STATISTICAL ANALYSIS PLAN

SEP361-202

A 26-WEEK OPEN-LABEL SAFETY AND TOLERABILITY EXTENSION STUDY OF SEP-363856 IN ADULT SUBJECTS WITH SCHIZOPHRENIA

AUTHOR:

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan Final V1.0 (dated 27Feb2019) for protocol SEP361-202.

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MODIFICATION HISTORY

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse Event
AIMS	Abnormal Involuntary Movement Scale
ATC	Anatomical Therapeutic Chemical
BARS	Barnes Akathisia Rating Scale
BLQ	Below the Lower Limit of Quantification
BMI	Body Mass Index
BNSS	Brief Negative Systems Scale
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
CSB	Cogstate Schizophrenia Battery
CSP	Clinical Study Protocol
CYP	Cytochrome
DB	Double-Blind
DEQ	Drug Effects Questionnaire
DMC	Data Monitoring Committee
DSM-5	Diagnostic and Statistical Manual of Mental Disorder, 5th Edition
ECG	Electrocardiogram
HLT	High Level Term

Abbreviation	Explanation
HR	Heart Rate
ICF	Informed Concern Form
IPD	Important Protocol Deviations
LOCF	Last Observation Carried Forward
MADRS	Montgomery-Asberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
OL	Open-Label
PANSS	Positive and Negative Syndrome Scale
PD	Pharmacodynamics
PK	Pharmacokinetic
PSQI	Pittsburgh Sleep Quality Index
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Simpson-Angus Scale
SI	International System of Units
SOC	System Organ Class
ULQ	Upper Limit of Quantification
UPSM	Uncorrelated PANSS Score Matrix
USPA-B	University of California, San Diego, Performance-Based Skills Assessment-Brief
VAS	Visual Analogue Scale

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of safety and efficacy data for protocol SEP361-202. 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 4.0 (13-Oct-2017). Hereafter, this protocol version is referred to as the Clinical Study Protocol (CSP).

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

To evaluate the long-term safety and tolerability of flexibly dosed SEP-363856 (25, 50, or 75 mg/day [ie, once daily]) in adult subjects with schizophrenia who have completed Study SEP361-201 by the incidence of overall adverse events (AEs), serious AEs (SAEs), and AEs leading to discontinuation.

2.2. SECONDARY OBJECTIVES

- To evaluate the long-term safety and tolerability of SEP-363856 by assessing vital signs, physical examinations (PE), body weight and body mass index (BMI), 12-lead electrocardiograms (ECG), clinical laboratory evaluations, and suicidal ideation and suicidal behavior using the Columbia – Suicide Severity Rating Scale (C-SSRS)

- To evaluate the long-term effectiveness of SEP-363856 using the Positive and Negative Syndrome Scale (PANSS) total score, Clinical Global Impression-Severity (CGI-S), PANSS subscale scores (positive, negative, general psychopathology), Brief Negative Symptom Scale (BNSS), and Montgomery-Asberg Depression Rating Scale (MADRS)

- To explore the long-term maintenance of response in subjects treated with SEP-363856 as measured by the time to relapse and the rate of relapse

2.3. OTHER OBJECTIVES

- To assess whether long-term treatment with 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 long-term effects of SEP-363856 as measured by the Drug Effects Questionnaire (DEQ)

- To characterize the subjective long-term effects of SEP-363856 on sleep as measured by the Pittsburgh Sleep Quality Index (PSQI)
- To explore the effects of SEP-363856 on cognition as assessed by the CogState Brief Battery (CBB) and the CogState Schizophrenia Battery (CSB)
- To explore the effects of SEP-363856 on functional outcomes as measured by the UPSA-B total score

3. STUDY DESIGN

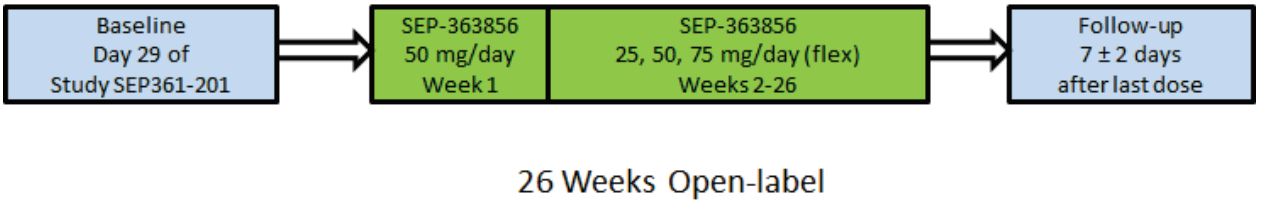
3.1. GENERAL DESCRIPTION

This is a 26-week, multiregional, open-label extension study designed to evaluate the long-term safety and tolerability of SEP-363856 for the treatment of subjects with schizophrenia who have completed the 4-week double-blind treatment phase of Study SEP361-201.

Subjects who meet the entry criteria will transition immediately from study SEP361-201 at Visit 7. Subjects will attend an initial visit on Day 1 (same day as Visit 7 of study SEP361-201). During the SEP361-202 study period, clinic visits will occur as shown in Table 1 Scheduled of Assessments.

Study schematic is shown in Figure 1. All subjects will receive open-label SEP-363856 50 mg/day from Day 1 through Day 3. Beginning on Day 4, flexible dosing ranging from 25 to 75 mg/day is permitted, if deemed clinically necessary (for reasons of safety, tolerability, or efficacy) by the Investigator. On Day 4, subjects are permitted (but not required) to titrate up to 75 mg/day for reasons of efficacy, at an unscheduled visit. Thereafter, an increase in dose should occur at weekly intervals in increments of one dose level at a time to a maximum dose of 75 mg/day. Dose reduction for tolerability purposes is allowed at any time during the study.

Figure 1: Study Schematic



Note: Titration up to 75 mg/day is permitted (but not required) on Day 4 for reasons of efficacy as an unscheduled visit.

3.2. SCHEDULE OF EVENTS

Schedule of events can be found in Table 1.

Table 1. Schedule of Assessments

Study Visit Number **Study Visit Week**	**Visit 1E[a] Baseline**	**Visit 2E Week 1**	**Visit 3E Week 2**	**Visit 4E Week 3**	**Visit 5E Week 4**	**Visit 6E Week 8**	**Visit 7E Week 12**	**Visit 8E Week 16**	**Visit 9E Week 20**	**Visit 10E Week 24**	**Visit 11E Week 26 or ET[b]**	**Visit 12E Week 27 Follow-up[c] EOS**
Study Visit Day	**1**	**8 ± 2**	**15 ± 2**	**22 ± 2**	**29 ± 3**	**57 ± 3**	**85 ± 3**	**113 ± 3**	**141 ± 3**	**169 ± 3**	**183 ± 3**	**190 ± 2**
Obtain informed consent	X											
Review inclusion/exclusion criteria	X											
Dispense study drug[d]	X[m]	X	X	X	X	X	X	X	X	X		
Study drug accountability		X	X	X	X	X	X	X	X	X	X	
Telephone Contacts[e]		Telephone calls to the subjects will be made between Weeks 1 and 2 and at Weeks 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, and 25. If subject appears to be symptomatic, an unscheduled visit will be made as early as possible.[f]										
Clinical and Laboratory Evaluations												
Adverse event (AE) monitoring	Performed at Visit 7 of study SEP361-201	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medication review		X	X	X	X	X	X	X	X	X	X	X
Physical and neurological examination					X	X		X			X	
Vital signs[g]		X		X	X	X	X	X	X	X	X	X
Weight (including BMI)		X		X	X	X	X	X	X	X	X	
Waist circumference		X		X	X	X	X	X	X	X	X	
Electrocardiogram (ECG)		X			X	X	X	X	X	X	X	
Clinical laboratory tests[h]		X			X			X			X	
Blood sample for POPPK[i]		X			X			X			X	
Urine drug screen[j]		X			X			X			X	
Urine β-hCG[k]		X	X	X	X	X	X	X	X	X	X	X
Positive and Negative Syndrome Scale (PANSS)		X	X	X	X	X	X	X	X	X	X	

Table 1. Schedule of Assessments (Continued)

Study Visit Number Study Visit Week	Visit1E[a] Baseline	Visit2E Week 1	Visit3E Week 2	Visit4E Week 3	Visit5E Week 4	Visit6E Week 8	Visit7E Week 12	Visit8E Week 16	Visit9E Week 20	Visit10E Week 24	Visit 11E Week 26 or ET[b]	Visit 12E Week 27 Follow-up[c] EOS
Study Visit Day	**1**	**8 ± 2**	**15 ± 2**	**22 ± 2**	**29 ± 3**	**57 ± 3**	**85 ± 3**	**113 ± 3**	**141 ± 3**	**169 ± 3**	**183 ± 3**	**190 ± 2**
Brief Negative Symptoms Scale (BNSS)		X	X	X	X	X	X	X	X	X	X	
Clinical Global Impression – Severity (CGI-S)		X	X	X	X	X	X	X	X	X	X	
Montgomery-Asberg Depression Rating Scale (MADRS)		X	X	X	X	X	X	X	X	X	X	
Columbia Suicide Severity Rating Scale (C-SSRS)		X	X	X	X	X	X	X	X	X	X	X
Drug effects questionnaire (DEQ)											X	X
Abnormal Involuntary Movement Scale (AIMS)[l]		X	X	X	X	X	X	X	X	X	X	
Barnes Akathisia Rating Scale (BARS)[l]		X	X	X	X	X	X	X	X	X	X	
Simpson-Angus Scale (SAS)[l]		X	X	X	X	X	X	X	X	X	X	
Pittsburg Sleep Quality Index (PSQI)		X			X		X			X	X	X
Cogstate Cognition Battery (CBB)												
Cogstate Schizophrenia Battery (CSB)							X				X	
USPA-B	X						X				X	

Abbreviations: AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; β-hCG = human chorionic gonadotropin; BNSS = Brief Negative Symptoms Scale; CGI-S = Clinical Global Impression – Severity; CBB = Cogstate Brief Battery; CSB = CogState Schizophrenia Battery; C-SSRS = Columbia Suicide Severity Rating Scale ; ECG = Electrocardiogram; ET = early termination; MADRS = Asberg Depression Rating Scale; SAS = Simpson-Angus Scale; PANSS = Positive and Negative Syndrome Scale; PK = pharmacokinetic; PSQI = Pittsburg Sleep Quality Index;

[a] Results of assessments from Visit 7 (Week 4) of Study SEP361-201 will serve as Baseline assessments for the present study. NOTE: Subjects may be hospitalized for the first week of the present study if deemed appropriate by the Investigator.
[b] If a subject discontinues from the study, all Visit 11E procedures should be performed at the discontinuation visit, within 48 hours of last study dose.
[c] All subjects will have a safety follow-up visit 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] Telephone calls will be made by a member of the research staff to the subjects between scheduled study visits (between Weeks 1 and 2, and at Weeks 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, and 25) to monitor clinical symptoms and adverse events. If subject appears to be symptomatic, an unscheduled visit will be made as early as possible.
[f] Procedures and assessments for unscheduled visit are: drug accountability, physical and neurological examination, vital signs, ECG, clinical laboratory tests, urine drug screen, PANSS, CGI-S, MADRS, BNSS, AIMS, BARS, SAS, and C-SSRS.
[g] Vital signs will include supine and standing measurements of blood pressure and heart rate and respiratory rate and temperature.
[h] Clinical laboratory tests include: hematology, serum chemistry, urinalysis, serum prolactin, glycosylated hemoglobin (HbA_{1c}), and glucose and lipid panel (subjects must be fasted [no food or drink except water at least 8 hours] prior to collection of blood samples for glucose and lipid panel).
[i] Blood samples for determination of plasma SEP-363856 and SEP-363854 concentrations will be collected at Visit 2E, 5E, 8E, and 11E (time and date of the 3 previous doses of study medication and the time of the blood sampling must be recorded). Time of food intake relative to study drug taken should be recorded.
[j] Urine drug screen may be ordered at other visits as deemed clinically appropriate. These results should be discussed with the Medical Monitor.
[k] Any positive urine β-hCG test should be confirmed by a serum β-hCG test.
[l] Unscheduled BARS, AIMS, and SAS scales should be administered if a subject develops extrapyramidal symptoms (EPS) requiring treatment.
[m] Titration up to 75 mg/day is permitted (but not required) on Day 4 for reasons of efficacy as an unscheduled visit. At the minimum Investigator will assess AEs, concomitant medications and perform drug accountability at Day 4 unscheduled visit, all other assessments are not required but permitted based on Investigators judgment.

Note: With the exception of the DEQ and the USPA-B, 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

All subjects who complete the 4-week double-blind treatment period of Study SEP361-201 are eligible. It is anticipated that approximately 180 subjects will enter this open-label extension study.

3.4. Method of Assigning Subjects to Treatment Groups

All subjects will receive flexible dosing with SEP-363856 (25, 50, or 75 mg/day).

3.5. Blinding

This an open-label study.

3.6. CHANGES IN THE CONDUCT OF THE STUDY

The first subject entered study SEP361-202 under protocol version 2.00 (23 June 2016). The protocol versions and amendments listed below were implemented after the enrollment 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)
- Protocol version 4.00 (13-Oct-2017); Amendment 3.00 (13-Oct-2017)

3.7. CHANGES TO ANALYSIS FROM PROTOCOL

- The protocol specified that for subjects *assigned* to double-blind SEP-363856, clinical response will be evaluated using the Day 29 data of study 361-201, against the DB baseline, and for subjects *assigned* to double-blind placebo, clinical response will be evaluated using the Day 29 data of study 361-202, against the OL baseline. Rather than the randomized treatment assigned to subjects, the analysis will be based on the *actual treatment received* during study 361-201. In addition, rather than using different baselines based on 361-201 treatment, DB baseline will be used for all subjects rolling over to 361-202, irrespective of the treatment they received in 361-201.
- The protocol specified that PANSS response rate will be calculated based on the DB baseline for subjects assigned to double-blind SEP-363856 and the OL baseline for subjects assigned to double-blind placebo. Rather than using different baselines based on 361-201 treatment, DB baseline will be used for all subjects rolling over to 361-202, irrespective of the treatment they received in 361-201.

- 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 protocol specified that one relapse criterion is emergence of suicidal ideation, homicidal ideation and/or risk of harm to self or others. The term 'suicidal ideation' is to be replaced by 'suicidality' and the term 'homicidal ideation' replaced by 'homicidality'. This is because the search criteria for AEs and C-SSRS data that meet this relapse criterion (see appendix 3) cover both suicidal ideation and suicidal behavior, and both homicidal ideation and homicidal behavior.

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 IQVIA Biostatistics following Sunovion authorization of this SAP, Sunovion authorization of analysis populations, and database lock.

5. ANALYSIS POPULATIONS

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

5.1. SAFETY POPULATION

The safety population includes all subjects who were enrolled and received at least one dose of study drug

during the 26-week open-label extension period.

The safety population will be used for the long-term safety, tolerability, and efficacy analyses.

5.2. RELAPSE POPULATION

The relapse population will include safety population subjects who demonstrated a clinical response to 4 weeks of treatment with SEP-363856. Clinical response is defined as meeting both of the following criteria:

- A decrease in PANSS total score of ≥ 20% from baseline
- A CGI-S score ≤ 4

For subjects who received double-blind SEP-363856 in study 361-201, clinical response will be evaluated using the Week 4 (Visit 7) PANSS and CGI-S data of study 361-201, against the double-blind baseline (see section 6.2). For subjects who received double-blind placebo, clinical response will be evaluated using the Week 4 (Visit 5E) PANSS and CGI-S data of study 361-202, against the double-blind baseline (see section 6.2).

The relapse population will be used for analysis of relapse of psychotic symptoms.

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 of study 361-202 (Day 1).

- If the date of the event is on or after the reference start date then:
  - Study day = (date of event – reference start date) + 1.
- If the date of the event is prior to the reference start date then:
  - 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, double-blind (DB) baseline is defined as the last non-missing measurement taken prior to the first dose of study medication of study 361-201, including unscheduled assessments.

Open-label (OL) baseline is defined as the last non-missing measurement taken prior to the first dose of extension study medication of study 361-202, 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 in study 361-201 or the date of first dose of extension study medication in study 361-202 coincide, that measurement will be considered baseline.

6.3. DERIVED TIME POINTS

The last post OL baseline measurement collected in study 361-202 will be carried forward and will be defined as the last observation carried forward (LOCF) endpoint, using the post OL baseline value up to and including the Week 26 visit data.

The LOCF endpoint will be derived for the following endpoints: PANSS total score, PANSS subscale scores, PANSS five-factor model (Marder) factor scores, PANSS seven-factor model (UPSM) factor scores, CGI-S score, BNSS total score, MADRS total score, AIMS total score, AIMS global severity score (item 8), BARS total score, BARS individual item scores, SAS mean score, PSQI global score, CBB composite score and individual standardized scores of the 4 tests in CBB, UPSA-B total score, and the C-SSRS suicidal ideation score. In addition, the LOCF endpoint will be derived for the following data: vital signs, body weight, BMI, waist circumference, ECG, clinical laboratories, and urine drug screen.

Both scheduled and unscheduled assessments as well as the early termination assessments that are collected post OL 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 in study 361-201 will contribute to the derivation of the DB baseline value. Unscheduled measurements collected prior to the first dose of extension study medication in study 361-202 will contribute to the derivation of the OL baseline value. Unscheduled measurements collected post OL baseline will contribute to the derivation of the LOCF endpoint, potentially clinically significant (PCS) value, best/ worst case value where required (e.g. shift tables), and identification of a relapse event (see section 16.2.6).

Early termination data collected post OL 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. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple sites in 5 countries. The centers will be pooled by country. PANSS total score and CGI-S score will be summarized by country.

7.2. MISSING DATA

For rating scales with more than one item, such as PANSS and MADRS, if any item score contributing to the total/subscale score is missing, then the total/subscale score will be set to missing.

In this study, missing data will not be imputed. All analyses will be based on the observed data.

7.3. MULTIPLE COMPARISONS/ MULTIPLICITY

No statistical comparison will be conducted, so no multiplicity adjustment will be performed.

7.4. EXAMINATION OF SUBGROUPS

Subgroup analyses will be conducted as stated in the respective efficacy and safety analysis sections.

The following subgroups will be assessed:

- Geographic region
  - US
  - Non-US
- Country
  - US
  - Hungary
  - Romania
  - Russia
  - Ukraine
- Sex
  - Female
  - Male
- Age group (years)
  - <25
  - >=25
- Race
  - White
  - Black
  - Other
- Number of prior hospitalizations for treatment of schizophrenia
  - 0
  - 1
  - 2
- Duration of schizophrenia (years)

o < 5
o >= 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 IQVIA Biostatistics.

9. DISPOSITION AND WITHDRAWALS

All subjects who entered study 361-202 will be accounted for in this analysis.

Subject disposition will be summarized and presented for the number and percentage of subjects who entered the extension study, received at least one dose of the extension study medication, and completed or discontinued the study (including reasons for discontinuation).

With respect to the above, the following definition applies:

- Enrolled subjects: All subjects who entered study 361-202 (i.e. signed the ICF of study 361-202 and was dispensed open-label study drug).

10. IMPORTANT PROTOCOL DEVIATIONS

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

- Did not satisfy important inclusion and/or exclusion criteria for the open-label extension study.
- Received any disallowed concomitant medication during the open-label extension period.

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

IPDs will be identified for all subjects who entered the extension study and presented in data listings. The number and percentage of subjects within each IPD category will be summarized for the safety population.

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the safety population. 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 of study 361-201; as a continuous variable and categorically

  - <18
  - 18 to <25
  - 25 to <=40
  - >40

- Sex

- Race

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

- Ethnicity

  - Hispanic or Latino
  - Not Hispanic or Latino

- Country

- Geographic region

- DB Baseline and OL Baseline for Weight (kg)

- Height (cm)

- DB Baseline and OL Baseline for Waist circumference (cm)

- DB Baseline and OL Baseline for BMI (kg/m^2), as a continuous variable and categorically:

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

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

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

- DB Baseline and OL Baseline for 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 safety population in a separate table:

- Time since initial onset of schizophrenia, in years, calculated relative to date of informed consent of study 361-201; 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 of study 361-201
- Diagnostic and Statistical Manual of Mental Disorder, 5th Edition (DSM-5) schizophrenia subtype diagnosis as collected in study 361-201
- Other current psychiatric diagnoses as collected in study 361-201
- Number (0, 1, 2, 3 or more) of prior hospitalizations for treatment of an acute exacerbation of schizophrenia as collected in study 361-201

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 of study 361-201, 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 extension study medication.

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

- Post-treatment medications are medications which started after the last dose of extension 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 during the open-label extension period will be summarized for the safety population.

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

- Number and percentage of subjects with drug exposure ≥ 1, ≥ 7, ≥ 14, ≥ 21, ≥ 28, ≥ 56, ≥ 84, ≥ 112, ≥ 140, ≥ 168 and ≥ 182 days;

- Number and percentage of subjects with drug exposure for 1 - 6, 7 - 13, 14 - 20, 21 - 27, 28 - 55, 56 - 83, 84 - 111, 112 - 139, 140 - 167, 168 - 181, and ≥ 182 days

Mean daily dose over the entire open-label extension period will be calculated for each subject as the cumulative dose (mg) of SEP-363856 divided by the duration of exposure (in days), where cumulative dose is the sum of all doses a subject received during the open-label extension period. The modal daily dose (i.e. the dose level that a subject was on for the most number of days among all doses taken) will be summarized:

- 25 mg/day
- 50 mg/day
- 75 mg/day
- Tie between 25 mg/day and 50 mg/day
- Tie between 25 my/day and 75 mg/day
- Tie between 50 mg/day and 75 mg/day
- Tie between 25 mg/day, 50 mg/day, and 75 mg/day

The number of days that a subject was on the 25 mg/day dose level, 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 – 6 days
- 7 – 13 days
- 14 – 20 days
- 21 – 27 days
- 28 – 55 days
- 56 – 83 days
- 84 – 111 days
- 112 – 139 days
- 140 – 167 days
- 168 – 181 days
- ≥ 182 days
- ≥ 168 days

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

14.1. DERIVATIONS

Duration of exposure (days) = last extension study dose date - first extension study dose date + 1. If the last extension study dose date is missing, the date will be imputed using the last known dosing end date.

15. STUDY MEDICATION COMPLIANCE

Compliance during the open-label extension period will be summarized for the safety population.

Percent compliance will be calculated by visit and overall for the open-label extension period. Non-compliance is defined as less than 75% or more than 125% non-missing compliance for the open-label extension 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 be calculated overall for the open-label extension period.

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.

16. EFFICACY OUTCOMES

All efficacy variables will be summarized descriptively by visit for the safety population or relapse population. For PANSS total score and CGI-S score, the data will also be summarized descriptively for each subgroup.

16.1. PANSS

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 (Marder) factor 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 (UPSM) factor 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 (item 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 PANSS total, subscale, and factor scores, if any item contributing to its calculation is missing then the score will be set to missing.

16.1.1. Observed Values and Change from Baseline in PANSS Total Score

The observed values of PANSS total score at both the DB baseline and the OL baseline, and at each scheduled post-OL baseline extension visit and LOCF, will be summarized descriptively.

Changes from baseline in PANSS total score will be summarized for each scheduled post-OL baseline extension visit and LOCF, based on both the DB baseline and the OL baseline.

PANSS total score will also be summarized by subgroups as listed in section 7.4.

16.1.2. Observed Values and Change from Baseline in PANSS Subscale Scores

The observed values of PANSS subscale scores at both the DB baseline and the OL baseline, and at each scheduled post-OL baseline extension visit and LOCF, will be summarized descriptively.

Changes from baseline in PANSS subscale score will be summarized for each scheduled post-OL baseline extension visit and LOCF, based on both the DB baseline and the OL baseline.

16.1.3. Observed Values and Change from Baseline in PANSS Five-Factor Model (Marder) Factor Scores

The observed values of PANSS five-factor model (Marder) factor scores at both the DB baseline and the OL baseline, and at each scheduled post-OL baseline extension visit and LOCF, will be summarized descriptively.

Changes from baseline in five-factor model (Marder) factor scores will be summarized for each scheduled post-OL baseline extension visit and LOCF, based on both the DB baseline and the OL baseline.

16.1.4. Observed Values and Change from Baseline in PANSS Seven-Factor Model (UPSM) Factor Scores

The observed values of PANSS seven-factor model (UPSM) factor scores at both the DB baseline and the OL baseline, and at each scheduled post-OL baseline extension visit and LOCF, will be summarized descriptively.

Changes from baseline in seven-factor model (UPSM) factor scores will be summarized for each scheduled post-OL baseline extension visit and LOCF, based on both the DB baseline and the OL baseline.

16.1.5. PROPORTION OF SUBJECTS WHO ACHIEVE A RESPONSE

PANSS response is defined as a 20% or greater improvement (i.e. decrease) in PANSS total score from the DB baseline to the Week 26 LOCF endpoint.

The percent change in PANSS total score from baseline will be calculated by:

$$\frac{\text{PANSS total score at the Week 26 LOCF endpoint - PANSS total score at DB baseline}}{\text{PANSS total score at DB baseline - 30}} \times 100\%$$

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.

The proportion of subjects who achieve a PANSS response will also be calculated for each scheduled post-OL baseline extension visit (i.e. Week 1/Visit 2E through Week 26/Visit 11E) using a similar method as above.

16.1.6. SUBJECTS WITH GIVEN PANSS PERCENT CHANGES FROM BASELINE

The proportion of subjects achieving a given PANSS percent change from DB baseline or lower at the Week 26 LOCF endpoint will be calculated. 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 DB baseline threshold on the x-axis and proportion of subjects on the y-axis.

16.2. OTHER EFFICACY VARIABLES

16.2.1. OBSERVED VALUES AND CHANGE FROM BASELINE IN CGI-S SCORE

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).

The observed values of CGI-S score at both the DB baseline and the OL baseline, and at each scheduled post-OL baseline extension visit and LOCF, will be summarized descriptively.

Changes from baseline in CGI-S score will be summarized for each scheduled post-OL baseline extension visit and LOCF, based on both the DB baseline and the OL baseline.

CGI-S score will also be summarized by subgroups as listed in section 7.4.

16.2.2. OBSERVED VALUES AND CHANGE FROM BASELINE IN MADRS TOTAL SCORE

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. If any item score contributing to the total score is missing, then the MADRS total score will be set to missing.

The observed values of MADRS total score at both the DB baseline and the OL baseline, and at each scheduled post-OL baseline extension visit and LOCF, will be summarized descriptively.

Changes from baseline in MADRS total score will be summarized for each scheduled post-OL baseline extension visit and LOCF, based on both the DB baseline and the OL baseline.

16.2.3. OBSERVED VALUES AND CHANGE FROM BASELINE IN BNSS TOTAL SCORE

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)). 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. The 13 individual items provide a composite total score (ranging from 0 to 78). In addition BNSS subscale scores will be calculated by summing the item scores under each subscale. If any item score contributing to the total score or a subscale score is missing or rated as “9” (i.e. not rated), then the BNSS total score or the subscale score will be set to missing.

The observed values of BNSS total score at both the DB baseline and the OL baseline, and at each scheduled post-OL baseline extension visit and LOCF, will be summarized descriptively.

Changes from baseline in BNSS total score will be summarized for each scheduled post-OL baseline extension visit and LOCF, based on both the DB baseline and the OL baseline.

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 several 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.

16.2.4. OBSERVED VALUES AND CHANGE FROM BASELINE IN CBB COMPOSITE SCORE AND OBSERVED VALUES AND CHANGE FROM OL WEEK 12 IN CSB COMPOSITE SCORE

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.

The Cogstate Schizophrenia Battery (CSB) includes the four tests of the CBB and three additional tests. The Internal Shopping List test (Verbal Learning Domain) measures the total number of correct responses made in remembering the word list on three consecutive learning trials. Higher scores correspond to better performance. The Groton Maze Learning test (Executive Function Domain) measures the total number of errors made in attempting to learn the same hidden pathway across five consecutive learning trials. Lower scores correspond to better performance. The Social Emotional Cognition test (Emotional Cognition Domain) measures the accuracy of performance. 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.

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, Groton Maze Learning Test);
- multiplicand = 1 when a higher score indicates improved performance (i.e. One Card Learning Test, International Shopping List Test, Social Emotional Cognition 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
Internal Shopping List Test (ISL)	25.17	4.30
Groton Maze Learning Test (GML)	34.59	15.85
Social Emotional Cognition Test (SECT)	1.14	0.12

A completion flag and an integrity flag are populated for each test, except for the Internal Shopping List test for which only the completion flag is populated. 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 and without the integrity criteria failures included.

Based on the z-scores of individual tests, a CBB composite score will be derived as the average of the z-scores of the Detection test, Identification test, One Card Learning test, and One Back test. If two or more tests are missing or are excluded from the analysis, the composite score will be set to missing.

Based on the z-scores of individual tests, a CSB composite score will be derived as the average of the z-scores of all seven tests. If three or more components are missing or are excluded from the analysis, the composite score will be set to missing.

The observed values of CBB composite score and the individual standardized scores of the four tests contained in CBB at the DB baseline and the OL baseline, and at each scheduled post-OL baseline extension visit and LOCF, will be summarized descriptively. Changes from baseline in CBB composite score and the individual standardized scores will be summarized for each scheduled post-OL baseline extension visit and LOCF, based on both the DB baseline and the OL baseline.

In addition, the observed values of CSB composite score and the individual standardized scores of the seven tests contained in CSB at Visit 7E (Week 12) and Visit 11E (Week 26) of study 361-202 will be summarized. Change from Visit 7E in CSB composite score and the individual standardized scores at Visit 11E will also be summarized.

16.2.5. Observed Values and Change from Baseline in UPSA-B Total Score

The UPSA-B is a role-play assessment designed to evaluate an individual's functional capacity in Financial Skills and Communication domains of basic living skills. The raw score of the financial subscale ranges from 0 to 11 and the raw score of communication subscale ranges from 0 to 9. Each subscale score is calculated by dividing the raw score by the highest possible raw score of that subscale and then multiplying by 50, so both subscale scores range from 0 to 50. The UPSA-B total score, calculated as the sum of two subscale scores, ranges from 0 to 100. Higher scores reflect better performance. If one or more items contributing to the subscale raw score are missing for a subject at a visit, the UPSA-B total score will be set to missing for that visit.

The observed values of UPSA-B total score at the OL baseline, and at each scheduled post-OL baseline extension visit and LOCF, will be summarized descriptively. Changes from the OL baseline in UPSA-B total score will be summarized at each scheduled post-OL baseline extension visit and LOCF.

16.2.6. Rate of Relapse and Time to Relapse

Subjects demonstrating a relapse of psychotic symptoms during the OL extension treatment period will be identified on the relapse population.

Relapse is defined as the earliest occurrence of any of the following:

- An increase in PANSS total score by ≥ 30% from the PANSS total score at clinical response and a CGI-S score ≥ 3

- Re-hospitalization for worsening of psychosis
- Emergence of suicidality, homicidality, and/or risk of harm to self or others

PANSS and CGI-S assessments taken at both scheduled and unscheduled visits will be considered when identifying the relapse event. Occurrence of re-hospitalization for worsening of psychosis will be identified by medical review of the data collected on the Psychiatric Hospitalization CRF page as well as the SAEs prior to database lock. Emergence of suicidality, homicidality, and/or risk of harm to self or others will be identified as outlined in Appendix 3. The evaluation period for relapse will be from the day/time of clinical response to 1 day after the day of the last dose of extension study medication.

The date of relapse is defined as the earliest of: the date of the assessment (based on the QSSTDTC variable in Bracket data) at which the qualifying PANSS and CGI-S data were collected, the date of hospital admission for worsening of psychosis, the date of the assessment (based on the QSSTDTC variable in Bracket data) at which a qualifying C-SSRS event is identified, or the start date of the qualifying adverse event.

The date of clinical response is defined as the date of the PANSS and CGI-S assessments (based on the QSSTDTC variable in Bracket data) which established clinical response.

Time-to-relapse (in days) is defined as the date of relapse – the date of clinical response + 1. Subjects completing/discontinuing from the study without meeting the criteria for relapse will be censored on the day after the last dose of extension study medication. Kaplan-Meier estimates of the median time-to-relapse and the 25th percentile and 75th percentile of time-to-relapse, along with the respective 95% confidence intervals, will be calculated. Kaplan-Meier estimate of the probability of relapse at the end of the OL extension treatment period, and its 95% confidence interval, will also be calculated. The time-to-relapse data will be presented in a Kaplan-Meier curve.

The rate of relapse will be calculated as the proportion of subjects demonstrating a relapse during the OL extension treatment period in the relapse population. The 95% confidence interval for the rate of relapse will also be calculated.

17. SAFETY OUTCOMES

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

There will be no statistical comparisons for safety data.

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.

The concept of “pre-treatment events” only applies to study 361-201. Pre-treatment events are untoward medical occurrences that started between 361-201 ICF and prior to the first dose of study medication in study 361-201. Adverse events of study 361-201 are untoward medical occurrences that started at the same time of or after the first dose of study medication in study 361-201, but before the first dose of extension

study medication in study 361-202. These events will be recorded in the 361-201 database.

Adverse events of study 361-202 are untoward medical occurrences that started at the same time of or after the first dose of extension study medication in study 361-202. These events will be recorded in the 361-202 database.

If an adverse event (or pre-treatment event) of study 361-201 was ongoing as of the first dose of extension 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, only adverse events of study 361-202 that started within 9 days after the last dose of extension 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 361-202 adverse events, including those that started beyond 9 days after the last dose of extension study medication, will be listed in data listings. Adverse events and pre-treatment events of study 361-201 that are carried over to the 361-202 database will be listed in data listings separately.

Whenever available, the time information should be taken into consideration when determining if a record in the AE database belongs to study 361-201 or 361-202. In the case where time isn't available, an event that started prior to the day of the first dose of extension study medication will be considered to belong to study 361-201; those that started after the day of the first dose of extension study medication will be considered to belong to study 361-202. Adverse events that started on the same day of the first dose of extension study medication will be assigned to study 361-201 or 361-202 depending on whether this AE record exists in the 361-201 database (see APPENDIX 2 for details).

See APPENDIX 2 for handling of partial dates for adverse events.

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.

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 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 at both DB baseline and OL baseline:

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

17.1.1. ADVERSE EVENTS POST LAST DOSE OF EXTENSION STUDY MEDICATION

Adverse events that started after last dose of extension study medication until 9 days after the last dose will be summarized separately.

17.2. LABORATORY EVALUATIONS

Laboratory data to be reported for this study include hematology, serum chemistry (including lipid panel and thyroid panel), urinalysis, 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, and urinalysis. 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) from baseline to post baseline extension visits according to the reference range criteria provided by the central laboratory.
- Summary of the number and percentage of subjects with at least one post-OL baseline PCS value for selected laboratory parameters (Table 3). The period of evaluation includes both the OL treatment period and the OL follow-up period.

Both the DB baseline and the OL baseline will be used in the calculation of change values and presenting the shift summaries.

All laboratory data will be provided in data listings, with the values outside the reference ranges 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
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
o 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 post-OL baseline extension visits and LOCF.

Both the DB baseline and the OL baseline will be used in the calculation of change values and presenting the shift summaries.

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 OL baseline time point (including unscheduled visits) not present at DB baseline
- > 450 msec at any post OL baseline time point (including unscheduled visits) not present at OL baseline
- > 480 msec at any post OL baseline time point (including unscheduled visits) not present at DB baseline
- > 480 msec at any post OL baseline time point (including unscheduled visits) not present at OL baseline
- > 500 msec at any post OL baseline time point (including unscheduled visits) not present at DB baseline
- > 500 msec at any post OL baseline time point (including unscheduled visits) not present at OL baseline
- ≥ 30 msec increase from DB baseline for at least one post OL baseline measurement (including unscheduled visits) and < 60 msec increase from DB baseline for all post OL baseline measurements (including unscheduled visits)
- ≥ 30 msec increase from OL baseline for at least one post OL baseline measurement (including unscheduled visits) and < 60 msec increase from OL baseline for all post OL baseline measurements (including unscheduled visits)
- ≥ 60 msec increase from DB baseline for at least one post OL baseline measurement (including unscheduled visits)
- ≥ 60 msec increase from OL baseline for at least one post OL 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 (^{o}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 by BMI category at both DB baseline and OL baseline:
  - Underweight: <18.5
  - Normal: 18.5 to <25.0
  - Overweight: 25.0 to <30.0
  - Obese: >=30.0
- Number and percentage of subjects with at least one post-OL baseline PCS value for selected vital signs parameters (Table 4). The period of evaluation includes both OL treatment period and OL follow-up period.

Both the DB baseline and the OL baseline will be used in the calculation of change values.

All vital signs data will be provided in data listings.

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 DB baseline, OL Baseline, and the overall post OL 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.

The observed values of AIMS total score at both the DB baseline and the OL baseline, and at each scheduled post-OL baseline extension visit and LOCF, will be summarized for the safety population. Changes from baseline in these measures will also be summarized for each scheduled post-OL baseline extension visit and LOCF, using both the DB baseline and the OL baseline to calculate the change values.

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-OL baseline assessments during the open-label extension period, using both the DB baseline and the OL baseline.

The AIMS global severity score (item 8) will be summarized both numerically and categorically by visit.

The post-OL 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-OL baseline changes will be summarized by visit, using both the DB baseline and the OL baseline.

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.

BARS total score (observed value and change from both the DB baseline and the OL 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-OL 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-OL baseline changes will be summarized by visit, using both the DB baseline and the OL baseline.

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.

SAS mean score (observed value and change from both the DB baseline and the OL 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-OL baseline assessments during the open-label extension period, using both the DB baseline and the OL baseline.

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

17.5.2. PITTSBURGH SLEEP QUALITY INDEX (PSQI)

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.

Observed PSQI global score at both the DB baseline and the OL baseline, and at each scheduled post-OL baseline extension visit and LOCF, will be summarized for the safety population. Change from baseline in PSQI global score will also be summarized for each scheduled post-OL baseline extension visit and LOCF, based on both the DB baseline and the OL baseline.

17.5.3. DRUG EFFECTS QUESTIONNAIRE (DEQ)

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

Data from the DEQ questionnaire at both the DB baseline and the OL baseline, and at each scheduled post-OL baseline extension visit and LOCF, will be summarized for the safety population. Change from baseline will also be summarized for each scheduled post-OL baseline extension visit and LOCF, based on both the DB baseline and the OL baseline. 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 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 of study 361-201 and the C-SSRS Since Last Visit Version is used from Visit 2 onward in study 361-201 and at all visits in study 361-202. 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-OL baseline” are defined as follows.

Time point	Study Visit	C-SSRS Version	Derivation Rule
DB Baseline	Screening/Visit 1 of study 361-201	Baseline/Screening – Past 1 Month	Most severe outcome
	Randomization/Visit 2 of study 361-201	Since Last Visit	
OL Baseline	Week 4/Visit 7 of study 361-201	Since Last Visit	As collected for that visit
Post OL Baseline Extension Period	All post OL baseline extension visits up to and including Week 26/Visit 11E, including unscheduled visits	Since Last Visit	Most severe outcome

C-SSRS composite endpoints will be derived for each time point of interest (i.e. DB baseline, OL baseline, post OL baseline extension period, and each extension 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. DB baseline, OL baseline, post OL baseline extension period, each extension study visit, and the Week 26 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:

- DB Baseline (as defined above)
- OL Baseline (as defined above)
- Post OL baseline extension period (as defined above)
- Each scheduled post OL baseline extension study visit, including Week 27/Visit 12E.

Shift in suicidal ideation score from baseline to the post OL baseline extension period and to each scheduled post OL baseline extension visit will be presented, using both the DB baseline and the OL baseline.

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 analysis 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

Not applicable.

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.

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 linesize (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.

- Ratios:
  - Ratios should be reported to one more decimal place than the raw data.
- Spacing:
  - There must be a minimum of 1 blank space between columns (preferably 2).
- Missing values:
  - A "0" should be used to indicate a zero frequency.
  - A blank will be used to indicate missing data in an end-of-text table or subject listing.
- Figures:
  - 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.
  - The CGM file itself should contain the title or footer.
  - The image should be clear and of high quality when viewed in the Word document, and when printed.
  - In general, boxes around the figures should be used.
- Footers should be defined as follows:
  - A continuous line of underscores ('_') will follow the body of the table or listing prior to any footnotes at the bottom of the page.
  - Table footnotes should be defined using compute statements in the proc report, and should appear directly after the body of the table.
  - 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, unless specified otherwise in the shell:

Group	For Tables, Graphs and Listings
Received Placebo in 361-201; Received SEP-363856 (25, 50 or 75 mg/day) in 361-202	PBO-SEP
Received SEP-363856 (50 or 75 mg/day) in 361-201; Received SEP-363856 (25, 50 or 75 mg/day) in 361-202	SEP-SEP
All subjects who entered 361-202	ALL EXT

LISTINGS

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

- Actual treatment received,
- 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,

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 361-202 database.

"Date & time": use this criterion when both date and time information is available. "Date": use this criterion when only the date information is available and time information isn't available.

‡By comparing reported term, coded term, and the start date (and time if available).

*The distinction between 361-201 pre-treatment event and 361-201 AE should be performed as specified in the 361-201 SAP.

START DATE	STOP DATE	ACTION
Known	Known	If start date & time < 361-202 open-label extension study med start date & time, then 361-201 pre-treatment event or 361-201 AE* If start date < 361-202 open-label extension study med start date, then 361-201 pre-treatment event or 361-201 AE* If start date & time >= 361-202 open-label extension study med start date & time, then 361-202 AE If start date > 361-202 open-label extension study med start date, then 361-202 AE If start date = 361-202 open-label extension study med start date and the record exists in 361-201 database‡, then 361-201 pre-treatment event or 361-201 AE* If start date = 361-202 open-label extension study med start date and the record does not exist in 361-201 database‡, then 361-202 AE

START DATE	STOP DATE	ACTION
Known	Partial	If start date & time < 361-202 open-label extension study med start date & time, then 361-201 pre-treatment event or 361-201 AE* If start date < 361-202 open-label extension study med start date, then 361-201 pre-treatment event or 361-201 AE* If start date & time >= 361-202 open-label extension study med start date & time, then 361-202 AE If start date > 361-202 open-label extension study med start date, then 361-202 AE If start date = 361-202 open-label extension study med start date and the record exists in 361-201 database‡, then 361-201 pre-treatment event or 361-201 AE* If start date = 361-202 open-label extension study med start date and the record does not exist in 361-201 database‡, then 361-202 AE
Known	Missing	If start date & time < 361-202 open-label extension study med start date & time, then 361-201 pre-treatment event or 361-201 AE* If start date < 361-202 open-label extension study med start date, then 361-201 pre-treatment event or 361-201 AE* If start date & time >= 361-202 open-label extension study med start date & time, then 361-202 AE If start date > 361-202 open-label extension study med start date, then 361-202 AE If start date = 361-202 open-label extension study med start date and the record exists in 361-201 database‡, then 361-201 pre-treatment event or 361-201 AE* If start date = 361-202 open-label extension study med start date and the record does not exist in 361-201 database‡, then 361-202 AE

START DATE	STOP DATE	ACTION
Partial, but known components show that it cannot be on or after 361-202 study med start date	Known	361-201 pre-treatment event or 361-201 AE*
Partial, but known components show that it cannot be on or after 361-202 open-label extension study med start date	Partial	361-201 pre-treatment event or 361-201 AE*
Partial, but known components show that it cannot be on or after 361-202 open-label extension study med start date	Missing	361-201 pre-treatment event or 361-201 AE*
Partial, could be on or after 361-202 open-label extension study med start date	Known	If stop date & time < 361-202 open-label extension study med start date & time, then 361-201 pre-treatment event or 361-201 AE* If stop date < 361-202 open-label extension study med start date, then 361-201 pre-treatment event or 361-201 AE* If stop date & time >= 361-202 open-label extension study med start date & time and the record exists in 361-201 database‡, then 361-201 pre-treatment event or 361-201 AE* If stop date & time >= 361-202 open-label extension study med start date & time and the record does not exist in 361-201 database‡, then 361-202 AE If stop date >= 361-202 open-label extension study med start date and the record exists in 361-201 database‡, then 361-201 pre-treatment event or 361-201 AE* If stop date >= 361-202 open-label extension study med start date and the record does not exist in 361-201 database‡, then 361-202 AE

START DATE	STOP DATE	ACTION
Partial, could be on or after 361-202 open-label extension 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 & time < 361-202 open-label extension study med start date & time, then 361-201 pre-treatment event or 361-201 AE* If stop date < 361-202 open-label extension study med start date, then 361-201 pre-treatment event or 361-201 AE* If stop date & time >= 361-202 open-label extension study med start date & time and the record exists in 361-201 database‡, then 361-201 pre-treatment event or 361-201 AE* If stop date & time >= 361-202 open-label extension study med start date & time and the record does not exist in 361-201 database‡, then 361-202 AE If stop date >= 361-202 open-label extension study med start date and the record exists in 361-201 database‡, then 361-201 pre-treatment event or 361-201 AE* If stop date >= 361-202 open-label extension study med start date and the record does not exist in 361-201 database‡, then 361-202 AE.
Partial, could be on or after 361-202 open-label extension study med start date	Missing	If the record exists in 361-201 database‡, then 361-201 pre-treatment event or 361-201 AE* If the record does not exist in 361-201 database‡, then 361-202 AE

START DATE	STOP DATE	ACTION
Partial, known components show that it is on or after 361-202 open-label extension study med start date	Known	If start date & time >= 361-202 open-label extension study med start date & time, then 361-202 AE If start date > 361-202 open-label extension study med start date, then 361-202 AE If start date = 361-202 open-label extension study med start date and the record exists in 361-201 database‡, then 361-201 pre-treatment event or 361-201 AE* If start date = 361-202 open-label extension study med start date and the record does not exist in 361-201 database‡, then 361-202 AE
Partial, known components show that it is on or after 361-202 open-label extension study med start date	Partial	If start date & time >= 361-202 open-label extension study med start date & time, then 361-202 AE If start date > 361-202 open-label extension study med start date, then 361-202 AE If start date = 361-202 open-label extension study med start date and the record exists in 361-201 database‡, then 361-201 pre-treatment event or 361-201 AE* If start date = 361-202 open-label extension study med start date and the record does not exist in 361-201 database‡, then 361-202 AE
Partial, known components show that it is on or after 361-202 open-label extension study med start date	Missing	If start date & time >= 361-202 open-label extension study med start date & time, then 361-202 AE If start date > 361-202 open-label extension study med start date, then 361-202 AE If start date = 361-202 open-label extension study med start date and the record exists in 361-201 database‡, then 361-201 pre-treatment event or 361-201 AE* If start date = 361-202 open-label extension study med start date and the record does not exist in 361-201 database‡, then 361-202 AE

START DATE	STOP DATE	ACTION
Missing	Known	If stop date & time < 361-202 open-label extension study med start date & time, then 361-201 pre-treatment event or 361-201 AE* If stop date < 361-202 open-label extension study med start date, then 361-201 pre-treatment event or 361-201 AE* If stop date & time >= 361-202 open-label extension study med start date & time and the record exists in 361-201 database‡, then 361-201 pre-treatment event or 361-201 AE* If stop date & time >= 361-202 open-label extension study med start date & time and the record does not exist in 361-201 database‡, then 361-202 AE If stop date >= 361-202 open-label extension study med start date and the record exists in 361-201 database‡, then 361-201 pre-treatment event or 361-201 AE* If stop date >= 361-202 open-label extension study med start date and the record does not exist in 361-201 database‡, then 361-202 AE

START DATE	STOP DATE	ACTION
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 & time < 361-202 open-label extension study med start date & time, then 361-201 pre-treatment event or 361-201 AE* If stop date < 361-202 open-label extension study med start date, then 361-201 pre-treatment event or 361-201 AE* If stop date & time >= 361-202 open-label extension study med start date & time and the record exists in 361-201 database‡, then 361-201 pre-treatment event or 361-201 AE* If stop date & time >= 361-202 open-label extension study med start date & time and the record does not exist in 361-201 database‡, then 361-202 AE If stop date >= 361-202 open-label extension study med start date and the record exists in 361-201 database‡, then 361-201 pre-treatment event or 361-201 AE* If stop date >= 361-202 open-label extension study med start date and the record does not exist in 361-201 database‡, then 361-202 AE
Missing	Missing	If the record exists in 361-201 database‡, then 361-201 pre-treatment event or 361-201 AE* If the record does not exist in 361-201 database‡, then 361-202 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 < open-label extension study med start date, assign as prior. If stop date >= open-label extension study med start date and start date <= end of open-label treatment, assign as concomitant. If stop date >= open-label extension study med start date and start date > end of open-label 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 open-label study visit). • If month and day unknown, impute as the earlier of (31st December; end date of the last open-label study visit). Then: If stop date < open-label extension study med start date, assign as prior. If stop date >= open-label extension study med start date and start date <= end of open-label treatment, assign as concomitant. If stop date >= open-label extension study med start date and start date > end of open-label treatment, assign as post treatment.
Known	Missing	If stop date is missing could never be assumed a prior medication. If start date <= end of open-label treatment, assign as concomitant. If start date > end of open-label 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 open-label treatment + 1). • If month and day unknown, impute as the later of (1st January; end of open-label 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; start date of the first open-label study visit [Visit 1E]). • If month and day unknown, impute as the later of (1st January; start date of the first open-label study visit [Visit 1E]). Then: If stop date < open-label extension study med start date, assign as prior. If stop date >= open-label extension study med start date and start date <= end of open-label treatment, assign as concomitant. If stop date >= open-label extension study med start date and start date > end of open-label 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 open-label treatment + 1). • If month and day unknown, impute as the later of (1st January; end of open-label 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; start date of the first open-label study visit [Visit 1E]). • If month and day unknown, impute as the later of (1st January; start date of the first open-label study visit [Visit 1E]). 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 open-label study visit). • If month and day unknown, impute as the earlier of (31st December; end date of the last open-label study visit). Then: If stop date < open-label extension study med start date, assign as prior. If stop date >= open-label extension study med start date and start date <= end of open-label treatment, assign as concomitant. If stop date >= open-label extension study med start date and start date > end of open-label 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 open-label treatment + 1). • If month and day unknown, impute as the later of (1st January; end of open-label 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; start date of the first open-label study visit [Visit 1E]). • If month and day unknown, impute as the later of (1st January; start date of the first open-label study visit [Visit 1E]). Then: If stop date is missing could never be assumed a prior medication. If start date <= end of open-label treatment, assign as concomitant. If start date > end of open-label treatment, assign as post treatment.
Missing	Known	If stop date < open-label extension study med start date, assign as prior. If stop date >= open-label extension 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	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 open-label study visit). • If month and day unknown, impute as the earlier of (31st December; end date of the last open-label study visit). Then: If stop date < open-label extension study med start date, assign as prior. If stop date >= open-label extension 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	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: 15th of the month, or date of 361-201 ICF.
- If both month and day unknown, impute as the earlier of: June 30th of the year, or date of 361-201 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: 15th of the month, or date of initial onset of schizophrenia (actual or imputed).
- If both month and day unknown, impute as the later of: June 30th of the year, or date of initial onset of schizophrenia (actual or imputed).

APPENDIX 3. IDENTIFICATION OF SUICIDALITY, HOMICIDALITY, AND/OR RISK OF HARM TO SELF OR OTHERS

Condition	Data Source	Criteria
Suicidality or Risk of Harm to Self	Adverse events	• AEs with preferred term of "Completed suicide" or "Suicide attempt" • Medical review of all AEs contained in the MedDRA SMQ of "Suicide/self-injury (SMQ)"
	C-SSRS	• C-SSRS findings of at least one occurrence of suicidal ideation (Item 4 and/or Item 5) or at least one occurrence of suicidal behavior • C-SSRS findings of self-injurious behavior, defined as a "Yes" answer to the following question in the Suicidal Behavior section: Has subject engaged in Non-Suicidal Self-Injurious behavior?
Homicidality or Risk of Harm to Others	Adverse events	• AEs with preferred term of "Aggression", "Anger", "Antisocial behaviour", "Belligerence", "Defiant behaviour", "Homicide", "Homicidal Ideation", "Hostility", "Physical abuse", "Physical assault", or "Violence-related symptom" contained in the MedDRA SMQ of "Hostility/aggression (SMQ)" • AEs with a verbatim term that contains text of "homicid*", "kill*", or "murder*".

APPENDIX 4. PSQI SCORING 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

APPENDIX 5. UPSA-B SUMMARY SCORING

UPSA-B SUMMARY SCORING:

Upon completion of the UPSA-B, scores are assigned for each of the 2 subscales. Points achieved for each subscale are summed and entered into the appropriate boxes in column 2 of the scoring worksheet. Subscale scores (column 6) are calculated using the formulae provided in columns 3, 4, and 5 of the worksheet. Fraction scores in column 6 are rounded to the nearest interval, whereby a score of 3.1 would be rounded to 3, and 3.51 would be rounded to 4). An UPSA-B Total Score (range = 0-100) is entered at the bottom of the worksheet by summing the subscales scores in column 6. See sample scoring worksheet calculations below. A blank summary scoring worksheet is provided on page 14.

UPSA-B "Sample" Summary Scoring Worksheet

1.	2.	3.		4.	5.		6.
Domain	Total Score	÷		Percent Correct	x 50		Subscale Score
Financial	5	÷ 11	=	.45	x 50	=	23
Communication	4	÷ 9	=	.44	x 50	=	22
					UPSA-B Total Score (Range = 0-100)		45

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