCF endpoint will be calculated for each treatment group. This calculation will be performed at multiple levels of percent change from baseline, from -100% to >=100%, with 5% increments. The results will be reported in a graph with the percent change from baseline threshold on the x-axis and proportion of subjects in each treatment group on the y-axis.

16.3. EXPLORATORY EFFICACY

Analyses of the exploratory efficacy variable will be performed on the mITT population.

16.3.1. EXPLORATORY EFFICACY VARIABLES & DERIVATION

16.3.1.1. Change from baseline in the CBB composite score at Week 4

The Cogstate Brief Battery (CBB) assesses four domains. The Detection test (Psychomotor Function Domain) measures speed of performance. The mean of the log10 transformed reaction times for correct responses is utilized to determine the score. Lower scores correspond to better performance. The Identification test (Attention Domain) also measures speed of performance. The mean of the log10 transformed reaction times for correct responses is utilized to determine the score. Lower scores correspond to better performance. The One Card Learning test (Visual Learning Domain) measures accuracy of performance. The arcsine transformation of the square root of the proportion of correct responses is utilized to determine the domain score. Higher scores correspond to better performance. The One Back test (Working Memory Domain) measures speed of performance. The mean of log10 transformed reaction times for correct responses is used to determine the domain score. Lower scores correspond to better performance.

A standardized z-score is derived for each test by using the following formula:

$$z = \frac{(\text{Subject score} - \text{Age-adjusted normalization table mean}) \times \text{Multiplicand}}{\text{Age-adjusted normalization table standard deviation}}$$

where

- multiplicand = -1 when a lower score indicates improved performance (i.e. Detection Test, Identification Test, One Back Test);
- multiplicand = 1 when a higher score indicates improved performance (i.e. One Card Learning Test)

The age-adjusted normalization table mean and standard deviation for each test is shown in the table below:

Cogstate Tests	Normative Mean and Standard Deviation	
Detection Test (DET)	2.46	0.09
Identification Test (IDN)	2.66	0.08
One Card Learning Test (OCL)	1.05	0.13
One Back Test (ONB)	2.79	0.10

A completion flag and an integrity flag are populated for each test. Test completion refers to criteria that determine whether a sufficient number of responses were recorded during the administration of a test to allow computation of reliable performance measures. Any tests that failed the completion criteria will be excluded from statistical analysis.

Test integrity is a measure of whether a subject performed in accord with the test requirements. When a particular test administration fails to meet criteria for data integrity, this suggests with high probability that the observed score may not reflect the study population or the effect of the compound under investigation. Statistical analysis will be performed both with the tests that failed the integrity criteria included and excluded

(as a sensitivity analysis).

Based on the z-scores of individual tests, a CBB composite score will be derived as the average of the z-scores of four tests. If two or more tests are missing or are excluded from the analysis, the composite score will be set to missing.

The change from baseline in CBB composite score and each individual standardized score at Week 4 will then be calculated for each subject.

16.3.2. Missing Data Method for Exploratory Efficacy Variables

The ANCOVA analysis of change from baseline in CBB composite score and the individual standardized scores at Week 4 will be based on observed data (with early termination data mapped as described in section 6.4). Missing data will not be imputed.

16.3.3. Analysis of Exploratory Efficacy Variables

16.3.3.1. Change from baseline in the CBB composite score at Week 4

Change from baseline in the CBB composite score and the individual standardized scores at Week 4 will be analyzed using an ANCOVA model with treatment and pooled center as categorical factors and baseline CBB composite score or individual standardized scores as a covariate. Between-group difference for baseline CBB composite score and the individual standardized scores will be based on an ANCOVA model adjusting for pooled center.

17. Safety Outcomes

All outputs for safety outcomes will be based on the safety population.

There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified in the relevant sections.

17.1. Adverse Events

Both adverse events (AEs) and pre-treatment events will be coded using MedDRA central coding dictionary, Version 18.1 or higher.

Adverse events are untoward medical occurrences that started at the same time of or after the first dose of study medication. Untoward medical occurrences that started between ICF and prior to the first dose of study medication are pre-treatment events.

Adverse events (including serious adverse events) are collected into the clinical database until the last study visit. For subjects who do not roll over to study 361-202, the last study visit will be the follow-up visit which per protocol should occur 7 (± 2) days after the last dose of study medication. For subjects continuing into study 361-202 (the open-label extension), the last study visit in study 361-201 will be Visit 7 which per protocol

should occur 1 day after the last dose of study medication. For these subjects, adverse events that started before the first dose of open-label study medication in study 361-202 are considered to belong to study 361-201 and will be recorded in the 361-201 database. Adverse events that started at the same time of or after the first dose of open-label study medication in study 361-202 are considered to belong to study 361-202 and will be recorded in the 361-202 database. If an adverse event (or pre-treatment event) started in study 361-201 and was ongoing as of the first dose of open-label study medication, this adverse event (pre-treatment event) will be carried over to the 361-202 database and its outcome will be monitored and updated in the 361-202 database.

For the purpose of statistical analysis, all adverse events in the 361-201 database which started within 9 days after the last dose of study medication, or had a partial or missing start date such that it cannot be determined whether the adverse event is within the 9-day window, will be included in table summaries. All adverse events in the 361-201 database, including those that started beyond 9 days after the last dose of study medication, will be listed in data listings.

Whenever available, the time information should be taken into consideration in the determination of adverse events vs. pre-treatment events. In the case where time isn't available, untoward medical occurrences that started on or after the day of the first dose of study medication will be considered adverse events; those that started before the day of the first dose of study medication will be considered pre-treatment.

See APPENDIX 2 for handling of partial dates for adverse events. In the case where it is not possible to define an untoward medical occurrence as adverse event or pre-treatment event, it will be classified by the worst case, i.e. adverse event.

An overall summary of the incidence of adverse events within each of the categories described in the following sections will be provided as specified in the templates. This summary will also be repeated by the region, sex, age, number of prior hospitalizations for acute exacerbation of schizophrenia, and duration of schizophrenia subgroups. The overall incidence summary will also be provided for AEs related to study medication.

Listings will be provided for all AEs, AEs leading to discontinuation of study medication, AEs leading to discontinuation from the study, serious adverse events (SAE), and AEs leading to death. A listing for pre-treatment events will also be presented.

For incidence summaries, each subject will be counted only once within each SOC and PT. If not otherwise specified, all summaries will present incidence (number of subjects and percentages) and number of events.

17.1.1. ALL AEs

AEs will be presented by SOC, High Level Term (HLT), and PT for AE incidence and number of events. AEs will also be presented by maximum severity and by strongest relationship to the study medication as specified in the sections below.

AEs that occurred in >= 5% of subjects in either treatment group will be summarized by SOC and PT.

17.1.1.1. Severity

Severity is classed as mild/ moderate/ severe (increasing severity). AEs with a missing severity will be summarized as missing severity. If a subject reports an AE more than once within the same SOC/ PT, the AE with the worst severity will be used in the corresponding severity summaries. For this summary, AEs will be presented by SOC and PT.

17.1.1.2. Relationship to Study Medication

Relationship, as indicated by the investigator, is classed as “not related”/ “possible”/ “probable”/ “definite” (increasing strength of relationship). A “related” AE is defined as an AE with a relationship to the study medication of “possible”, “probable” or “definite”. A “not related” AE is defined as an AE with a relationship to the study medication of “not related”. AEs with a missing relationship to the study medication will be regarded as “related” to the study medication. If a subject reports the same AE more than once within the same SOC/ PT, the AE with the strongest relationship to study medication will be used in the corresponding relationship summaries. For this summary, AEs will be presented by SOC and PT.

17.1.2. AEs Leading to Discontinuation of Study Medication

AEs leading to permanent discontinuation of study medication are AEs for which “Drug Withdrawn” is selected for “Action Taken with Study Treatment” on the AE CRF page. A summary of AEs leading to discontinuation of study medication by SOC and PT will be presented.

17.1.3. AEs Leading to Discontinuation from the Study

AEs leading to discontinuation from the study are AEs with “Caused Study Discontinuation” = “Yes” on the AE CRF page. A summary of AEs leading to discontinuation from the study by SOC and PT will be presented.

17.1.4. Serious Adverse Events

SAEs are those AEs recorded as “Serious” on the AE CRF page. Summaries of serious AEs and non-serious AEs by SOC and PT will be prepared.

17.1.5. Adverse Events Leading to Death

AEs leading to death are those AEs which are recorded as having an outcome of “Fatal” on the AE CRF page. A summary of AEs leading to death by SOC and PT will be prepared.

17.1.6. Adverse Events by Subgroup

As stated above, overall incidence summaries will be presented by the subgroups of region, sex, age, prior number of hospitalizations for acute exacerbation of schizophrenia, and duration of schizophrenia. The same subgroup factors will also apply to the by-subgroup summaries for the following events:

- All AEs, by SOC and PT
- SAEs, by SOC and PT
- AEs leading to discontinuation of study medication, by SOC and PT

- AEs leading to discontinuation from the study, by SOC and PT

In addition, all AEs (by SOC and PT) will be summarized by the BMI (kg/m^2) category:

- Underweight: <18.5
- Normal: 18.5 to <25.0
- Overweight: 25.0 to <30.0
- Obese: >=30.0

17.2. LABORATORY EVALUATIONS

Laboratory data to be reported for this study include hematology, serum chemistry (including lipid panel and thyroid panel), urinalysis, coagulation, urine drug screening, and urine and serum pregnancy test (only listed).

Presentations will use international system of units (SI).

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in listings.

The following summaries will be provided for laboratory data:

- By visit summary of observed values and changes from baseline for continuous data in hematology, chemistry, urinalysis, and coagulation. Prolactin results will be summarized separately by gender. Glucose and lipid panel results will be summarized separately by fasting status.

- By visit summary of the number and percentage of subjects in each outcome category for categorical data in urinalysis and urine drug screening. For urine drug screening, the results will be reported as "Positive"/ "Negative".

- Shift in lab results (chemistry, hematology, urinalysis, coagulation) from baseline to Week 4 according to the reference range criteria provided by the central laboratory.

- Summary of the number and percentage of subjects with at least one post-baseline PCS value for selected laboratory parameters (Table 3). The period of evaluation includes both double-blind treatment period and the double-blind follow-up period.

The change from baseline values at Week 4 for selected laboratory parameters will be evaluated using a nonparametric rank ANCOVA analysis. Baseline values and change from baseline values will be ranked. A linear regression analysis will be performed on the change from baseline value ranks with the baseline value ranks as the independent variable, to produce regression residuals. Using the values of the residuals as scores, the Cochran-Mantel-Haenszel row mean scores test will be used to compare between the treatment groups. This analysis will be conducted for prolactin, lipid panel, HbA_{1c}, and glucose. Prolactin will be analyzed separately by gender.

All laboratory data will be provided in data listings, with the values outside the reference ranges and PCS values flagged.

Table 3. PCS Criteria for Laboratory Parameters – SI Units

Category Parameter Name Age/Gender Restriction, if any	PCS Low	PCS High
HEMATOLOGY		
WBC	≤ 2.8 x 10^9/L	≥ 16 x 10^9/L
Neutrophils (abs)	< 0.5 x 10^9/L	> 13.5 x 10^9/L
Lymphocytes (abs)	N/A	> 12 x 10^9/L
Monocytes (abs)	N/A	> 2.5 x 10^9/L
Eosinophils (abs)	N/A	> 1.6 x 10^9/L
Basophils (abs)	N/A	> 1.6 x 10^9/L
Neutrophils (relative)	≤ 0.15	> 0.85
Lymphocytes (relative)	N/A	≥ 0.75
Monocytes (relative)	N/A	≥ 0.15
Eosinophils (relative)	N/A	≥ 0.10
Basophils (relative)	N/A	≥ 0.10
Hemoglobin		
Male	≤ 115 g/L	≥ 190 g/L
Female	≤ 95 g/L	≥ 175 g/L
Hematocrit		
Male	≤ 0.37	≥ 0.60
Female	≤ 0.32	≥ 0.54
RBC	≤ 3.5 x 10^{12}/L	≥ 6.4 x 10^{12}/L
Platelet Count	≤ 75 x 10^9/L	≥ 700 x 10^9/L
SERUM CHEMISTRY		
Sodium	< 130 mmol/L	> 150 mmol/L
Potassium	< 3 mmol/L	> 5.5 mmol/L
Chloride	≤ 90 mmol/L	≥ 118 mmol/L
Calcium	< 1.75 mmol/L	≥ 3.1 mmol/L
Phosphate	< 0.65 mmol/L	> 1.65 mmol/L
Bicarbonate	< 15.1 mmol/L	> 34.9 mmol/L
Magnesium	< 0.4 mmol/L	> 1.23 mmol/L
AST (IU/L)	N/A	≥ 3 x ULN
ALT (IU/L)	N/A	≥ 3 x ULN
Alkaline Phosphatase (IU/L)	N/A	≥ 1.5 x ULN
CK (IU/L)	N/A	> 2.5 x ULN
Creatinine	N/A	≥ 177 umol/L
BUN	N/A	≥ 10.7 mmol/L
Total bilirubin (mg/dL)	N/A	≥ 34.2 umol/L OR > 2 x ULN
Total protein	≤ 45 g/L	≥ 100 g/L
Albumin	≤ 25 g/L	N/A
Total Cholesterol	N/A	> 7.76 mmol/L
HDL-Cholesterol	< 0.78 mmol/L	N/A
LDL-Cholesterol	N/A	> 4.14 mmol/L
Triglycerides	N/A	> 3.42 mmol/L

Uric acid		
Male	N/A	> 595 umol/L
Female	N/A	> 476 umol/L
Glucose	< 2.78 mmol/L	> 13.9 mmol/L
HbA1c	N/A	≥ 0.075
Prolactin	N/A	≥ 5 x ULN
COAGULATION		
aPTT (sec)	N/A	> 1.5 x ULN
INR (ratio)	N/A	> 1.5 x ULN
THYROID FUNCTION		
Free T3	< 3.07 pmol/L	> 6.38 pmol/L
Free T4	< 9.65 pmol/L	> 22.5 pmol/L
TSH	< 0.34 mIU/L	> 5.6 mIU/L
URINALYSIS		
RBC	N/A	> 25 hpf
WBC	N/A	> 25 hpf

17.3. ECG EVALUATIONS

Results from the central ECG (Electrocardiogram) will be included in the reporting of this study.

The following ECG parameters will be reported for this study:

- PR Interval (msec)
- RR Interval (msec)
- QRS Duration (msec)
- QRS Axis (deg)
- QT Interval (msec)
- QTcF Interval (msec) [derived]
- QTcB Interval (msec) [derived]
- Heart rate (HR) (beats/min)
- ECG findings
- Overall assessment of ECG (investigator's judgment):

o Normal
o Abnormal, Significant

- Abnormal, Insignificant

The following summaries will be provided for ECG data:

- By visit summary of observed values and changes from baseline (for quantitative measurements)
- Number and percentage of subjects with QTc levels in each of the QTc categories
- By visit summary of ECG overall assessment results
- Shift in ECG overall assessments from baseline to Week 4.

The number and percentage of subjects with QTc values in the following categories will be identified. The same criteria apply to both QTcF and QTcB.

- > 450 msec at any post-baseline time point (including unscheduled visits) not present at baseline
- > 480 msec at any post-baseline time point (including unscheduled visits) not present at baseline
- > 500 msec at any post-baseline time point (including unscheduled visits) not present at baseline
- ≥ 30 msec increase from baseline for at least one post-baseline measurement (including unscheduled visits) and < 60 msec increase from baseline for all post-baseline measurements (including unscheduled visits)
- ≥ 60 msec increase from baseline for at least one post-baseline measurement (including unscheduled visits)

All ECG parameters, overall interpretation, and findings will be provided in data listings.

17.4. VITAL SIGNS

The following vital signs measurements will be reported for this study:

- Supine Systolic Blood Pressure (mmHg)
- Standing Systolic Blood Pressure (mmHg)
- Supine Diastolic Blood Pressure (mmHg)
- Standing Diastolic Blood Pressure (mmHg)
- Supine Pulse Rate (beats/min)

- Standing Pulse Rate (beats/min)
- Respiratory Rate (breaths/min)
- Temperature (°C)
- Weight (kg)
- BMI (kg/m^2)
- Waist Circumference (cm)

The following summaries will be provided for vital signs data:

- Observed value and change from baseline by visit
- Observed value and change from baseline by visit for baseline BMI category:

o Underweight: <18.5
o Normal: 18.5 to <25.0
o Overweight: 25.0 to <30.0
o Obese: >=30.0

- Number and percentage of subjects with at least one post-baseline PCS value for selected vital signs parameters (Table 4). The period of evaluation includes both double-blind treatment period and the double-blind follow-up period.

Change from baseline at the Week 4 LOCF endpoint in weight and BMI will be analyzed using nonparametric rank ANCOVA similarly to those described in section 17.2.

All vital signs data will be provided in data listings, with the PCS values flagged.

Table 4. PCS Criteria for Vital Signs Parameters

Parameter Name	PCS Low	PCS High
Systolic Blood Pressure (mmHg)	Value ≤ 90 and ≥ 20 decrease from baseline	Value ≥ 180 and ≥ 20 increase from baseline
Diastolic Blood Pressure (mmHg)	Value ≤ 50 and ≥ 15 decrease from baseline	Value ≥ 105 and ≥ 15 increase from baseline
Pulse Rate (beats/min)	Value ≤ 50 and ≥ 15 decrease from baseline	Value ≥ 120 and ≥ 15 increase from baseline
Weight (kg)	≥ 7% decrease from baseline	≥ 7% increase from baseline
Temperature (°C)	NA	Value ≥ 38.3°C and ≥ 0.8°C increase from baseline

17.4.1. ORTHOSTATIC EFFECTS

Orthostatic hypotension is defined as a decrease of >= 20 mmHg in systolic blood pressure or >= 10 mmHg in diastolic blood pressure after the subject had been standing for at least 2 to 4 minutes, compared to the systolic blood pressure and diastolic pressure measured in the supine position, respectively.

Orthostatic tachycardia is defined as a heart rate increase of >= 20 beats per minute (bpm) and a heart rate of >100 bpm after the subject was standing for at least 2 to 4 minutes, compared to the heart rate measured in the supine position.

The number and percentage of subjects with orthostatic hypotension and orthostatic tachycardia will be summarized for baseline and the overall post-baseline period, as well as by visit. As specified in section 6.4 of the statistical analysis plan, any orthostatic hypotension or tachycardia events that occurred at the early termination visit will be assigned to the next planned visit.

17.5. OTHER SAFETY ASSESSMENTS

17.5.1. MOVEMENT DISORDER MEASURES

Abnormal Involuntary Movement Scale (AIMS)

The AIMS is a clinician-rated assessment of abnormal movements. It contains 12 items that assess facial and oral movements (items 1 - 4), extremity movements (items 5 - 6), trunk movements (item 7), global judgments (items 8 - 10) and dental status (items 11 - 12). AIMS total score will be calculated as the sum of items 1 through 7 (ranging from 0 to 28). Higher values of AIMS total score indicate increased severity in abnormal movement. If any item score contributing to the calculation of AIMS total score is missing, the total score will be set to missing. Items 8 through 12 will not be used in total score calculation. The global severity score (item 8) will be summarized separately.

Change from baseline in AIMS total score will be analyzed using MMRM similarly to the primary analysis of the primary efficacy variable (see section 16.1.3), with baseline AIMS total score as a covariate. The MMRM analysis will be repeated for subgroups based on whether or not the subjects took concomitant medications for treatment of movement disorders. The list of medications will be determined by a review of the coded medication terms before database lock.

In addition, ANCOVA analysis on change from baseline in AIMS total score will be performed, similarly to the analysis described in section 16.1.4.4.

AIMS total score (observed value and change from baseline) will be summarized numerically by visit. In addition, the AIMS total score at each visit will be classified as “abnormal” if: either at least two items (out of items 1 - 7) have a response of “mild” or higher, or at least one item (out of items 1 - 7) has a response of “moderate” or higher. Otherwise, the non-missing total score will be classified as “normal”. This is a modification of the Schooler-Kane criteria for tardive dyskinesia. Shifts from baseline in AIMS total score classification will be summarized by visit and overall for all post-baseline assessments during the double-blind treatment period.

The AIMS global severity score will be summarized both numerically and categorically by visit.

The post-baseline AIMS global severity assessment will be classified as “worsened” (score is higher than baseline), “unchanged” (score is equal to baseline), or “improved” (score is lower than baseline), relative to a subject’s baseline response. These post-baseline changes will be summarized by visit.

Barnes Akathisia Rating Scale (BARS)

The BARS is a clinician-rated assessment to measure the observable, restless movements that characterize drug-induced akathisia. It contains 4 items: an objective rating (objective restlessness), 2 subjective ratings (awareness of restlessness, distress related to restlessness), and a global clinical assessment of akathisia. The subjective and objective items (items 1 through 3) will be summed to yield the BARS total score (ranging from 0 to 9). Higher values of BARS total score indicate higher severity of akathisia. If any item score contributing to the calculation of BARS total score is missing, the total score will be set to missing. The global clinical assessment rating will be analyzed separately.

Change from baseline in BARS total score will be analyzed using MMRM similarly to the primary analysis of the primary efficacy variable (see section 16.1.3), with baseline BARS total score as a covariate. The MMRM analysis will be repeated for subgroups based on whether or not the subjects took concomitant medications for treatment of movement disorders. The list of medications will be determined by a review of the coded medication terms before database lock. Similar analyses will be performed on the BARS global clinical assessment rating score.

In addition, ANCOVA analysis on change from baseline in BARS total score will be performed, similarly to the analysis described in section 16.1.4.4. A similar analysis will be performed on the BARS global clinical assessment rating score.

BARS total score (observed value and change from baseline) will be summarized numerically by visit. In addition, the BARS item scores for the four items will be summarized both numerically and categorically by visit.

The post-baseline BARS global clinical assessment of akathisia will be classified as “worsened” (score is higher than baseline), “unchanged” (score is equal to baseline), or “improved” (score is lower than baseline), relative to a subject’s baseline response. These post-baseline changes will be summarized by visit.

Simpson-Angus Scale (SAS)

The SAS is a clinician-rated assessment of neuroleptic-induced Parkinsonism consisting of 10 items (each ranging from 0 to 4). SAS mean score is calculated as the average of all 10 item scores. Lower values of SAS mean score indicate milder symptoms. If any item score is missing, the mean score will be set to missing.

Change from baseline in SAS mean score will be analyzed using MMRM similarly to the primary analysis of the primary efficacy variable (see section 16.1.3), with the baseline SAS mean values as a covariate. The MMRM analysis will be repeated for subgroups based on whether or not the subjects took concomitant medications for treatment of movement disorders. The list of medications will be determined by a review of the coded medication terms before database lock.

In addition, ANCOVA analysis on change from baseline in SAS mean score will be performed, similarly to the analysis described in section 16.1.4.4.

SAS mean score (observed value and change from baseline) will be summarized numerically by visit. In addition, SAS mean score at each visit will be classified as “abnormal” if it exceeds 0.3. Otherwise, non-missing mean scores will be classified as “normal”. Shifts from baseline in SAS mean score classification will be summarized by visit and overall for all post-baseline assessments during the double-blind treatment period.

All data from the three scales will be presented in the data listings.

17.5.2. PITTSBURGH SLEEP QUALITY INDEX

The Pittsburgh Sleep Quality Index (PSQI) contains 19 self-rated questions and 5 questions rated by the bed partner or roommate (if one is available). Only self-rated questions are included in the scoring. The 19 self-rated items are combined to form seven "component" scores, each of which has a range of 0-3 points. The seven component scores are then added to yield one global score, with a range of 0-21 points, "0" indicating no difficulty and "21" indicating severe difficulties in all areas (Buysse et al. 1989).

If any of the component scores are missing, the PSQI global score will be set to missing. The PSQI scoring algorithm as downloaded from the University of Pittsburgh Sleep and Chronobiology Center is inserted in Appendix 4.

Change from baseline in the PSQI global score at Week 4 will be analyzed using an ANCOVA model similar to that described in section 16.3.3.1.

17.5.3. DRUG EFFECTS QUESTIONNAIRE

The Drug Effects Questionnaire (DEQ) consists of 3 questions scored on a visual analog scale (VAS).

Data from the DEQ questionnaire will be summarized descriptively by visit. For Describe Drug Effect and Like Drug Effect, if the Result is "Negative", the numeric measurement will first be converted to a negative number before being summarized.

17.5.4. COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS)

The C-SSRS is a tool designed to systematically assess and track suicidal behavior and suicidal ideation for life time, one month (30 days) prior to the screening visit, and throughout the study. The strength of this suicide classification system is in its ability to comprehensively identify suicidal events while limiting the over-identification of suicidal behavior. The C-SSRS Baseline/Screening Version is used at the screening visit and the C-SSRS Since Last Visit Version is used from Visit 2 onward. Subjects with Type 4 (active suicidal ideation with some intent to act, without specific plan) or Type 5 (active suicidal ideation with specific plan and intent) suicidal ideation during the study will be discontinued from the study and referred to a mental health professional.

C-SSRS includes four sections: Suicidal Ideation, Intensity of Ideation, Suicidal Behavior, and Answer for Actual Suicide Attempts.

The following outcomes are C-SSRS categories and have binary responses (yes/no). The categories are re-ordered from the scale to facilitate the definitions of the C-SSRS endpoints, and to provide clarity in the presentation of the results.

Suicidal ideation is measured by 5 categories, representing 5 subtypes of suicidal ideation with increasing severity:

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

Suicidal behavior is measured by 5 categories, representing 5 subtypes of suicidal behavior:

Category 6: Preparatory Acts or Behavior

Category 7: Aborted Attempt

Category 8: Interrupted Attempt

Category 9: Actual Attempt (non-fatal)

Category 10: Completed Suicide

The 10 categories above are not mutually exclusive. Subjects will be counted in each category for which they have an event.

Self-injurious behavior without suicidal intent is a non-suicide-related C-SSRS outcome, and also has a binary response (yes/no).

For the purpose of C-SSRS analysis, “baseline” and “post-baseline” are defined as follows.

Time point	Study Visit	C-SSRS Version	Derivation Rule
Baseline	Screening/Visit 1	Baseline/Screening – Past 1 Month	Most severe outcome
	Randomization/Visit 2	Since Last Visit	
Post-baseline	All post-baseline visits up to and including Week 4/Visit 7, including unscheduled visits	Since Last Visit	Most severe outcome

C-SSRS composite endpoints will be derived for each time point of interest (i.e. baseline, post baseline, and each study visit) as follows:

- Any suicidal ideation: A “yes” answer to any one of the 5 suicidal ideation questions on C-SSRS (Categories 1-5).
- Any suicidal behavior: A “yes” answer to any one of the 5 suicidal behavior questions on the C-SSRS (Categories 6-10).
- Any suicidality: A “yes” answer to any one of the 10 suicidal ideation and behavior questions on the C-SSRS (Categories 1-10).

For each subject, the suicidal ideation score at each time point of interest (i.e. baseline, post baseline, each study visit, and the Week 4 LOCF endpoint) is defined as the maximum suicidal ideation category (1-5) present for the time of interest. If no ideation is present a score of 0 is assigned. A suicidal ideation score of 4 or 5 is considered serious.

The number and percentage of subjects with any suicidality, any suicidal ideation and subtypes of ideation, any suicidal behavior and subtypes of behavior, and any non-suicidal self-injurious behavior will be presented for:

- Baseline (as defined above)

- Post-baseline (as defined above)
- Each scheduled study visit: Screening (lifetime; past 1 month), Randomization/Visit 2, Day 4/Visit 3, Week 1/Visit 4, Week 2/Visit 5, Week 3/Visit 6, Week 4/Visit 7, Follow-up/Visit 8.

Difference between treatment groups for any post-baseline suicidality, suicidal behavior, and suicidal ideation will be evaluated using Fisher's Exact test.

Shift in suicidal ideation score from baseline to the post-baseline time point and to each the following study visits will be presented by treatment: Day 4/Visit 3, Week 1/Visit 4, Week 2/Visit 5, Week 3/Visit 6, Week 4/Visit 7, Week 4 LOCF, and Follow-up/Visit 8.

Intensity of ideation for the most severe ideation subtype is measured in terms of frequency, duration, controllability, deterrents, and reasons for ideation. Each is measured with responses ranging from 0 to 5 for frequency and duration, and from 1 to 5 for controllability, deterrents, and reasons for ideation. The ideation intensity total score is the sum of responses to the five items and can range from 2 to 25 for subjects with endorsed suicidal ideation. If one or more of these five items are missing at an assessment, the total score will be set to missing. If a subject did not endorse any suicidal ideation, a score of 0 for the ideation intensity total score will be given.

Actual lethality associated with actual attempts is rated on a 6-point scale from 0 = 'No physical damage or very minor physical damage' to 5 = 'Death'. Potential lethality of actual attempts (if actual lethality = 0) is rated on a 3-point scale from 0 = 'Behavior not likely to result in injury' to 2 = 'Behavior likely to result in death despite available medical care.

The ideation intensity total score and the actual lethality and potential lethality of actual attempts will be presented in data listings.

18. PHARMACOKINETIC ANALYSIS

18.1. POPULATION PHARMACOKINETIC ANALYSIS

All plasma concentrations of SEP-363856 and SEP-363854 will be presented in data listings.

Population pharmacokinetic (PK) analysis will be performed using plasma SEP-363856 concentrations. The results will be reported separately.

18.2. PHARMACODYNAMIC ANALYSIS

The relationship between PANSS total score and plasma SEP-363856 exposure using population PK/pharmacodynamics (PD) methods will be explored. The results will be reported separately.

The impact of cytochrome (CYP) P450 CYP2D6 metabolizer status on plasma SEP-363856 exposure will be explored. The results will be reported separately.

19. DATA NOT SUMMARIZED OR PRESENTED

The data not summarized or presented are:

- Any data other than disposition, demographics and adverse events that are collected on screen failures and on enrolled subjects at the previously failed screenings.

These data will not be summarized or presented, but will be avialble in the clinical study database, SDTM and/or ADaM datasets.

20. CHANGES IN THE ANALYSIS SPECIFIED IN THE STATISTICAL ANALYSIS PLAN

Any changes or deviations during the analysis and reporting process from the statistical analysis plan designed will be described and justified in the final report.

21. REFERENCES

Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193-213.

Hopkins SC, Ogirala A, Loebel A, Koblan KS. Transformed PANSS factors intended to reduce pseudospecificity among symptom domains and enhance understanding of symptom change in antipsychotic-treated patients with schizophrenia. Schizophr Bull 2018;44(3):593-602.

Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. J Clin Psychiatry 1997;58:538–46.

Ratitch B, O'Kelly M, Tosiello R. Missing data in clinical trials: from clinical assumptions to statistical analysis using pattern mixture models. Pharm Stat 2013;12(6):337-47.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

OUTPUT CONVENTIONS

Where applicable, the Appendix Compilation Working Guidelines Final 07May2014 .pdf document – provided by Sunovion – will be followed.

In addition, the following output conventions are to be followed:

- The first row in the body of the table or listing should be blank
- The left hand column should start in column 1. No indenting or centering of the output should occur.
- Rounding should be done with the SAS function ROUND.
- Numbers in tables should be rounded, not truncated.
- Alphanumeric output should be left aligned.
- Numbers should be decimal point aligned.
- Whole numbers should be right aligned.
- Text values should be left aligned.
- The first letter of a text entry should be capitalized.
- The width of the entire output should match the line size (134)

  - Univariate Statistics:

- If the raw data has N decimal places, then the summary statistics should have the following decimal places:
  - Minimum and maximum: N
  - Mean, median, Q1, and Q3: N + 1
  - SD: N + 2

  - Frequencies and percentages (n and %):

- Percent values should be reported inside parentheses, with one space between the count (n) and the left parenthesis of the percentage. Parentheses should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percent is less than 100.0.
- Percentages will be reported to one decimal place, except cases where percent <100.0% but >99.9% will be presented as '>99.9%' (e.g., 99.99% is presented as >99.9%); and cases where percent < 0.1% will be presented as '<0.1%' (e.g., 0.08% is presented as <0.1%). Rounding will be applied after the <0.1% and >99.9% rule.
- Where counts are zero, no percentage should appear in the output.

  - Confidence Intervals:

- Confidence intervals and estimates are presented to one place more than the raw data, and standard errors to two places more than the raw data.
- Confidence intervals should be justified so that parentheses displayed on consecutive lines of a table "line up".
- Boundary values of confidence intervals should be separated by a comma.
- Boundary values should be padded as necessary to accept negative values and to allow alignment of the decimal place.

- P-values:

o P-values should be reported to three decimal places, except values <1.000 but >0.999 will be presented as '>0.999' (e.g., 0.9998 is presented as >0.999); and values <0.001 will be presented as '<0.001' (e.g., 0.0009 is presented as <0.001). Rounding will be applied after the <0.001 and >0.999 rule.

- Ratios:

o Ratios should be reported to one more decimal place than the raw data.

- Spacing:

o There must be a minimum of 1 blank space between columns (preferably 2).

- Missing values:

o A "0" should be used to indicate a zero frequency.
o A blank will be used to indicate missing data in an end-of-text table or subject listing.

- Figures:

o Figures should be provided in RTF files using the SAS Output Delivery System (ODS), as Computer Graphics Metafile (CGM) formatted graphical output generated by SAS.
o The CGM file itself should contain the title or footer.
o The image should be clear and of high quality when viewed in the Word document, and when printed.
o In general, boxes around the figures should be used.

- Footers should be defined as follows:

o A continuous line of underscores ('_') will follow the body of the table or listing prior to any footnotes at the bottom of the page.
o Table footnotes should be defined using compute statements in the proc report, and should appear directly after the body of the table.
o If text wraps across more than one line (for a note), the first letter for all lines of text after the first one will be indented to align beneath the first letter of the text in the first line.

DATES & TIMES

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

SPELLING FORMAT

English US.

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in that order:

Treatment Group	For Tables, Graphs and Listings
Placebo	Placebo
SEP-363856 (50 or 75 mg/day)	SEP-363856

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- Actual treatment received, displaying SEP-363856 first and then placebo,
- Subject ID,
- Date/Time (where applicable) - listings of adverse events, concomitant medications, medical histories etc. should be sorted in chronological order, with earliest adverse event, medication or history coming first,
- For listings where non-randomized subjects are included, these will appear in a category after the randomized treatment groups labelled 'Not Randomized'.

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will not be presented in the listings.

ALGORITHM FOR ADVERSE EVENTS:

The algorithm below applies to all AE and pre-treatment event records contained in the 361-201 database.

The concept of "date" below should also include time information whenever available.

START DATE	STOP DATE	ACTION
Known	Known	If start date < 361-201 study med start date, then pre-treatment events If start date >= 361-201 study med start date, then 361-201 AE
Known	Partial	If start date < 361-201 study med start date, then pre-treatment events If start date >= 361-201 study med start date, then 361-201 AE
Known	Missing	If start date < 361-201 study med start date, then pre-treatment events If start date >= 361-201 study med start date, then 361-201 AE
Partial, but known components show that it cannot be on or after 361-201 study med start date	Known	Pre-treatment events
Partial, but known components show that it cannot be on or after 361-201 study med start date	Partial	Pre-treatment events
Partial, but known components show that it cannot be on or after 361-201 study med start date	Missing	Pre-treatment events
Partial, could be on or after 361-201 study med start date	Known	If stop date < 361-201 study med start date, then pre-treatment events If stop date >= 361-201 study med start date, then 361-201 AE

START DATE	STOP DATE	ACTION
Partial, could be on or after 361-201 study med start date	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown). Then: If stop date < 361-201 study med start date, then pre-treatment events If stop date >= 361-201 study med start date, then 361-201 AE
Partial, could be on or after 361-201 study med start date	Missing	Assumed 361-201 AE
Partial, and known components show that it is on or after 361-201 study med start date	Known	361-201 AE
Partial, and known components show that it is on or after 361-201 study med start date	Partial	361-201 AE
Partial, and known components show that it is on or after 361-201 study med start date	Missing	361-201 AE
Missing	Known	If stop date < 361-201 study med start date, then pre-treatment events If stop date >= 361-201 study med start date, then 361-201 AE
Missing	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown). Then: If stop date < 361-201 study med start date, then pre-treatment events If stop date >= 361-201 study med start date, then 361-201 AE
Missing	Missing	Assumed 361-201 AE

ALGORITHM FOR PRIOR / CONCOMITANT / POST-TREATMENT MEDICATIONS:

The concept of "date" below should also include time information whenever available.

For the case where the medication start date is known and is equal to the end of treatment date, and the medication start time is unknown, or the case where the imputed medication start date is equal to the end of treatment date:

- If CRF question '*Started after last dose of study medication?*' = *No*, then assign as concomitant.
- If CRF question '*Started after last dose of study medication?*' = *Yes*, then assign as post treatment.

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior. If stop date >= study med start date and start date <= end of treatment, assign as concomitant. If stop date >= study med start date and start date > end of treatment, assign as post treatment.
Known	Partial	Impute stop date as latest possible date: • If only day unknown, impute as the earlier of (last day of the month; end date of the last study visit). • If month and day unknown, impute as the earlier of (31st December; end date of the last study visit). Then: If stop date < study med start date, assign as prior. If stop date >= study med start date and start date <= end of treatment, assign as concomitant. If stop date >= study med start date and start date > end of treatment, assign as post treatment.
Known	Missing	If stop date is missing could never be assumed a prior medication. If start date <= end of treatment, assign as concomitant. If start date > end of treatment, assign as post treatment.

START DATE	STOP DATE	ACTION
Partial	Known	Impute start date as earliest possible date: *CRF questions: 'Started prior to study?' = Yes; 'Started after last dose of study medication?' = No.* • If only day unknown, impute as the later of (first day of the month; date of birth). • If month and day unknown, impute as the later of (1st January; date of birth). *CRF questions: 'Started prior to study?' = No; 'Started after last dose of study medication?' = Yes.* • If only day unknown, impute as the later of (first day of the month; end of treatment + 1). • If month and day unknown, impute as the later of (1st January; end of treatment + 1). *CRF questions: 'Started prior to study?' = No; 'Started after last dose of study medication?' = No.* • If only day unknown, impute as the later of (first day of the month; date of ICF). • If month and day unknown, impute as the later of (1st January; date of ICF). Then: If stop date < study med start date, assign as prior. If stop date >= study med start date and start date <= end of treatment, assign as concomitant. If stop date >= study med start date and start date > end of treatment, assign as post treatment.

START DATE	STOP DATE	ACTION
Partial	Partial	Impute start date as earliest possible date: *CRF questions: 'Started prior to study?' = Yes; 'Started after last dose of study medication?' = No.* • If only day unknown, impute as the later of (first day of the month; date of birth). • If month and day unknown, impute as the later of (1st January; date of birth). *CRF questions: 'Started prior to study?' = No; 'Started after last dose of study medication?' = Yes.* • If only day unknown, impute as the later of (first day of the month; end of treatment + 1). • If month and day unknown, impute as the later of (1st January; end of treatment + 1). *CRF questions: 'Started prior to study?' = No; 'Started after last dose of study medication?' = No.* • If only day unknown, impute as the later of (first day of the month; date of ICF). • If month and day unknown, impute as the later of (1st January; date of ICF). Impute stop date as latest possible date: • If only day unknown, impute as the earlier of (last day of the month; end date of the last study visit). • If month and day unknown, impute as the earlier of (31st December; end date of the last study visit). Then: If stop date < study med start date, assign as prior. If stop date >= study med start date and start date <= end of treatment, assign as concomitant. If stop date >= study med start date and start date > end of treatment, assign as post treatment.

START DATE	STOP DATE	ACTION
Partial	Missing	Impute start date as earliest possible date: *CRF questions: 'Started prior to study?' = Yes; 'Started after last dose of study medication?' = No.* • If only day unknown, impute as the later of (first day of the month; date of birth). • If month and day unknown, impute as the later of (1st January; date of birth). *CRF questions: 'Started prior to study?' = No; 'Started after last dose of study medication?' = Yes.* • If only day unknown, impute as the later of (first day of the month; end of treatment + 1). • If month and day unknown, impute as the later of (1st January; end of treatment + 1). *CRF questions: 'Started prior to study?' = No; 'Started after last dose of study medication?' = No.* • If only day unknown, impute as the later of (first day of the month; date of ICF). • If month and day unknown, impute as the later of (1st January; date of ICF). Then: If stop date is missing could never be assumed a prior medication. If start date <= end of treatment, assign as concomitant. If start date > end of treatment, assign as post treatment.
Missing	Known	If stop date < study med start date, assign as prior. If stop date >= study med start date and CRF question 'Started after last dose of study medication?' = No, assign as concomitant. If CRF question 'Started after last dose of study medication?' = Yes, assign as post treatment.
Missing	Partial	Impute stop date as latest possible date: • If only day unknown, impute as the earlier of (last day of the month; end date of the last study visit). • If month and day unknown, impute as the earlier of (31st December; end date of the last study visit). Then: If stop date < study med start date, assign as prior. If stop date >= study med start date and CRF question 'Started after last dose of study medication?' = No, assign as concomitant. If CRF question 'Started after last dose of study medication?' = Yes, assign as post treatment.

START DATE	STOP DATE	ACTION
Missing	Missing	If CRF question 'Started after last dose of study medication?' = No, assign as concomitant. If CRF question 'Started after last dose of study medication?' = Yes, assign as post treatment.

PARTIAL DATE IMPUTATION RULES FOR INITIAL ONSET OF SCHIZOPHRENIA:

For subjects with partial onset dates of schizophrenia, impute the onset date using the following rules:

- If only day unknown, impute as the earlier of: last day of the month, or date of ICF.
- If both month and day unknown, impute as the earlier of: 31st December of the year, or date of ICF.

PARTIAL DATE IMPUTATION RULES FOR ONSET OF ACUTE EXACERBATION:

For subjects with partial onset dates of acute exacerbation, impute the onset date using the following rules:

- If only day unknown, impute as the later of: first day of the month, or date of initial onset of schizophrenia (actual or imputed).
- If both month and day unknown, impute as the later of: 1st January of the year, or date of initial onset of schizophrenia (actual or imputed).

APPENDIX 3. STATISTICAL MODEL SPECIFICATIONS (SAMPLE SAS CODE)

Definition	Variable
Subject number (character)	SUBJID
Planned double-blind treatment group (numeric)	TRT01PN (1=" SEP-36385 50 or 75 mg/day"; 2="Placebo")
Visit (numeric)	AVISITN (3="Day 4"; 4="Week 1"; 5="Week 2"; 6="Week 3"; 7="Week 4")
Change from baseline values (numeric)	CHG
PANSS total score at each post-baseline visit	PANSS3 to PANSS7
Last visit with PANSS total score available (numeric)	LASTVISN (3="Day 4"; 4="Week 1"; 5="Week 2"; 6="Week 3"; 7="Week 4")

MIXED MODEL FOR REPEATED MEASURES (MMRM)

```
ODS OUTPUT LSMEstimates=xxxx CovParms=xxxx Tests3=xxxx Coef=xxxx;
PROC MIXED DATA=xxxx;
   CLASS SUBJID <Pooled study center> TRT01PN AVISITN;
   MODEL CHG = <Baseline PANSS total score> <Pooled study center> TRT01PN AVISITN
               TRT01PN*AVISITN / DDFM=KR SOLUTION;
   REPEATED AVISITN / SUB=SUBJID TYPE=UN;
   LSMESTIMATE TRT01PN*AVISITN "SEP-363856 at Day 4"  [1, 1 1],
                               "SEP-363856 at Week 1" [1, 1 2],
                               "SEP-363856 at Week 2" [1, 1 3],
                               "SEP-363856 at Week 3" [1, 1 4],
                               "SEP-363856 at Week 4" [1, 1 5] / E CL;

   LSMESTIMATE TRT01PN*AVISITN "Placebo at Day 4"  [1, 2 1],
                               "Placebo at Week 1" [1, 2 2],
                               "Placebo at Week 2" [1, 2 3],
                               "Placebo at Week 3" [1, 2 4],
                               "Placebo at Week 4" [1, 2 5] / E CL;

   LSMESTIMATE TRT01PN*AVISITN
               "SEP-363856 vs Placebo at Day 4"  [1, 1 1] [-1, 2 1],
               "SEP-363856 vs Placebo at Week 1" [1, 1 2] [-1, 2 2],
               "SEP-363856 vs Placebo at Week 2" [1, 1 3] [-1, 2 3],
               "SEP-363856 vs Placebo at Week 3" [1, 1 4] [-1, 2 4],
               "SEP-363856 vs Placebo at Week 4" [1, 1 5] [-1, 2 5] / E CL;
```

```
RUN;
```

In case the MMRM model assuming unstructured covariance model fails to converge, the spatial exponential model and then the spatial power model will be assumed sequentially.

```
DATA xxxx;
   SET xxxx;
   IF AVISITN=3 THEN AVDY=4;
   ELSE IF AVISITN=4 THEN AVDY=8;
   ELSE IF AVISITN=5 THEN AVDY=15;
   ELSE IF AVISITN=6 THEN AVDY=22;
   ELSE IF AVISITN=7 THEN AVDY=29;
RUN;

ODS OUTPUT LSMEstimates=xxxx CovParms=xxxx Tests3=xxxx Coef=xxxx;
PROC MIXED DATA=xxxx EMPIRICAL;
   CLASS SUBJID <Pooled study center> TRT01PN AVISITN;
   MODEL CHG = <Baseline PANSS total score> <Pooled study center> TRT01PN AVISITN
               TRT01PN*AVISITN / SOLUTION;
   /* only retain one of the following two REPEATED statements */
   REPEATED AVISITN / SUB=SUBJID TYPE=SP(EXP)(AVDY); /* spatial exponential */
   REPEATED AVISITN / SUB=SUBJID TYPE=SP(POW)(AVDY); /* spatial power */
   LSMESTIMATE TRT01PN*AVISITN "SEP-363856 at Day 4"  [1, 1 1],
                               "SEP-363856 at Week 1" [1, 1 2],
                               "SEP-363856 at Week 2" [1, 1 3],
                               "SEP-363856 at Week 3" [1, 1 4],
                               "SEP-363856 at Week 4" [1, 1 5] / E CL;

   LSMESTIMATE TRT01PN*AVISITN "Placebo at Day 4"  [1, 2 1],
                               "Placebo at Week 1" [1, 2 2],
                               "Placebo at Week 2" [1, 2 3],
                               "Placebo at Week 3" [1, 2 4],
                               "Placebo at Week 4" [1, 2 5] / E CL;

   LSMESTIMATE TRT01PN*AVISITN
               "SEP-363856 vs Placebo at Day 4"  [1, 1 1] [-1, 2 1],
               "SEP-363856 vs Placebo at Week 1" [1, 1 2] [-1, 2 2],
               "SEP-363856 vs Placebo at Week 2" [1, 1 3] [-1, 2 3],
               "SEP-363856 vs Placebo at Week 3" [1, 1 4] [-1, 2 4],
               "SEP-363856 vs Placebo at Week 4" [1, 1 5] [-1, 2 5] / E CL;
RUN;
```

PATTERN-MIXTURE MODEL (PMM) WITH PLACEBO-BASED MI

Step 1: Partial imputation to get monotone missing pattern.

```
PROC MI DATA=xxxx OUT=xxxx_mono NIMPUTE=500 SEED=123 MINIMUM=30 MAXIMUM=210
        MINMAXITER=100;
```

```
   BY TRT01PN;
   VAR <Baseline PANSS total score> PANSS3 PANSS4 PANSS5 PANSS6 PANSS7;
   MCMC CHAIN=MULTIPLE INITIAL=EM IMPUTE=MONOTONE NBITER=5000 NITER=200;
RUN;
```

Step 2: Impute with sequential regression method.

Step 2.1: Separate dataset `xxxx_mono` into two parts: Part 1 includes all subjects in the placebo group and those subjects in the SEP-363856 group with PANSS total score missing for the Day 4 visit; Part 2 includes those subjects in the SEP-363856 group with PANSS total score available for the Day 4 visit. Impute missing PANSS total scores in Part 1. Then put the two parts back together.

```
DATA mono_imp3 mono_rest3;
   SET xxxx_mono;
   IF TRT01PN=1 AND LASTVISN>=3 THEN OUTPUT mono_rest3;
   ELSE OUTPUT mono_imp3;
RUN;

PROC SORT DATA=mono_imp3; BY _IMPUTATION_; RUN;

PROC MI DATA=mono_imp3 OUT=mono_reg3 NIMPUTE=1 SEED=234 MINIMUM=. 30 30
        MAXIMUM=. 210 210 MINMAXITER=100;
   BY _IMPUTATION_;
   VAR <Pooled study center> <Baseline PANSS total score> PANSS3;
   CLASS <Pooled study center>;
   MONOTONE REG(PANSS3);
RUN;

DATA mono_panss3;
   SET mono_reg3 mono_rest3;
RUN;
```

Note: If an imputation failed because the imputed value is not within the specified min-max range, that particular imputation won't exist in `mono_reg3`. In that case need to remove the corresponding imputation in `mono_rest3` before re-assembling the 2 datasets together.

Step 2.2: Separate dataset `mono_panss3` into two parts: Part 1 includes all subjects in the placebo group and those subjects in the SEP-363856 group with PANSS total score missing for the Week 1 visit; Part 2 includes those subjects in the SEP-363856 group with PANSS total score available for the Week 1 visit. Impute missing PANSS total scores in Part 1. Then put the two parts back together.

```
DATA mono_imp4 mono_rest4;
   SET mono_panss3;
   IF TRT01PN=1 AND LASTVISN>=4 THEN OUTPUT mono_rest4;
   ELSE OUTPUT mono_imp4;
RUN;

PROC SORT DATA=mono_imp4; BY _IMPUTATION_; RUN;
```

```
PROC MI DATA=mono_imp4 OUT=mono_reg4 NIMPUTE=1 SEED=345 MINIMUM=. 30 30 30
        MAXIMUM=. 210 210 210 MINMAXITER=100;
   BY _IMPUTATION_;
   VAR <Pooled study center> <Baseline PANSS total score> PANSS3 PANSS4;
   CLASS <Pooled study center>;
   MONOTONE REG(PANSS4);
RUN;

DATA mono_panss4;
   SET mono_reg4 mono_rest4;
RUN;
```

Note: If an imputation failed because the imputed value is not within the specified min-max range, that particular imputation won't exist in `mono_reg4`. In that case need to remove the corresponding imputation in `mono_rest4` before re-assembling the 2 datasets together.

Steps 2.3 – 2.5: Continue with the above step to impute missing PANSS total scores for the Week 2, Week 3, and Week 4 visits. The seed number for the respective imputation steps are 456, 567, and 678.

Step 3: Fit the primary MMRM model and calculate the effect size on each imputed dataset.

Step 3.1: Re-format dataset `mono_panss7` from Step 2, which has all missing PANSS total scores imputed, into long format. Suppose the new dataset is `analysis`. Derive change from baseline values `CHG` for each post-baseline visit. Other variables in `analysis` should include: `SUBJID`, `TRT01PN`, `<Pooled study center>`, `AVISITN`, `<Baseline PANSS total score>`, `AVAL` (PANSS total score at each post-baseline visit), and `_IMPUTATION_`.

Suppose the primary MMRM model adopted the unstructured covariance model:

```
ODS OUTPUT LSMEstimates=lsmest_pbomi CovParms=xxxx Tests3=xxxx;
PROC MIXED DATA=analysis;
   BY _IMPUTATION_;
   CLASS SUBJID <Pooled study center> TRT01PN AVISITN;
   MODEL CHG = <Baseline PANSS total score> <Pooled study center> TRT01PN AVISITN
               TRT01PN*AVISITN / DDFM=KR SOLUTION;
   REPEATED AVISITN / SUB=SUBJID TYPE=UN;
   LSMESTIMATE TRT01PN*AVISITN "SEP-363856 at Day 4"  [1, 1 1],
                               "SEP-363856 at Week 1" [1, 1 2],
                               "SEP-363856 at Week 2" [1, 1 3],
                               "SEP-363856 at Week 3" [1, 1 4],
                               "SEP-363856 at Week 4" [1, 1 5] / E CL;

   LSMESTIMATE TRT01PN*AVISITN "Placebo at Day 4"  [1, 2 1],
                               "Placebo at Week 1" [1, 2 2],
                               "Placebo at Week 2" [1, 2 3],
                               "Placebo at Week 3" [1, 2 4],
                               "Placebo at Week 4" [1, 2 5] / E CL;

   LSMESTIMATE TRT01PN*AVISITN
               "SEP-363856 vs Placebo at Day 4"  [1, 1 1] [-1, 2 1],
```

```
                "SEP-363856 vs Placebo at Week 1" [1, 1 2] [-1, 2 2],
                "SEP-363856 vs Placebo at Week 2" [1, 1 3] [-1, 2 3],
                "SEP-363856 vs Placebo at Week 3" [1, 1 4] [-1, 2 4],
                "SEP-363856 vs Placebo at Week 4" [1, 1 5] [-1, 2 5] / E CL;
RUN;
```

Step 3.2: Extract the diagonal elements of the R matrix (from `CovParms`). Suppose the diagonal elements are stored in variable `COVAREST` in dataset `covar`. Dataset `covar` should also include variables `_IMPUTATION_` and `AVISITN`. Add variable `AVISITN` also to dataset `lsmest_pbomi`. Merge `covar` with `lsmest_pbomi` by `_IMPUTATION_` and `AVISITN`. Then calculate the within group and between group effect sizes at each time point.

```
DATA lsmest_pbomi;
   SET lsmest_pbomi;
   EFFSIZE=ESTIMATE/SQRT(COVAREST);
RUN;
```

Step 4: Combine results using Rubin's imputation rules.

```
PROC SORT DATA=lsmest_pbomi; BY LABEL _IMPUTATION_; RUN;

ODS OUTPUT ParameterEstimates=lsmest_pbomi_mian;
PROC MIANALYZE PARMS=lsmest_pbomi;
   BY LABEL;
   MODELEFFECTS TRT01PN*AVISITN;
RUN;

ODS OUTPUT summary=mean_effsize_pbomi;
PROC MEANS DATA=lsmest_pbomi N MEAN STD MIN MAX Q1 Q3;
   VAR EFFSIZE;
   CLASS LABEL;
RUN;
```

TIPPING POINT ANALYSIS

Step 1: Run the primary MMRM analysis. Obtain LS mean difference between SEP-363856 group and the placebo group at each visit. Suppose these values are stored in variable `LSMDIFF` in dataset `diff`. This dataset should also contain variable `AVISITN`. These differences will be used when applying penalty on the imputed values.

Step 2: Partial imputation to get monotone missing pattern.

```
PROC MI DATA=xxxx OUT=xxxx_mono NIMPUTE=500 SEED=123 MINIMUM=30 MAXIMUM=210
        MINMAXITER=100;
   BY TRT01PN;
   VAR <Baseline PANSS total score> PANSS3 PANSS4 PANSS5 PANSS6 PANSS7;
   MCMC CHAIN=MULTIPLE INITIAL=EM IMPUTE=MONOTONE NBITER=5000 NITER=200;
```

```
RUN;
```

Step 3: Impute the remaining missing data using an MAR-based regression model.

```
PROC MI DATA=xxxx_mono OUT=xxxx_impute NIMPUTE=1 SEED=234
        MINIMUM=. . 30 30 30 30 30 30 MAXIMUM=. . 210 210 210 210 210 210
        MINMAXITER=100;
   BY _IMPUTATION_;
   VAR TRT01PN <Pooled study center> <Baseline PANSS total score> PANSS3 PANSS4
       PANSS5 PANSS6 PANSS7;
   CLASS TRT01PN <Pooled study center>;
   MONOTONE REGRESSION;
RUN;
```

Step 4: For a range of penalty values (i.e. 10%, 20%, 30%, etc. of the LS mean difference obtained in Step 1), apply penalty to the change from baseline values calculated from imputed PANSS total scores in the SEP-363856 group at each post-baseline visit.

Suppose `analysis` is the dataset reformatted from `xxxx_impute` that contains each subject's data in long format. It should contain the missing value flag `MISSVAL` (i.e. whether the PANSS total score for a given visit is missing in the monotone missing data): `1` = missing; `0` = available. Other variables in `analysis` should include: `SUBJID`, `TRT01PN`, `<Pooled study center>`, `AVISITN`, `<Baseline PANSS total score>`, `AVAL` (PANSS total score at each post-baseline visit), `CHG`, `LSMDIFF`, and `_IMPUTATION_`.

```
DATA analysis_penalty;
   SET analysis;
   /* store the original CHG values in ORIGCHG */
   ORIGCHG = CHG;

   /* if a PANSS total score is missing in the original dataset, apply a penalty
      to the CHG value in the SEP-363856 group only */
   DELTA = xxx;
   IF MISSVAL=1 AND TRT01PN=1 THEN CHG = ORIGCHG - ((DELTA/100)*LSMDIFF);
RUN;
```

Repeat the above step for all delta values, i.e. 10, 20, 30, …, 100.

Step 5: Fit the MMRM model on each imputed and penalized dataset.

Suppose the MMRM model adopted the unstructured covariance model:

```
ODS OUTPUT LSMEstimates=lsmest_tipping CovParms=xxxx;
PROC MIXED DATA=analysis_penalty;
   BY DELTA _IMPUTATION_;
   CLASS SUBJID <Pooled study center> TRT01PN AVISITN;
   MODEL CHG = <Baseline PANSS total score> <Pooled study center> TRT01PN AVISITN
               TRT01PN*AVISITN / DDFM=KR;
   REPEATED AVISITN / SUB=SUBJID TYPE=UN;
   LSMESTIMATE TRT01PN*AVISITN
```

```
                "SEP-363856 vs Placebo at Week 4" [1, 1 5] [-1, 2 5] / E CL;
RUN;
```

Step 6: Combine results using Rubin's imputation rules.

```
PROC SORT DATA=lsmest_tipping; BY DELTA LABEL _IMPUTATION_; RUN;

ODS OUTPUT ParameterEstimates=lsmest_tipping_mian;
PROC MIANALYZE PARMS=lsmest_tipping;
   BY DELTA LABEL;
   MODELEFFECTS TRT01PN*AVISITN;
RUN;
```

APPENDIX 4. PSQI SOCRING SHEET

Source: http://www.sleep.pitt.edu/research/instruments.html

Pittsburgh Sleep Quality Index (PSQI)

Form Administration Instructions, References, and Scoring

Form Administration Instructions

The range of values for questions 5 through 10 are all 0 to 3.

Questions 1 through 9 are not allowed to be missing except as noted below. If these questions are missing then any scores calculated using missing questions are also missing. Thus it is important to make sure that all questions 1 through 9 have been answered.

In the event that a range is given for an answer (for example, '30 to 60' is written as the answer to Q2, minutes to fall asleep), split the difference and enter 45.

Reference

Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ: The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Research* 28:193-213, 1989.

Scores – reportable in publications

On May 20, 2005, on the instruction of Dr. Daniel J. Buysse, the scoring of the PSQI was changed to set the score for Q5J to 0 if either the comment or the value was missing. This may reduce the DISTB score by 1 point and the PSQI Total Score by 1 point.

PSQIDURAT **DURATION OF SLEEP**

IF Q4 $\geq$ 7, THEN set value to 0
IF Q4 < 7 and $\geq$ 6, THEN set value to 1
IF Q4 < 6 and $\geq$ 5, THEN set value to 2
IF Q4 < 5, THEN set value to 3
Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQIDISTB **SLEEP DISTURBANCE**

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) = 0, THEN set value to 0

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) $\geq$ 1 and $\leq$ 9, THEN set value to 1

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) > 9 and $\leq$ 18, THEN set value to 2

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) > 18, THEN set value to 3

Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQILATEN **SLEEP LATENCY**

First, recode Q2 into Q2new thusly:
IF Q2 ≥ 0 and ≤ 15, THEN set value of Q2new to 0
IF Q2 > 15 and ≤ 30, THEN set value of Q2new to 1
IF Q2 > 30 and ≤ 60, THEN set value of Q2new to 2
IF Q2 > 60, THEN set value of Q2new to 3
Next
IF Q5a + Q2new = 0, THEN set value to 0
IF Q5a + Q2new ≥ 1 and ≤ 2, THEN set value to 1
IF Q5a + Q2new ≥ 3 and ≤ 4, THEN set value to 2
IF Q5a + Q2new ≥ 5 and ≤ 6, THEN set value to 3

Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQIDAYDYS **DAY DYSFUNCTION DUE TO SLEEPINESS**

IF Q8 + Q9 = 0, THEN set value to 0
IF Q8 + Q9 ≥ 1 and ≤ 2, THEN set value to 1
IF Q8 + Q9 ≥ 3 and ≤ 4, THEN set value to 2
IF Q8 + Q9 ≥ 5 and ≤ 6, THEN set value to 3
Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQIHSE **SLEEP EFFICIENCY**

Diffsec = Difference in seconds between day and time of day Q1 and day Q3
Diffhour = Absolute value of diffsec / 3600
newtib =IF diffhour > 24, then newtib = diffhour – 24
IF diffhour ≤ 24, THEN newtib = diffhour
(NOTE, THE ABOVE JUST CALCULATES THE HOURS BETWEEN GNT (Q1) AND GMT (Q3))
tmphse = (Q4 / newtib) * 100

IF tmphse ≥ 85, THEN set value to 0
IF tmphse < 85 and ≥ 75, THEN set value to 1
IF tmphse < 75 and ≥ 65, THEN set value to 2
IF tmphse < 65, THEN set value to 3
Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQISLPQUAL **OVERALL SLEEP QUALITY**

Q6
Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQIMEDS **NEED MEDS TO SLEEP**

Q7
Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQI **TOTAL**

DURAT + DISTB + LATEN + DAYDYS + HSE + SLPQUAL + MEDS
Minimum Score = 0 (better); Maximum Score = 21 (worse)

Interpretation: TOTAL ≤ 5 associated with good sleep quality
TOTAL > 5 associated with poor sleep quality