Official Title: A Phase II, Multi-Center, Randomized, Double-Blind, Parallel Group, Placebo-Controlled Trial of The Efficacy and The Safety of RO6889450 (Ralmitaront) vs. Placebo in Patients With an Acute Exacerbation of Schizophrenia Or Schizoaffective Disorder

NCT Number: NCT04512066

Document Date: SAP Version 1: 25-Mar-2022

TECHNICAL DOCUMENT FOR STATISTICAL ANALYSIS

Interim Analysis

TITLE: **A PHASE II, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL GROUP, PLACEBOCONTROLLED TRIAL OF THE EFFICACY AND THE SAFETY OF RO6889450 (RALMITARONT) VS. PLACEBO IN PATIENTS WITH AN ACUTE EXACERBATION OF SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER**

PROTOCOL NUMBER: BP41743

STUDY DRUG: RO6889450

VERSION NUMBER: 1.0

IND NUMBER: [redacted]

EUDRACT NUMBER: 2019-003788-23

SPONSOR: F. Hoffmann-La Roche Ltd

PLAN PREPARED BY: [redacted]

DATE FINAL: 25 Mar 2022

Signatures

_____

Date, [redacted] Statistician

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1. BACKGROUND

This Technical Document for Statistical Analysis (TDSA) in an internal document that provides the data-handling rules, derivation rules, and statistical methods of summarizing and analyzing the efficacy and safety data that will be used for the data analysis and the reporting of the (first) interim analysis (IA) results from study BP41743. This IA will serve as main efficacy analysis for internal decision making will be performed when all non-Japanese patients are randomized and compled the Week 12 visit or dropped out from the study earlier. The IA will include all patients randomized until 25-Nov-2021, i.e all patinets from USA, Russia and Ukraine and those patients from Japan who had been randomized up to 25-Nov-2021.

2. STUDY DESIGN

Study Design

This is a Phase II, multi-center, randomized, double-blind, parallel group, placebo-controlled study in participants with an acute exacerbation of schizophrenia or schizoaffective disorder. Participants who are experiencing an exacerbation of their schizophrenia, starting within 8 weeks prior to the screening visit, will be included.

After eligibility is confirmed during the screening period (Study Period 1), approximately 280 participants will be randomized outside Japan (United States [US] and rest of the world [ROW]) in equal proportions (approximately 70 per group) to one of the following treatments: 150 mg QD of RO6889450, 45 mg QD of RO6889450, placebo, or risperidone 4 mg QD (titration period: 2 mg of risperidone on Day 1, 4 mg of risperidone from Day 2) in a double-blind fashion for 4 weeks. In addition to these 280 participants, approximately 28 participants will be recruited in Japan.

After completion of the 4-week Study Period 2, the participants may enter a double-blind 8-week extension period (Study Period 3) if agreed between Investigator and participant based on clinical status. Participants treated with risperidone, or 150 mg QD of RO6889450, or 45 mg QD of RO6889450 during the Study Period 2 will continue with their respective treatments in the Study Period 3, while participants assigned to placebo will be randomized to either 150 mg QD or 45 mg QD of RO6889450 in a blinded fashion.

At the beginning of the Study Period 3, participants will be discharged from the hospital or may remain inpatient for the first weeks if required according to the clinical judgment of the Investigator.

After completion of Study Period 3, participants may be offered continuation in the optional 36-Week Safety Extension Phase if they meet additional inclusion criteria. Participants will continue to receive the same treatments as those they received during Study Period 3, in a double-blind fashion.

The assessment of the primary endpoint (PANSS) will be performed by trained centralized raters independent from the investigational sites. Participants who discontinue study medication during Study Period 2 are required to complete the Study Period 2 EOT visit as soon as possible after the last dose of study drug (if possible, PANSS assessment should be performed before rescue medications are taken). These participants are also required to return to the clinic 4 weeks after the first dose of study drug (at the end of the 4-week Study Period 2) for Week 4 early termination visit (ETV). Participants will also be asked to return for the follow up visit (4 weeks after the last dose of study drug).

Anti-psychotic medication

All anti-psychotics are prohibited in the study during Study Periods 2 and 3 and with a minimum washout period of 72 hours before the initiation of study medication.

Rescue anti-psychotic treatment

If the clinical state of the participant would require treatment with an anti-psychotic other than the study medication, in the judgment of the Investigator, an antipsychotic should be prescribed, and the participant will be immediately withdrawn from the study drug. Investigators should make a reasonable effort to complete a final assessment including efficacy endpoints before starting antipsychotic medication. The reasons for use of rescue medication should be documented in detail.

Length of Study

The total duration of the study for each participant will be approximately 17 weeks divided as follows:

- Study Period 1: Screening: approximately 3 to 7 days (1 week: inpatient).
- Study Period 2: Double-blind treatment period: 28 days (4 weeks: inpatient).
- Study Period 3: Double-blind extension treatment period: 56 days (8 weeks). At the beginning of the extension period, participants will be discharged from the hospital or may remain inpatient for the first weeks if required according to the clinical judgment of the Investigator
- 36-Week Safety Extension Phase (optional): 36 weeks. Participants, who have completed Study Period 3 and in the opinion of the Investigator may benefit from the prolonged treatment, may enter 36-Week Safety Extension Phase if they meet additional eligibility criteria. Participants with worsening of their psychiatric or medical status that would preclude their safe participation in the 36-Week

Safety Extension Phase or their ability to comply with the required procedures will not be eligible for the 36-Week Safety Extension Phase of this study.

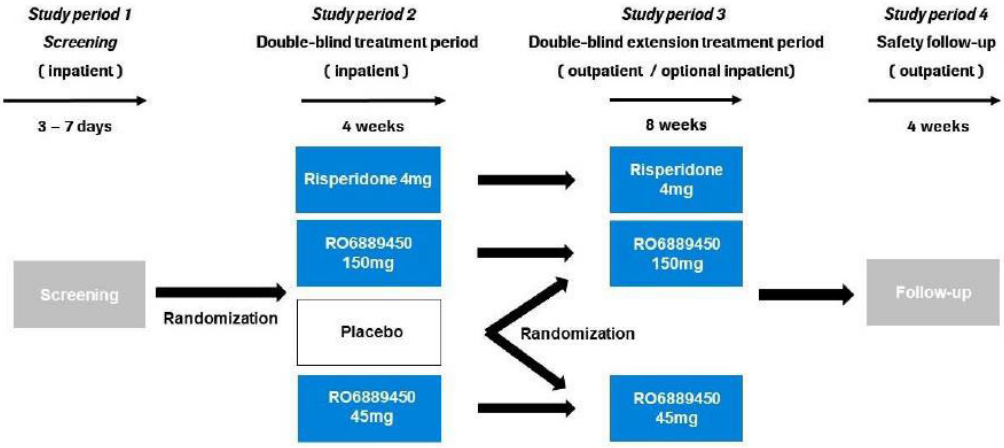
- Study Period 4: Safety follow-up/Follow-up Period for 36-Week Safety Extension Phase: 28 days (4 weeks). Mandatory follow-up assessments for all participants 4 weeks after the last dose of study drug.

- End of study visit: 1 day

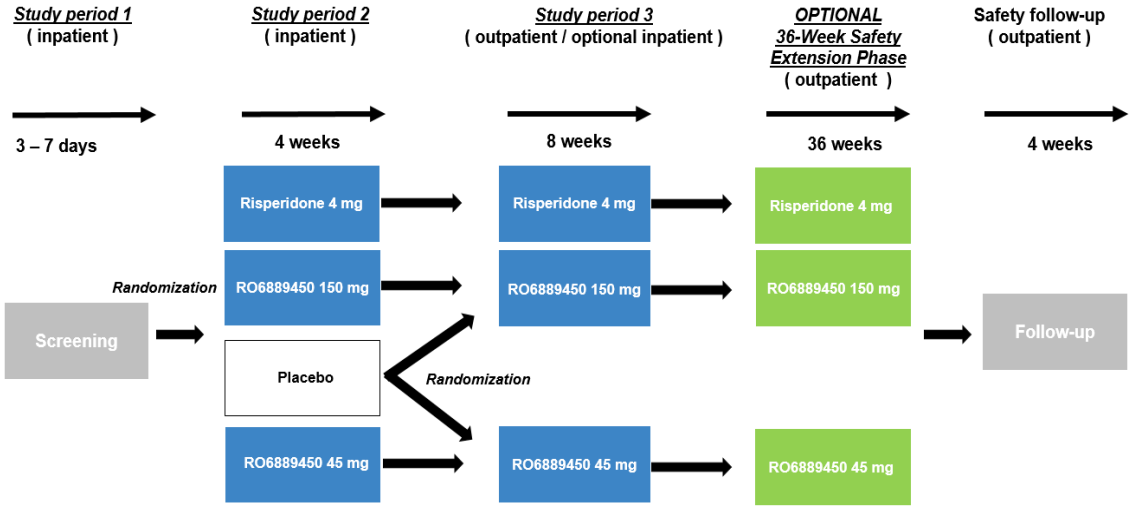
An overview of the study design is provided in Figure 1. The study is designed to collect potential efficacy data as well as safety and tolerability data in a patient population.

Figure 1 Overview of Study Design

A. Without 36-Week Safety Extension Phase



B. With Optional 36-Week Safety Extension Phase



2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1

Appendix 1. For additional details, see the Schedule of Assessments of Part A in Appendix 2.

2.2 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To compare the effect of 4-week treatment with two doses of RO6889450 (45 mg and 150 mg) vs. placebo in participants with acute symptoms of schizophrenia or schizoaffective disorder.	• Change from baseline at Week 4 in the Positive and Negative Syndrome Scale (PANSS) total score.
Secondary	
• To compare the effect of 4–week treatment with two doses of RO6889450 (45 mg and 150 mg) with placebo on symptoms of schizophrenia or schizoaffective disorder as assessed with PANSS.	• Proportion of participants with at least 20% or 50% improvement from baseline on PANSS total score. • Changes from baseline in the PANSS factor scores and proportion of participants with at least 20% or 50% improvement from baseline in the PANSS factor scores.
• To compare the effect of 4–week treatment with two doses of RO6889450 (45 mg and 150 mg) with placebo on: Clinical Global Impression Severity (CGI-S) and improvement (CGI-I).	• Change from baseline (CGI-S and CGI-S MTS scores) • CGI-I and CGI-I MTS scores
• To compare the effect of 4–week treatment with two doses of RO6889450 (45 mg and 150 mg) with placebo on time-to-readiness for discharge from inpatient unit.	• Time from first randomized treatment intake to readiness for discharge as assessed by the Readiness for Discharge Questionnaire (RDQ) or actual discharge or censoring if the participant discontinues the study early.

Objectives	Endpoints
• To compare the safety and tolerability of 4-week treatment with two doses of RO6889450 (45 mg and 150 mg) vs. placebo.	• Incidence, nature, and severity of adverse events (AEs). • Incidence, nature, and severity of serious AEs (SAEs). • Incidence, nature, and severity of treatment discontinuations due to AEs. • Change from baseline in standing vital signs recordings. • Change from screening in electrocardiogram (ECG) intervals: heart rate, PQ (PR), QRS, QT, RR, and QTcF along with information on T- and U-waves. • Incidence of laboratory abnormalities based on hematology, clinical chemistry, and urinalysis test results. • Change from baseline in Columbia-Suicide Severity Rating Scale (C-SSRS) and Extrapyramidal symptom rating scale, abbreviated (ESRS-A).
• To observe the effect of treatment with two doses of RO6889450 (45 mg and 150 mg) up to 12 weeks.	• Proportion of participants with at least 20% or 50% improvement from baseline on PANSS total score. • Changes from baseline in the PANSS total and factor scores and proportion of participants with at least 20% or 50% improvement from baseline in the PANSS factor scores. • CGI-S and CGI-S MTS. • CGI-I and CGI-I MTS.
• To observe the safety and tolerability of extended treatment with two doses of RO6889450 (45 mg and 150 mg) up to 12 weeks.	• Incidence, nature, and severity of AEs. • Incidence, nature, and severity of SAEs. • Incidence, nature, and severity of treatment discontinuations due to AEs. • Change from baseline in standing vital signs recordings. • Change from baseline in ECG intervals: heart rate, PQ (PR), QRS, QT, RR and QTcF along with information on T- and U-waves • Incidence of laboratory abnormalities based on hematology, clinical chemistry, and urinalysis test results. • Change from baseline in C-SSRS and ESRS-A.

Objectives	Endpoints
• To evaluate the pharmacokinetics (PK) of RO6889450 and RO6889450-derived metabolite(s).	• Concentration per time point. • AUCss of RO6889450 and, if feasible, RO6889450-derived metabolite(s) at Week 4. • Cmax of RO6889450 and, if feasible, RO6889450-derived metabolite(s) at Week 4. • Other PK parameters as appropriate.
Exploratory	
• To evaluate the changes in Sleep, Mood, Well-being, Cognitive Functioning and Treatment Expectancy.	• Smartphone App Questionnaire.
• To assess the changes in ReQoL.	• Change in ReQoL from baseline, proportion of patients with 10 points improvement or more.
• To compare the effect of two doses of RO6889450 (45 mg and 150 mg) with placebo on: Patient Global Impression - Change (PGI-C).	• PGI-C.
• To assess the relationship between the levels of inflammatory biomarkers and cognitive subtype.	• Differences in levels of inflammatory biomarkers between subgroups of patients defined by pre-morbid and current IQ estimate (Wide Range Achievement Test [WRAT-4] and Wechsler Abbreviated Scale of Intelligence – Second Edition [WASI-II]).
• To evaluate the change in the level of depression in schizophrenia measured by Calgary Depression Scale for Schizophrenia (CDSS) up to 48 weeks.	• Calgary Depression Scale for Schizophrenia.
• To evaluate the changes in the level of insight into mental disorder.	• Scale to Assess Unawareness of Mental Disorder (SUMD). • VAGUS insight into Psychosis Scale • Beck Cognitive Insight Scale (BCIS).
• To explore the changes in nicotine addiction measured by Fagerström Test for Nicotine Dependence.	• Fagerström Test for Nicotine Dependence.
• To explore the effects of RO6889450 on levels and patterns of social and general activity and psychotic symptoms	• Ecological Momentary Assessment
• To assess patients perception of changes relative to their condition and relevance and ease of understanding of the PRO instruments used in the study	• Feedback questions
• To evaluate relationship between the premorbid functioning and treatment response	• Premorbid Adjustment Scale (PAS)

Objectives	Endpoints
• To observe the effect of treatment with two doses of RO6889450 (45 mg and 150 mg) up to 48 weeks	• Changes from baseline in the PANSS total and factor scores at Week 48. Analysis by the following groups: risperidone, RO6889450 45 mg, RO6889450 150 mg, placebo/ RO6889450 45 mg, placebo/RO6889450 150 mg • CGI-S • CGI-I
• To observe the safety and tolerability of long-term treatment with RO6889450 up to 48 weeks	• Incidence, nature, and severity of AEs • Incidence, nature, and severity of SAEs • Incidence, nature, and severity of treatment discontinuations due to AEs • Change from baseline in standing vital signs recordings • Change from screening in ECG intervals: heart rate, PQ (PR), QRS, QT, RR, and QTcF along with information on T- and U-waves • Incidence of laboratory abnormalities based on hematology, clinical chemistry, and urinalysis test results • Change from baseline in C-SSRS and ESRS-A

2.3 DETERMINATION OF SAMPLE SIZE

Assuming a true difference of approximately 8.23 between two groups in mean PANSS reduction at Week 4 and a standard deviation of 16.5, approximately 50 participants per group will provide 80% power to see an effect with a two-sided type I error of 0.1. Allowing for about 25% of the participants randomized not completing 4 weeks of treatment approximately 70 participants per treatment group will be randomized to the study outside Japan (US and ROW). Approximately 28 participants will be recruited in Japan.

The primary analysis will be based on all participants recruited outside Japan (US and ROW) and in Japan and will be performed when all randomized patients complete the study.

With an anticipated sample size of 50 participants per group any observed reductions (versus placebo) by approximately 5.5 or more points is expected to be statistically significant.

2.4 ANALYSIS TIMING AND UNBLINDING

2.4.1 Interim Analysis (IA)

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct up to two efficacy IAs for internal decision making. The decision to conduct an optional efficacy IA and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the IA. Any IA will be performed and interpreted by members of the Sponsor project team (not in contact with study sites) and appropriate senior management personnel, who will be unblinded at the treatment group level. Access to treatment assignment information will follow the Sponsor's standard procedures.

This IA will serve as main efficacy analysis for internal decision making and will be performed when all non-Japanese patients are randomized and compled the Week 12 visit or dropped out from the study earlier.

2.4.2 Primary Analysis

The primary analysis of the study as per protocol will be performed and interpreted when all randomized patients have completed Period 2 (Week 4) or withdrawn from the study earlier and Period 2 data from all patients have been verified and locked. This includes all participants recruited outside Japan (US and ROW) and in Japan if the participants completed Period 2 at the time of the clinical cut-off. The cinical cut-off date is 21-Feb-2022.

2.4.3 Final Analysis

The final analysis of data from the trial will be performed when all patients of the study, including patients from Japan, have either completed the study, or discontinued early from the study.

3. STUDY CONDUCT

3.1 RANDOMIZATION

Study Period 2:

An Interactive Voice/Web Response System (IxRS) is used to randomize participants in equal proportion (approximately 70 per group) to one of the following treatments:

- 150 mg QD of RO6889450,
- 45 mg QD of RO6889450,
- placebo, or
- risperidone 4 mg QD

Outside Japan randomization will be stratified according to the following factors:

- region (North America, Eastern Europe, and Asia),

- baseline PANSS total score (80-95 and 96 and above),
- duration of the disease (≤ 5 years and > 5 years),
- and sex.

In Japan randomization will be stratified according to the following factor:

- baseline PANSS total score (80-95 and 96 and above).

Study Period 3:

After completion of the 4-week Study Period 2, the participants may enter a double-blind extension period (Study Period 3). Participants treated with risperidone, or 150 mg QD of RO6889450, or 45 mg QD of RO6889450 during the Study Period 2 will continue with their respective treatments in the Study Period 3, while participants assigned to placebo will be randomized to either 150 mg QD or 45 mg QD of RO6889450 in a blinded fashion.

Outside Japan randomization will be stratified according to the following factors:

- region (North America, Eastern Europe, and Asia),
- baseline PANSS total (80-95 and 96 and above),
- duration of the disease (≤ 5 years and > 5 years),
- and sex.

In Japan randomization will be stratified according to the following factor:

- baseline PANSS total (80-95 and 96 and above).

3.2 INDEPENDENT REVIEW FACILITY

The primary endpoint PANSS will be assessed live via secure videoconference by trained remote centralized raters. If a remote administration session cannot occur for an unforeseen reason, it will be rescheduled.

The assessment of the primary endpoint (PANSS) will be performed by trained centralized raters independent from the investigational sites. Remote independent raters will administer assessments live via secure videoconference. In exceptional situations, PANSS assessment by an approved remote centralized rater can be accessed via phone link if the video link is not available. The independent rater may be observed by another clinician for quality control purposes. If a remote administration session cannot occur for an unforeseen reason, it will be rescheduled.

3.3 DATA MONITORING

3.3.1 Independent Data Monitoring Committee (iDMC)

No iDMC is utilized for this study.

4. STATISTICAL METHODS

4.1 ANALYSIS POPULATIONS

For purposes of analysis, the following populations are defined in Table 1.

Note: Patients randomized to RO6889450 whom RO6889450 and RO6889450-derived metabolite RO7208008 concentrations are below quantification limit (BQL) over the whole treatment Period 2 will be regarded as having not received their randomized study medication and will be excluded from all analysis populations. PK samples collected at Day 28 (or the last sample collected before Day 28 for those patients who discontinued earlier) from patients randomized to placebo or risperidone will be analyzed for RO6889450 and RO7208008 concentrations. Those patients with positive concentrations will be regarded as having not received their randomized study medication and will be excluded from all analysis populations.

Table 1 Interim Analysis Populations

Population	Description
Population Evaluable for Efficacy Analysis [EAP]	All randomized participants who received at least one dose of randomized study medication regardless of whether they withdrew prematurely or not. Participants who received study medication different from that to which they were randomized will be included in the group to which they were randomized.
Population Evaluable for Efficacy Analysis [EAPP3]	Participants who received at least one dose of randomized study medication in Period 3 (8 week out-patient period) of the study.
Per Protocol [PP]	The per-protocol (PP) analysis population will be defined as a subset of the EAPpopulation, excluding those who have major protocol violations affecting efficacy assessment. Efficacy variables will be analyzed for this population based on the initial actual treatment received. PP analysis will only be performed if it contains less than 90% of the EAPpatients.
Safety [SE]	The safety analysis population will consist of all participants who received at least one dose of randomized study medication, regardless of whether they withdrew prematurely or not. Participants will be analyzed according to the treatment group to which they were randomized.
Pharmacokinetic [PK]	All participants who have received at least one dose of study treatment and who have data from at least one post-dose sample will be included in the PK analysis population. Participants will be excluded from the PK analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete which may influence the PK analysis. Excluded cases will be documented together with the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.

Major protocol violations leading to exclusion from PP analysis population are:

- Concomitant use of prohibited medications (not related to treatment of an AE) or therapy.
- Improper use of non-benzodiazepines hypnotics or benzodiazepines, including max doses.
- PANSS missed at any scheduled clinic or phone visit
- Repeat misuse of study drug or repeated under dosing or over soding <80% or >120% of doses (weekly).
- Subject repeatedly failing to attend study visit in which safety & efficacy assessments are done.

- Violation of any exclusion criteria discovered after randomization.
- Violation of any inclusion criteria discovered after randomization.

4.2 ANALYSIS OF STUDY CONDUCT

4.2.1 Disposition of Participants

For all patients in the EAP analysis population, withdrawal of study drug and reason for withdrawal will be summarized per treatment arm to which participants are randomized.

4.2.2 Protocol Violations

The major protocol violations will be identified before database snaphot. The number and percentage of participants with major protocol violations will be summarized per protocol violation criterion and treatment arm to which participants are randomized.

4.2.3 Overview of Analysis Population

The number (percentage) of participants excluded from the analysis populations will be summarized by reason for exclusion per treatment arm.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

The evaluation of treatment arm comparability between the two treatment arms will include summaries of demographics and baseline characteristics. Data will be summarized by treatment arm to which participants were randomized.

Descriptive statistics (mean, standard deviation, median, and minimum-maximum) will be presented by treatment arm for continuous variables. Frequency counts and proportions will be presented by treatment arm for categorical variables.

4.3.1 Demographic and Baseline Characteristics

Summary tables of demographics and baseline characteristics will be produced for the EAP analysis populations by treatment arm to which participants were randomized. The following variables will be summarized:

Categorical variables:

- Sex (Male vs. Female)
- Age (continuous) at baseline
- Race (Black or African American vs. White vs. Asian) or Ethnicity (Hispanic or Latino vs. non-Hispanic or Latino)

Continuous variables:

- Weight [kg], Height [cm], Body Mass Index (BMI) [kg/m2] at baseline
- Age (years) at baseline

and others if appropriate.

Baseline data for efficacy scales will be included in the respective efficacy outputs.

4.3.2 History of Schizophrenia or Schizoaffective Disorder

Summary statistics will be generated for the EAP analysis populations by treatment group and will include each patient's history of schizophrenia or schizoaffective disorder. The key variables from the electronic Case Report Form (eCRF) listed in the psychiatric history page will be summarized.

- Diagnosis (schizophrenia, schizoaffective disorder depressed subtype, schizoaffective disorder bipolar subtype)
- Duration of disease (years), calculated relative to the year of randomization (year of randomization – year of diagnosis)
- Number of hospitalizations for worsening of schizophrenia/schizoaffective disorder in the past year
- Duration (in months) since the most recent hospitalization for worsening of schizophrenia, calculated relative to the randomization date.

4.3.3 Previous and Current Diseases at Baseline

For all diseases at baseline (other than schizophrenia), the term entered by the investigator describing the disease (the "verbatim term") will be assigned to a standardized term (the "preferred term") and System Organ Class from MedDRA. All analyses will be performed using these preferred terms and body systems. Diagnoses will be categorized by condition at baseline (ongoing with treatment/ongoing without treatment/resolved) with use of the responses from the medical history page of the eCRF.

The number and percentage of patients with previous (resolved) diseases will be summarized by treatment group in the EAP. Diseases concurrent (ongoing with or without treatment) at baseline will be summarized similarly in a separate table. Multiple occurrences of a disease (i.e., same coded term) will be counted only once.

4.3.4 Previous and Concomitant Treatments (Other than Study Medication)

For all medications, the term entered by the investigator describing the medication (the "verbatim term") will be assigned to a standardized term (the "preferred term") and drug class from the WHO drug dictionary. All analyses will use these preferred terms and medication classes.

The number and percentage of patients who received previous or concomitant treatment (medication, medical procedure, or non-medical therapy) will be summarized by treatment group.

Multiple occurrences of a medication in an individual (i.e., same coded term) will be counted only once. All summary tables will be sorted by medication class (in decreasing order of overall incidence), then by preferred term (in decreasing order of overall incidence).

4.4 DEFINITION OF BASELINE

Baseline for all efficacy and safety analyses is defined as the last non-missing value recorded prior to or on the first day of randomized double-blind study drug administration.

4.5 EFFICACY ANALYSIS

4.5.1 Definition of Time Windows

Table 2 Analysis Time Windows for Double Blind Treatment Period 2

Applicable to all patients

Analysis Window Label	Baseline	Day 7	Day 14	Day 21	Day 28
Planned Study Day	**1**	**7**	**14**	**21**	**28**
***PANSS, CGI-S, CGI-S MTS, CGI-I*(4), *CGI-I MTS*(4)**					
Study Day	≤ 1(1)	2 to 10(2)	11 to 17	18 to 24	≥ 25(3)
RDQ, PGI-C					
Study Day	NA	2 to 10(2)	11 to 17	18 to 24	≥ 25(3)
ReQoL, FTND					
Study Day	≤ 1(1)	NA	2 to 21	NA	≥ 22(3)
CDSS, SUM-D, VAGUS, BCIS					
Study Day	≤ 1(1)	NA	NA	NA	≥ 2(3)

(1) Latest assessment prior to intake of first study medication. Use date and time, if available.
(2) May include assessments on day 1 if AFTER time of first study medication.
(3) Includes any assessments on that study day or later but prior to the date of first dose in the double-blind extension treatment period (Period 3).
(4) No baseline for CGI-I and CGI-I MTS.

- For analysis and reporting: all patients entering Period 2 will be included as per the population definitions in the section 4.1.
- Summaries will use the time windows as above and analysis flags as defined below and only include the time windows shown in the table. Hence summaries will not include “screening” or “follow-up”.
- Listings will include the analysis window label as above as well as the label which was assigned in the database. All values, also duplicates per window, will be included in listings.

- All analyses will have 4 treatment arms, as per randomization in Period 2.
- The analysis dataset will contain all assessment results. Analysis flags will be created to indicate the values that will enter the respective stats analysis and associated summary tables:
  - ANAFLAG = ‘Y’ if the assessment (1) is in time window AND (2) the assessment is within 4 days after the last dose of study drug. If more than one assessment is in the same time window after applying (1) and (2) the assessment that is closest to planned study day (see above) will be selected.
  - ANAFLAG1 =’Y’, for the “Hypothetical Estimand”, if the assessment (1) is in time window AND (2) the assessment is within 4 days after the last dose of study drug AND (3) the assessment is prior to ICE3 as defined in section 4.5.2.3 or within 4 days of ICE2. If more than one assessment is in the same time window after applying (1), (2) and (3) the assessment that is closest to planned study day (see above) will be selected.
  - ANAFLAG2 =’Y’, for the “Treatment Policy Estimand”, if the assessment (1) is in time window AND (2) the assessment is closest to planned study day (see above) if more than one assessment is in same window.

Table 3 Analysis Time Windows for Double Blind Extension Period 3

Applicable to all patients randomized to Period 3

Analysis Window Label	Period 3 Baseline	Day 35	Day 42	Day 49	Day 56	Day 70	Day 84	Week 24	Week 36	Week 48
PANSS, ReQoL, FTND										
Study Day	Last assessment before first dose in Period 3[(1)]	NA	NA	NA	First assessment after first dose in Period 3[(2)] to 70	NA	70[(2)] to 126	127 to 210 [(4)]	211 to 294 [(4)]	≥295 [(3)] [(4)]
CGI-S, CGI-S MTS, CGI-I, CGI-I MTS										
Study Day	Last assessment before first dose in Period 3[(1)]	First assessment after first dose in Period 3[(1)] to 38	39 to 45	46 to 52	53 to 63	64 to 77	78[(2)] to 126	127 to 210 [(4)]	211 to 294 [(4)]	≥295 [(3)] [(4)]
PGI-C										
Study Day	Last assessment before first dose in Period 3[(1)]	NA	First assessment after first dose in Period 3[(2)] to 49	NA	50 to 63	NA	≥64[(2)]	NA	NA	NA
CDSS, SUM-D, VAGUS, BCIS										
Study Day	Last assessment before first dose in Period 3[(1)]	NA	NA	NA	NA	NA	>Last assessment before first dose in Period 3[(1)(2)] to 126	127 to 210	211 to 294	≥295 [(3)] [(4)]

(1) Use date and time, if available. The first dose in Period 3 is the first dose after the last dose in Period 2.
(2) Includes any assessments on that study day or later and either (1) within 4 days after last dose for patients not entering the long-term safety extension period or (2) up to study day 126 for patients entering the long-term safety extension period.
(3) As drug intake is not recorded for the long-term extension study, the day of last dose of study drug intake cannot be assessed. Therefore, any assessments reported with the Follow-up folder will not be included.
(4) Not for FTND, CGI-S MTS, CGI-I MTS, SUM-D, VAGUS, BCIS

- For analysis and reporting: all patients entering Period 3 will be included as per the population definitions in the section 4.1.
- The analysis dataset will contain analysis flags as defined in Table 2.
- All analyses will have 5 treatment arms, per randomization in Period 3: “pbo -> ralmi150”, “pbo -> ralmi45”, “risp -> risp”, “ralmi45 -> ralmi45”, and “ralmi150 -> ralmi150”.
- Separate listings, summary tables and analyses will be created for these patients.

4.5.2 Primary Efficacy Endpoint

The primary efficacy endpoint of the study is the change from baseline in the PANSS Total Score at Week 4.

4.5.2.1 PANSS Total Scores

The PANSS is a 30-item rating scale clinician-rated instrument for assessing positive, negative, and other symptoms in partients with schizophrenia. The symptoms are rated on a 7-point scale capturing absent to extreme psychopathology, and the tool demonstrated sensitivity to effects seen with medication. The Positive Scale assesses the features exhibited in schizophrenia that are not present in those with a normal mental state. The Negative sub-scale assesses features that are absent in schizophrenia but that would be present in those with a normal mental state. The General sub-scale assesses the overall severity of the disorder and the risk of aggression. PANSS assessments are performed by an approved remote centralized rater.

Each item of the PANSS is rated on a 7-point scale based on the following anchors: 1 = Absent, 2 = Minimal, 3 = Mild, 4 = Moderate, 5 = Moderately Severe, 6 = Severe, and 7 = Extreme.

The assessment for each of the 30 items is to allow calculation of a total score describing overall symptomatology (see Table 4 and Appendix 3).

Table 4 PANSS Total Score

Score	Number of items	Items
Total Score	30	N01-N07, P01-P07, G01-G16

If any item contributing to its calculation is missing, then the scores will be set to missing.

A higher score indicates more positive and negative symptoms. Hence negative values for change from baseline indicate improvement in symptoms.

PANSS is assessed at Screening (day -7 to -3), Day 1 (Baseline), Day 7, Day 14, Day 21, Day 28/EOT Period 2, Day 56, Day 84/EOT Period 3, Day 112 (FU if patients do not participate in the 36-Week Safety Extension Phase). If patients participate in the 36-Week Safety Extension Phase additional PANSS assessments are done at Week 24 (Day 168), Week 36 (Day 252), Week 48 (Day 336) and Week 52 (Day 364, FU).

During Study Period 2: If a participant voluntarily withdraws from the study or is withdrawn by the Investigator, the participant will be asked to complete Study Period 2 EOT visit as soon as possible after the last dose of study drug. This may be sooner than Day 28. Participant will also be asked to return to the clinic 4 weeks after the first dose of

study drug (at the end of the 4-week Study Period 2) for Week 4 ETV to complete assessments of the primary and secondary efficacy outcomes. Participants will also be asked to return for the follow-up visit (4 weeks after the last dose of study drug).

During Study Period 3: If a participant voluntarily withdraws from the study or is withdrawn by the Investigator, the participant should return to complete Study Period 3 EOT visit as soon as possible after the last dose of study drug. This may be sooner than Day 84. Participant will also be asked to return for the follow-up visit assessments (4 weeks after the last dose of study drug).

All assessments will be assigned to analysis study days according to section 4.5.1.

RSCAT = PANSS

4.5.2.2 Statistical Hypotheses

The primary objective of the study is to demonstrate that at least one RO6889450 dose is significantly different from placebo at Week 4 for the primary endpoint.

A higher PANSS total score indicates a greater pathology. The change from baseline of PANSS total score at Week 4 will be calculated as the total score at Week 4 minus the total score at baseline. A negative change from baseline in PANSS total score indicates improvement.

The following null (H_0) and alternative (H_1) hypotheses will be tested at a one-sided α=0.05 level between each RO6889450 dose level and placebo to assess efficacy of each RO6889450 dose.

- H_0: $MEAN_{RO6889450} \geq MEAN_{placebo}$ versus
- H_1: $MEAN_{RO6889450} < MEAN_{placebo}$

where $MEAN_{RO6889450}$ and $MEAN_{placebo}$ refer to the mean change from baseline for RO6889450, and placebo, respectively.

4.5.2.3 Primary Estimand

The clinical question of interest is to assess whether RO6889450 is working as an antipsychotic, evaluated in the hypothetical scenario that patients continue with there randomized drug until Week 4.

In alignment with the Addendum to ICH E9 [ICH 1998], ICH E9 (R1) [ICH 2019] **Fehler! Verweisquelle konnte nicht gefunden werden.**, the primary efficacy estimand is described by the following attributes:

- **Target Population:** adult patients with schizophrenia as defined by the inclusion/exclusion criteria, see Sections 5.1 and 5.2 of the study protocol.

- **Variable:** change from baseline at Week 4 in PANSS total score.

- **Treatment:** randomized study drug: placebo, RO6889450 45 mg, RO6889450 150 mg. Risperidone is added only to check internal validity of the study.

- **Population-level summary:** difference in variable means between each RO6889450 dose arm and placebo treatment arm.

- **Intercurrent events (ICE):**

  (ICE1) Withdrawal from treatment in Period 2 regardless of reasons for withdrawal. The date of the ICE is the date of withdrawal.

  (ICE2) Drug interruption or missed dose of more than 4 consecutive days or more than 8 days in total in Period 2. The date of the ICE is the day of the first interruption/missed dose as defined.

  (ICE3) Use of antipsychotic medication defined as medication class 'other antipsychotic'. The date of the ICE is the day of first intake of antipsychotic medication.

  ICEs will be handled by a hypothetical strategy to estimate what the outcome would have been at the designated time point if all patients adhered to their randomized treatment through that time point. Consequently, data post ICEs even if collected will not be used for the primary estimand, unless data was collected within 4 days after last dose before ICE and will be handled under the missing-at-random (MAR) assumption in the same way as missing data are handled for the analysis (mixed effects model for repeated measues (MMRM)). The frequencies of ICE will be summarized by treatment arm.

4.5.2.4 Missing Data Assumptions

For intermittent missing data and missing data after ICE, the missing observations are assumed to be similar to those from the other participants in the same treatment group with no such missing data. There will be no missing data imputation, data will be analysed with MMRM as described in the following section. This is compatible with a MAR assumption.

To understand the pattern of missing data after ICE observed and thus the missing data mechanism, the following data will be reviewed:

- Frequency of ICEs by treatment group

4.5.2.5 Statistical Analysis

Descriptive summary statistics will be presented for the PANSS Total Score up to Week 4, for the EAP analysis population by the treatment arm to which participants were randomized at baseline (placebo, RO6889450 45 mg, RO6889450 150 mg, risperidone). The same descriptive summary statistics will be presented for the change from baseline.

As **primary analysis** the change from baseline in PANSS Total Score at Week 4 will be analyzed, using a mixed effects model for repeated measures (MMRM) to utilize all the data collected over time with consideration of the variance-covariance matrix of the repeated measures. Changes from baseline in PANSS total score at study Day 7, Day 14, Day 21 and Day 28, will be included. All patients in the EAP will be included. The analysis will be repeated for the PP, if applicable.

The MMRM analysis provides an unbiased estimate of the treatment effect under the assumption that missing data are MAR. Published data support the robustness of the MMRM analysis regarding protection against type I error and against bias, also in situations with a non-negligible proportion of missing data. Using extensive simulations, it has been demonstrated that the type I error is only affected to a limited extent and that the bias is small under the assumption that 1/3 of the missing data are missing-not-at-random (MNAR), even when there is a severe imbalance between the treatment groups in the proportion of withdrawals [Siddiqui 2009].

A treatment-by-time interaction contrast will be constructed to estimate the difference between active treatment and placebo in mean change from baseline to Week 4. Least squares means per treatment group as well as visit will be reported with 2-sided 90% confidence intervals in alignment with assumptions for the sample size considerations. Likewise, at each visit, differences between each active treatment group and placebo will be estimated and also reported with 2-sided 90% confidence intervals.

The model can be expressed as the following:

$$Y_{ijk} = \mu + b_k + d_k + r_k + s_k + \tau_i + t_j + (\tau t)_{ij} + \varepsilon_{ijk}.$$

Therein Y_{ijk} denotes the change from baseline in PANSS Total Score of participant k at visit j (j =1 (Day 7), 2 (Day 14), 3 (Day 21), 4 (Day 28)), μ denotes the general mean, τ_i is the fixed effect of treatment i (i =0 (placebo), 1 (45 mg RO6889450), 2 (150 mg RO6889450), 3 (risperidone)), t_j is the fixed effect of visit j, and b_k is the baseline value of the PANSS Total Score on a continuous scale for participant k, $(\tau t)_{ij}$ is the treatment-by-time interaction. Furthermore, d_k denotes the years since diagnosis of schizophrenia disease at time of screening (continuous variable), r_k denotes the class variable for the region (North America, Eastern Europe, and Asia) of participant k, while s_k is a class variable for sex (male vs. female) of participant k. The random errors ε_{ijk} are assumed to be independent across different participants, while within each participant an unspecified

covariance structure will be modelled. If, unexpectedly, this analysis fails to converge, the following structures will be applied, in the following order: heterogeneous Toeplitz, first-order ante-dependence, heterogeneous compound symmetry, compound symmetry. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Sex, years since diagnosis of schizophrenia disease at time of screening and region will be taken from the eCRF, PANSS Total Score at baseline will be taken from the rating vendor.

4.5.2.6 Sensitivity Analysis

Impact of COVID-19 pandemic

COVID-19 pandemic has started approximately in March 2020, the first patient was randomized in September 2020. As all patients have been randomized after start of COVID-19 pandemic and patients are treated in clinic until Week 4, COVID-19 pandemic is considered as having no relevant impact on the primary estimator. No sensitivity analysis will be performed with regards to impact of COVID-19 pandemic.

4.5.2.7 Supplementary Analyses

Treatment policy estimand

ICEs will be handled with a treatment policy strategy. All observed data until Week 4 will be included into the analysis regardless of occurrence of any ICE. Missing values in the placebo, the RO6889450 and the risperidone arms will be imputed based on the placebo arm using reference based imputation with a Copy Increments from Reference (CIR) assumption [Carpenter 2013], [Cro 2020]. CIR assumes that changes in the primary endpoint after the ICE in a participant randomized to active drug, here RO6889450 and risperidone, can be represented by, i.e., imputed from, that of participants randomized to placebo; and that changes after ICE in participants who discontinue from the placebo group will exhibit the same future evolution of schizophrenia as subjects in the placebo group remaining in the study. This approach does not assume a sustained benefit of experimental treatment after the ICE. In the placebo arm, this is compatible with a MAR assumption whereas in the active treatment arm, the imputation is under a MNAR assumption. Note that the attributes of population, variables, treatment, and population level summary will remain the same as for the primary estimand.

Two separate imputation procedures are used to impute missing values. Firstly, the Markov chain Monte Carlo (MCMC) method is used to perform partial imputation to obtain datasets with monotone missing patterns (using SAS MI procedure with MCMC statement). These steps are repeated to obtain 200 datasets with monotone missingness. Then a multiple imputation method is used to impute the monotone missing values (SAS MI procedure with MONOTONE REG statement). Each of the 200 imputed datasets will be analyzed using the same MMRM model as the primary efficacy analysis. Results from the analysis of each imputed dataset, i.e. the LS means of each

treatment group, the LS mean treatment difference, and their standard errors, will be combined using Rubin's imputation rules (using SAS MIANALYZE procedure) to produce pooled LS mean estimates, their standard errors and 90% CI.

Subgroups

PANSS Total Score up to Week 4 and change from baseline will be summarized and analyzed descriptively by

- Sex (male and female).
- Geographic region (North America, Eastern Europe). It is expected that there is no relevant difference in drug effect between geographic regions.
- Median baseline PANSS total.
- Median duration of the disease.

The primary analysis for the PANSS Total Score at Week 4.

4.5.2.8 Adjustment for Multiple Testing

The primary objective of the study is to demonstrate that at least one RO6889450 dose level is significantly (overall type I error rate of 0.1, 2-sided) different from placebo.

To maintain an overall type I error rate for multiple testing of each of the two RO6889450 dose levels vs. placebo, the hypotheses described in 0 will be tested for the primary efficacy variable applying the Hochberg procedure:

- The larger p-value will be tested at the 0.05 (one-sided) level. When the larger pvalue is ≤ 0.05, both null hypotheses are rejected.
- If the larger p-value is > 0.05, the smaller p-value will be tested at the 0.025 level. If it is ≤ 0.025, the null hypothesis is rejected.

Raw p-values for the two hypotheses will be computed using the MMRM method described in Section 4.5.2.3.

The difference between risperidone and placebo will be assessed independently to check internal validity of the study.

4.5.3 Secondary Efficacy Endpoints

Descriptive summary statistics will be presented for secondary efficacy endpoints for the EAP analysis population by visit and by treatment arm to which participants were randomized. The same descriptive summary statistics and will be presented for the change from baseline.

Descriptive summary statistics will include the number of patients contributing to the summary statistic as well as the mean, median, lower and upper quartile, standard deviation, minimum and maximum.

In general, if at least one item score is missing or not ratable, the total/factor/subscale scores that include the item will be set to missing.

4.5.3.1 PANSS Total Scores at Week 12

Descriptive summary statistics will be presented for the PANSS Total Score from Baseline up to Week 12, for the EAPP3 analysis population (patients who received at least one dose of randomized study medication and have at least one efficacy assessment in Period 3) by the treatment arm to which participants were randomized at baseline/at end of Period 2 (placebo followed by RO6889450 45 mg, placebo followed by RO6889450 150 mg, RO6889450 45 mg, RO6889450 150 mg, risperidone). The same descriptive summary statistics will be presented for the change from baseline. PANSS assessments up to 4 days after last dose in Period 3 will be included in any descriptive or statistical analysis.

Additionally, change from Week 4 will be calculated and summarized descriptively by treatment arm.

The change from baseline in PANSS Total Score at week 12 will be analyzed in the EAPP3 analysis population using a mixed effects model for repeated measures (MMRM) to utilize all the data collected from baseline to Week 12 with consideration of the variance-covariance matrix of the repeated measures.

The model can be expressed as the following:

$$Y_{ijk} = \mu + b_k + d_k + r_k + s_k + \tau_i + t_j + (\tau t)_{ij} + \varepsilon_{ijk}.$$

Therein Y_{ijk} denotes the change from baseline in PANSS Total Score of participant k at visit j (j =1 (Week 1), 2 (Week 2), 3 (Week 3), 4 (Week 4), 8 (Week 8), 12 (Week 12)), μ denotes the general mean, τ_i is the fixed effect of treatment i (i =0 (placebo followed by 45 mg RO6889450), 1 (placebo followed by 150 mg RO6889450), 2 (45 mg RO6889450), 3 (150 mg RO6889450), 4 (risperidone)), t_j is the fixed effect of visit j, and b_k is the baseline value of the PANSS Total Score on a continuous scale for participant k, $(\tau t)_{ij}$ is the treatment-by-time interaction. Same covariates as for the primary efficacy parameter will be include (d_k: years since diagnosis of schizophrenia, r_k: region, s_k: sex). The random errors ε_{ijk} are assumed to be independent across different participants, while within each participant an unspecified covariance structure will be modelled. If, unexpectedly, this analysis fails to converge, the following structures will be applied, in the following order: heterogeneous Toeplitz, first-order ante-dependence, heterogeneous compound symmetry, compound symmetry. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The model-

based estimates and the 90% CI for the change from baseline for individual treatment arms and combined 45 mg RO6889450 (45 mg RO6889450 plus placebo followed by 45 mg RO6889450) and 150 mg RO6889450 (150 mg RO6889450 plus placebo followed by 150 mg RO6889450) treatment treatment arms will be presented.

Sensitivity analysis:

Impact of COVID-19: Remote scale administration. Remote scale administration was authorized in exceptional cases during 8 weeks out-patient period due to COVID-19 related restrictions. In case a substantial number (>10%) assessments were done remotely or at home a sensitivity analysis will be conducted for which all PANSS assessments performed remotely will be excluded and treated as missing data. All other aspects of the primary analysis will remain the same.

AICure data: a sensitivity analysis might be performed using only AICure confirmed drug intake to derive the date of last drug intake.

Subgroup

PANSS Ttotal Score up to Week 4 and 12 and change from baseline and Week 4 will be summarized and analyzed descriptively the subgroup of

- Patients with at least 20% improvement from baseline PANSS total score.

4.5.3.2 PANSS Symptom Factor Scores

PANSS-PSFS and PANSS-NSFS factors scores at Week 4 and Week 12 are secondary endpoints and are calculated from PANSS items as displayed in Table 5.

Table 5 PANSS Factor Scores

Score	Number of items	Items
Negative Symptom Factor Sum Score (Marder)	7	N01-N04, N06, G07, G16
Positive Symptom Factor Sum Score (Marder)	8	P01, P03, P05, P06, N07, G01, G09, G12

[Marder 1997][Marder 1997]

If any item contributing to its calculation is missing, then the score will be set to missing.

Higher scores indicate more positive and negative symptoms. Hence negative values for change from baseline indicate improvement in symptoms.

Descriptive summary statistics will be presented for the PANSS PSFS and NSFS factor scores as for the PANSS total score.

The primary analysis described for the PANSS Total Score at Week 4 and the analysis described for the PANSS Total Score at Week 12 will be applied to the PANSS PSFS and NSFS. The models will use the same covariates (baseline value of the PANSS Total Score on a continuous scale, years since diagnosis of schizophrenia disease at time of screening (continuous variable), region (North America, Eastern Europe, and Asia), sex (male vs. female)). Additionally, the baseline factor scale value will be added to the model.

Subgroup

PANSS NS and NSFS up to Week 4 and 12 and change from baseline and Week 4 will be summarized and analyzed descriptively the subgroup of

- Patients classified prominently negative as per the algorithm described in [Hopkins 2020] at baseline.

- Patients with at least 20% improvement from baseline PANSS total score at the Week 4 assessment.

Supplementary Analysis: Seven-factor model scores

The PANSS item scores of each subject at each visit will be transformed using the uncorrelated PANSS score matrix (UPSM, see Appendix 4), to obtain the scores of 7 transformed PANSS factors [Hopkins 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).

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

If any item contributing to its calculation is missing, then the score will be set to missing.

The primary analysis described for the PANSS Total Score at Week 4 and the analysis described for the PANSS Total Score at Week 12 will be applied to the PANSS NAA and NDE factors. The models will use the same covariates (baseline value of the PANSS Total Score on a continuous scale, years since diagnosis of schizophrenia disease at time of screening (continuous variable), region (North America, Eastern Europe, and Asia), sex (male vs. female)). Additionally, the baseline factor scale value will be added to the model.

4.5.3.3 PANSS Total and Symptom Factor Score Responder

The proportion of participants with at least 20% or 50% improvement from baseline on PANSS total score and the proportion of participants with at least 20% or 50% improvement from baseline in the PANSS PSFS and NSFS are secondary efficacy endpoints.

The number and percentage of of participants with at least 20%, 30% or 50% improvement from baseline on PANSS total score, PSFS and NSFS will be summarized descriptively (30% was added as payers are looking more on 30% than on 20%).

Percentage improvement from baseline (%IfB) is calculated as

$$\%IfB_{w4} = \frac{-1*(PANSS_{Week\,x} - PANSS_{BL})}{PANSS_{BL} - 30}\ x\ 100\ ,$$

The proportion of participants with at least 20%, 30% or 50% improvement from baseline at Week x (x=1, 2, 3, 4, 8, 12) on PANSS total score, PANSS PSFS and NSFS will be derived. The numerator will be the number of participants with a Week x PANSS assessment and with at least 20%, 30% or 50% improvement from baseline at Week x. The denominator will be the number of patients in EAP (Weeks 1- 4) and EAPP3 (Week 8 and 12), i.e., patients with missing PANSS scores at Week x, e.g., due to drop out, will be regarded as having had no improvement:

$$resp_p = \frac{N(\%IfB_{p,w4})}{N(analysis\ population)}\ ,$$

where $resp_p$ is the proportion of participants with at least p% improvement (p=20, 30 or 50), N(…) is the number of participants fulfilling the criteria in the brackets.

The proportion of responders will be summarized descriptively for the EAP analysis population by timepoint (Week 1, 2, 3 and 4) and the treatment arm to which participants were randomized at baseline.

The proportion of responders will be summarized descriptively for the EAPP3 analysis population by timepoint (Week 8 and 12) and the treatment arm to which participants were randomized at baseline and end of Period 2 (5 arms).

4.5.3.4 CGI-S and CGI-I

The CGI rating scales are tools used to evaluate both the severity of illness and change from baseline. It provides an overall clinician-determined summary measure that considers all available information, including a knowledge of the participants' history, psychological circumstances, symptoms, behavior, and the impact of the symptoms on the participant's ability to function.

CGI-S

The CGI-S is a 7-point scale ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill patients) (see Appendix 5). On the scale, the value 0 corresponds to 'Not assessed', which will be excluded from the analyses. The CGI-S is an absolute measure assessing how mentally ill the participant is at the time of the assessment.

Smaller values indicate less severity of illness. Hence negative values for change from baseline indicate improvement.

The CGI-S is assessed at Screening (day -7 to -3), Day 1 (Baseline), Day 7, Day 14, Day 21, Day 28/EOT Period 2, Day 35, Day 42, Day 49, Day 56, Day 70, Day 84/EOT Period 3, Day 112 (FU if patients do not participate in the 36-Week Safety Extension Phase). If patients participate in the 36-Week Safety Extension Phase additional assessments are done at Week 24 (Day 168), Week 36 (Day 252), Week 48 (Day 336) and Week 52 (Day 364, FU).

All assessments will be assigned to analysis study days according to section 4.5.

The CGI-S scores and change from baseline will be summarized descriptively.

The primary analysis described for the PANSS Total Score at Week 4 and the analysis described for the PANSS Total Score at Week 12 will be applied to the CGI-S score. The models will use the covariates: baseline value of the PANSS Total Score on a continuous scale, years since diagnosis of schizophrenia disease at time of screening (continuous variable), region (North America, Eastern Europe, and Asia), sex (male vs. female). Additionally, the baseline CGI-S score value will be added to the model.

QSCAT = CGI, QSTEST = CGI02-Severity

CGI-I

The CGI-I, a 7-point scale rating, is used to assess the clinical changes as compared to symptoms at baseline. The scale requests an assessment by how much, compared to baseline, the condition of the participant has changed (see Appendix 5). Values range

from 1 (very much improved) to 7 (very much worse) where the value 0 corresponds to 'Not assessed', which will be excluded from any analyses. The values 1 to 7 might be centered prior to analysis so that 0 becomes 'no change' and the values -3 and +3 correspond to 'very much improved' and 'very much worse', respectively.

The CGI-I is assessed at Day 7, Day 14, Day 21, Day 28/EOT Period 2, Day 35, Day 42, Day 49, Day 56, Day 70, Day 84/EOT Period 3, Day 112 (FU if patients do not participate in the 36-Week Safety Extension Phase). If patients participate in the 36-Week Safety Extension Phase additional assessments are done at Week 24 (Day 168), Week 36 (Day 252), Week 48 (Day 336) and Week 52 (Day 364, FU).

All assessments will be assigned to analysis study days according to section 4.5.

The The CGI-I scores will be summarized descriptively for EAP (Period 2) and EAPP3 (Period 3). There is not baseline value for CGI-I, therefore no change from baseline can be derived.

QSCAT = CGI, QSTEST = CGI02-Improvement

4.5.3.5 CGI-S MTS and CGI-I MTS

At screening, clinicians will gather information from the patient's past psychiatric history, caregiver feedback, and clinical judgement to determine one to two most troubling symptoms (MTS) (see Appendix 5). The patient's MTS (including frequency, intensity, interference with daily function or family life, and other salient consequences) will be recorded and these symptoms evaluated using the CGI-S MTS. At post-baseline visits, the clinician will use the MTS description and re-evaluate the MTS using the CGI-S and CGI-I.

CGI-S MTS and CGI-I MTS will be evaluated at the same timepoints than CGI-S and CGI-I for the double-blind 4 weeks and 12 weeks treatment periods but will not be assessed during the 36-Week Safety Extension Phase. The same time windows for assignment to analysis study days as for CGI-S and CGI-I will be used.

The The CGI-S MTS (MTS1, MTS2, and the average score) and the change from baseline will be summarized for EAP (Period 2) and EAPP3 (Period 3). The The CGI-I MTS (MTS1, MTS2, and the average score) will be summarized for EAP (Period 2) and EAPP3 (Period 3).

CGI-S MTS: QSCAT = CLINICAL GLOBAL IMPRESSIONS FOR MOST TROUBLING SYMPTOMS - SEVERITY SCORE - BP41743 VERSION, QSTEST = CSMT6-CGI-S-MTS1, CSMT6-CGI-S-MTS2

CGI-I MTS: QSCAT = CLINICAL GLOBAL IMPRESSIONS FOR MOST TROUBLING SYMPTOMS - IMPROVEMENT SCORE - BP41743 VERSION, CSMT7-CGI-I-MTS1, QSTEST = CSMT7-CGI-I-MTS1, CSMT7-CGI-I-MTS2

4.5.3.6 Readiness for Discharge from Hospital

The Readiness for Discharge Questionnaire (RDQ) is a tool used to assess inpatients with schizophrenia on their readiness for discharge, independent of socio-economic factors. The RDQ consists of five items using a 4-level Likert scale to assess suicidality/homicidality, control of aggression/impulsivity, activities of daily living, medication-taking, and delusions/hallucinations interfering with functioning and global status. The sixth item examines the overall clinical state of the patient using the CGI-S as an anchor. A final question assesses readiness for discharge. The RDQ has been shown to be significantly correlated with PANSS total and factor scores as well as actual discharge.

Readiness for discharge is assessed at Day 7, Day 14, Day 21, Day 28/EOT Period 2.

Time from first randomized treatment intake to readiness for discharge as assessed by the RDQ or actual discharge or censoring if the participant discontinues from study Period 2 early is a secondary endpoint.

The first documented date of readiness for discharge or actual discharge (RD) will be used. Data from patients who have not been ready for discharge before or at end of Period 2 and for whom the date of actual discharge is not known, either because the patient discontinued from the study before being ready for discharge or actually discharged or because the date of actual discharge is not known, will be included in the analysis as censored observations (censoring date = date of discontinuation/completion of Period 2).

The RDQ is collected by Medavante and mapped to SDTM domain QS (QSCAT= RDDQ). A patient is considered ready for discharge if the question “Based on your clinical judgment of symptomatic improvement, and independent of social or economic factors, is this subject ready for discharge?” (QS.TESTCD=RDDQ108) is answered ‘YES’.

The date of actual discharge, if known, is collected on the Hospitalization eCRF form.

A patient is considered as discontinued from the study Period 2 if there is a record in the SDTM DS domain for Period 2 with DSTERM is other than COMPLETED. The date of study Period 2 discontinuation is taken from the DS.DSSTDTC. If there are more than one records indicating discontinuation, the earliest date is taken. The date of discontinuation will be the censoring date for patients who have not been ready for discharge and no actual discharge date is available.

The Kaplan-Meier method will be used to estimate median time to RD for each treatment arm (placebo, RO6889450 45 mg, RO6889450 150 mg, risperidone). The 2-sided log-rank test, stratified by region (North America, Eastern Europe, and Asia), baseline PANSS total (80-95 and 96 and above), duration of the disease (≤ 5 years and > 5 years), and sex will be used to compare time to RD between each of the RO6889450 arms and the placebo arm.

QSCAT = RDDQ

4.5.4 Exploratory Endpoints

4.5.4.1 Sleep, Mood, Well-being, Cognitive Functioning and Treatment Expectancy

To evaluate the changes in Sleep, Mood and Well-being, Cognitive Functioning and Treatment Expectancy in total up to 28 questionnaires for assessment of Sleep, Mood, Well-being and Cognitive Functioning and Treatment Expectancy will be presented on the smartphone as part of AiCure app or the Medavante Virgil platform at selected time points that will appear as random to the participant (Appendix 10). Assessments are optional. Participants continuing in the 36-Week Safety Extension Phase will have the option to continue using this smartphone app for the first 4 weeks (Weeks 13-16).

Questions are:

- S00101: How did you sleep last night?
- S00102: How are you feeling today?
- S00103: How is your energy level today?
- S00104: How is your concentration and memory today?
- S00105: Do you expect that the study drug will help you?
- S00106: Do you think the drug is helping you?
- S00107: Do you think you were taking placebo or study drug?

The Likert scale is a 6-point scale rating values range from 0 to 5. The higher the values, the better is the subjective well-being and cognitive functioning. Hence positive values for change from baseline indicate improvement.

Scales are assessed as follows:

Baseline: S00101, S00102, S00103, S00104, S00105

Day 28: S00101, S00102, S00103, S00104, S00106, S00107

Days 4, 17, 39, 53, 66, 79: S00101, S00102, S00103, S00104, S00106

Days 10, 23, 32, 38, 45, 52, 59, 61, 63, 74, 80: S00101, S00102, S00103, S00104

QNN-GENERAL - this asks about sleep, mood, memory/concentration and is scheduled from 4:00 am-23:59 pm on days 1, 11, 17, 24, 31, 38, 40, 42, 53, 57, 59, 67, 70, 74, 77, 80, 84, 87. This questionnaire can be completed at any time within the scheduled window, regardless of dosing status.

QNN-GENERAL(POST) - this asks about sleep, mood, memory/concentration and is scheduled from 4:00 am-23:59 pm on days 0, 3, 7, 10, 13, 17, 20. As this is a post dose questionnaire, it can only be completed after dosing had been completed.

QNN-GEN&TREAT - this asks about sleep, mood, memory/concentration and also if the participant thinks the drug is helping them and is scheduled from 4:00 am-23:59 pm on days 4, 18, 32, 45, and 58. This questionnaire can be completed at any time within the scheduled window, regardless of dosing status.

Period 2:

- For analysis and reporting: all patients entering Period 2 will be included as per the population definitions in the section 4.1.
- Summaries will use the collection time points as per schedule.
- All analyses will have 4 treatment arms, as per randomization in Period 2.
- The analysis dataset will contain all assessment results.

Period 3:

- For analysis and reporting: all patients entering Period 3 will be included as per the population definitions in the section 4.1.
- Summaries will use the collection time points as per schedule.
- All analyses will have 5 treatment arms, per randomization in Period 3: “pbo -> ralmi150”, “pbo -> ralmi45”, “risp -> risp”, “ralmi45 -> ralmi45”, and “ralmi150 -> ralmi150”.
- The analysis dataset will contain all assessment results.

Long-Term Safety Extension:

Same rules as for Period 3 will be applied.

The Likert scale scores and change from baseline will be summarized by scheduled assessment day for EAP (Period 2) and EAPP3 (Period 3). Question "*Do you think you were taking placebo or study drug?*" will be summarized by treatment arm. Baseline is scheduled Day 1.

QSCAT=LIKERT SCALE ASSESSMENT – BP41743 VERSION.

4.5.4.2 Recovering Quality of Life (ReQoL-20)

ReQoL-20 measures mental health service users' own perspectives of 'recovery' and quality of life and consist of 20 mental health questions. The scoring options of the items are: None of the time, Only occasionally, Sometimes, Often, and Most or all of the time. The assessment will not be performed in non-English speaking countries without linguistic validated translation. This applies also to patients who do not speak English as a first language but are living in an English-speaking country. Validated translations of the ReQoL-20 were available in other study languages.

The positively worded questions are: Q2, Q4, Q5, Q7, Q8, Q10, Q11, Q15 and Q19. They are scored from 0 to 4. Example:

Last week	None of the time	Only occasionally	Sometimes	Often	Most or all of the time
2. I felt able to trust others	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

The negatively worded questions are: Q1, Q3, Q6, Q9, Q12, Q13, Q14, Q16, Q17, Q18 and Q20. The scores are reversed for the negatively worded items which are scored from 4 to 0. Example:

Last week	None of the time	Only occasionally	Sometimes	Often	Most or all of the time
1. I found it difficult to get started with everyday tasks	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0

The ReQoL-20 sum score will be calculated from the numbers for questions 1-20. The minimum score is 0 and the maximum is 80, where 0 indicates poorest quality of life and 80 indicates highest quality of life. If a maximum of two questions are unanswered in the whole measure, the mean value of the other responses is used to fill the gap to calculate the overall index. If three or more questions are unanswered, then the overall index score cannot be calculated.

The ReQoL-20 is assessed at Day 1 (Baseline), Day 14, Day 28/EOT Period 2, Day 56, Day 84/EOT Period 3, Day 112 (FU if patients do not participate in the 36-Week Safety Extension Phase). If patients participate in the 36-Week Safety Extension Phase

additional assessments are done at Week 24 (Day 168), Week 36 (Day 252), Week 48 (Day 336) and Week 52 (Day 364, FU).

All assessments will be assigned to analysis study days according to section 4.5.

The change from baseline in ReQoL-20 sum scores and the change from baseline will be summarized for EAP (Period 2) and EAPP3 (Period 3). Higher values indicate better quality of life, hence positive values for change from baseline indicate improvement.

The proportion of participants with at least 10 points improvement from baseline in ReQoL-20 at Week 4 and Week 12, respectively, will be derived. The numerator will be the number of participants with a Week 4 or Week 12 ReQoL-20 assessment, respectively, and with at least 10 points improvement from baseline in sum score at Week 4 or Week 12, respectively. The denominator will be the number of patients in EAP (Week 4) and EAPP3 (Week 12), i.e. patients with missing data will be regarded as having had no improvement:

$$impr = \frac{N(10pts\ improvement)}{N(analysis\ population)}\ ,$$

where *impr* is the proportion of participants with at least 10 points improvement, N(…) is the number of participants fulfilling the criteria in the brackets.

The proportion of of participants with at least 10 points improvement in ReQoL-20 sum score will be summarized descriptively for the EAP analysis population by timepoint (Day 1, 14, and 28) and the treatment arm to which participants were randomized at baseline. The proportion will be summarized descriptively for the EAPP3 analysis population by timepoint (Day 56 and 84) and the treatment arm to which participants were randomized at baseline and end of Period 2 (5 arms).

Time from first randomized treatment intake to 10 points improvement in ReQoL-20 sum score or censoring if the participant discontinues the study early will be caluclated.

The first documented date of 10 points improvement in ReQoL-20 sum score will be used. Data from patients for whom no 10 points improvement (or more) is documented will be included in the analysis as censored observations (censoring date = date of last ReQoL-20 assessment).

The Kaplan-Meier method will be used to estimate median time to 10 points improvement in ReQoL-20 sum score for each treatment arm (RO6889450 45 mg, RO6889450 150 mg, placebo, risperidone).

QSCAT = REQOL-20

4.5.4.3 Patient Global Impression-Change (PGI-C)

The generic Global Impression is a measure commonly used in clinical trials to provide concise information on overall health state compared to the previously assessed protocol specified time point. The change component is intended as a measure of change in health state and can be adapted for participant selfassessment (PGI-C). A 7-point participant-based (PGI-C) global impression of change will be employed.

PGI-C: 1 = Very much improved; 2 = Much improved; 3 = Somewhat improved; 4 = No change; 5 = Somewhat worse; 6 = Much worse; 7 = Very much worse.

PGI-C is assessed at Day 7, Day 14, Day 21, Day 28/EOT Period 2, Day 42, Day 56, Day 84/EOT Period 3, Day 112 (FU if patients do not participate in the 36-Week Safety Extension Phase).

All assessments will be assigned to analysis study days according to section 4.5.

PGI-C will be summarized for EAP (Period 2) and EAPP3 (Period 3). Higher values indicate worsening, hence negative values for change from baseline indicate improvement.

QSCAT = PGI

4.5.4.4 Inflammatory Biomarkers and Cognitive Subtype

To assess the relationship between the levels of inflammatory biomarkers and cognitive subtype.

A dedicated exploratory biomarker assessment is performed to investigate the role of the immune system in the study population and assess the potential predictive value of these markers to the ralmitaront response.

Analysis will be described in separate document.

4.5.4.5 Calgary Depression Scale for Schizophrenia (CDSS)

The CDSS is a scale used to assess the level of depression in schizophrenia (assess depressive symptoms separate from positive, negative and extrapyramidal symptoms). The instrument has nine items with a 4-point Likert scale (ranging from 0 = absent, 1 = mild, 2 = moderate, 3 = severe) (see Appendix 12). The CDSS is applied by the local investigator.

CDSS is assessed at Day 1 (Baseline), Day 28/EOT Period 2, Day 84/EOT Period 3 and Day 112 (FU if patients do not participate in the 36-Week Safety Extension Phase). If patients participate in the 36-Week Safety Extension Phase additional assessments are done at Week 24 (Day 168), Week 36 (Day 252), Week 48 (Day 336) and Week 52 (Day 364, FU).

All assessments will be assigned to analysis study days according to section 4.5.

The total score is calculated by the sum of all 9 item scores. Higher scores indicate worse symptoms. Missing items will be replaced by the average of the remaining items.

CDSS total score and change from baseline will be summarized for EAP (Period 2) and EAPP3 (Period 3). Higher values indicate a higher level of depression, hence negative values for change from baseline indicate improvement.

QSCAT = CDSS

4.5.4.6 Scale to Assess Unawareness of Mental Disorder (SUMD-9)

The Scale to Assess Unawareness of Mental Disorder (SUMD) short form is a 9-item clinician-reported outcome designed to measure current awareness of mental illness (see Appendix 13). The instrument consists of three general items and six symptom items. Each item is scored on a 3-point Likert scale, with following response options: “not applicable” (0), “aware” (1), “somewhat/unaware” (2) and “severely unaware” (3), hence higher scores indicating poorer awareness.

SUMD-9 is assessed at Day 1 (Baseline), Day 28/EOT Period 2, Day 84/EOT Period 3 and Day 112 (FU if patients do not participate in the 36-Week Safety Extension Phase).

All assessments will be assigned to analysis study days according to section 4.5.

To evaluate the changes in the level of insight into mental disorder the total sum score over all 9 items and the subscores Awareness of Disease (sum of items 1-3), Awareness of Positive Symptoms (sum of items 4-6) and Awareness of Negative Symptoms (sum of items 7-9) will be calculated and summarized for EAP (Period 2) and EAPP3 (Period 3). Higher values indicate indicating poorer awareness, hence negative values for change from baseline indicate improvement.

QSCAT = SUMD-9

4.5.4.7 VAGUS insight into Psychosis Scale

The VAGUS is the insight into psychosis scale with both self-report and clinician-rated versions. The assessment will not be performed in non-English speaking countries without linguistic validated translation. This applies also to patients who do not speak English as a first language but are living in an English-speaking country. Validated translations of VAGUS-SR and VAGUS-CR were available in other study languages.

VAGUS Self-reported (VAGUS-SR)

The VAGUS-SR is a 10-item patient reported outcome measure designed to measure clinical insight into psychosis (Appendix 14). Each item utilizes a 10-point Likert scale ranging from “strongly disagree” (0) to “strongly agree” (10). Four sub scores, Illness

Awareness (2 items), Symptom Attribution (4 items), Awareness of Need for Treatment (3 items) and Awareness of Negative Consequences (1 item) are generated form this instrument. Items 2, 3, 7 and 8 are reverse scored, hence 10 minus the actual score. Each sub score is summed and then divided by the number of responses. The total score is the sum of scores divided by 4 (Appendix 15).

VAGUS Clinician-reported (VAGUS-CR)

VAGUS-CR is a 5-item clinician reported outcome measure designed to measure clinical insight into psychosis (Appendix 16). Each item utilizes a 10-point Likert scale ranging from “strongly disagree” (0) to “strongly agree” (10). Four sub scores, Illness Awareness (1 item), Symptom Attribution (2 items), Awareness of Need for Treatment (1 items) and Awareness of Negative Consequences (1 item) are generated by this instrument. Item 4 is reverse scored, hence 10 minus the actual score. Each sub score is summed and then divided by the number of responses. The total score is the sum of scores divided by 4 (Appendix 17).

VAGUS-SR and VAGUS-CR are assessed at the same time points as SUMD-9. All assessments will be assigned to analysis study days according to section 4.5.

To evaluate the changes in the level of insight into mental disorder the VAGUS-SR and VAGUS-CR total scores as provided by the vendor and change from baseline will be summarized for EAP (Period 2) and EAPP3 (Period 3). Higher scores indicate more insight into psychosis, hence positive values for change from baseline indicate improvement.

QSCAT = VAGUS-SR and VAGUS-CR

4.5.4.8 Beck Cognitive Insight Scale (BCIS)

The BCIS is a 15-item patient-reported outcome. The instrument was developed to evaluate patients’ self-reflectiveness and their overconfidence in their interpretations of their experiences. It encompasses two sub scales covering self-reflectiveness (9 items) and self-certainty (6 items). Each item utilizes a 4-point scale ranging from “do not agree at all” (0) to “agree completely” (3). Items 1, 3, 4, 5, 6, 8, 12, 14, and 15 are summed to form the self-reflectiveness score, whereas items 2, 7, 9, 10, 11, and 13 are summed to form the self-certainty score. A composite index of the BCIS reflecting cognitive insight is calculated by subtracting the score for the self-certainty scale from that of the self-reflectiveness scale, see Appendix 18.

BCIS is assessed at the same time points as SUMD-9. All assessments will be assigned to analysis study days according to section 4.5.

To evaluate the changes in the level of insight into mental disorder the BCIS sub scores as provided by the vendor and the calculated composite score and change from baseline

will be summarized for EAP (Period 2) and EAPP3 (Period 3). Higher self-reflectiveness scores are better, hence higher values for change from baseline indicate improvement. Higher self-certainty scores are worse, hence negative values for change from baseline indicate improvement. Higher composite scores indicate more cognitive insight, hence positive values for change from baseline indicate improvement.

QSCAT = BCIS

4.5.4.9 Smoking Dependence

To explore the effects of RO6889450 on changes in smoking dependence Fagerstrom Test for Nicotine Dependence (FTND) total score is employed.

The Fagerstrom Tolerance Scale is used to assess nicotine consumption during the study. The Fagerstrom test is a standard instrument for assessing the intensity of physical addiction to nicotine providing an ordinal measure of nicotine dependence related to cigarette smoking. It contains six items that evaluate the quantity of cigarette consumption, the compulsion to use, and dependence. Yes/No items are scored from 0 to 1 and multiple choices are scored from 0 to 3. The items are summed to yield a total score of 0 to 10, see Appendix 6. The higher the total Fagerstrom score, the more intense is the participant's physical dependence on nicotine.

FTND is assessed at screening, Day 1 (baseline), Day 14, Day 28/EOT Period 2, Day 56, Day 84/EOT Period 3 and Day 112 (FU).

All assessments will be assigned to analysis study days according to section 4.5.

In general, if at least one item score is missing or not ratable, the sum score will be set to missing.

The FTND items and sum score and the change from baseline in items and sum score will be summarized by assessment visit and randomized treatment arm. Mean change from baseline in items and sum score and 90% calculated confidence intervals will be displayed by time for subgroups of trough concentration at week 2 (cut by Q1, median, Q4) including patients who were smokers at baseline.

QSCAT = FTND

4.5.4.10 Ecological Momentary Assessment (EMA)

To explore the effects of RO6889450 on levels and patterns of social and general activity and psychotic symptoms. EMA is an ambulatory data collection technique that allows the real-time in vivo assessment of functioning behaviors, including educational, employment, socialization, active leisure, self-care, and home-care activities. EMA will be used to assess the participants' functioning associated to positive and negative symptoms in schizophrenia through the use of smartphones. A pop-up visualization will

signal participants 3 times throughout the day, 5 days a week (not at the visit day) to respond to very brief (e.g., 3 minutes) questionnaires about their daily lives, see Appendix 20. EMA assessment will not be performed in Japan.

All assessments will be assigned to analysis time windows according to the following table.

Table 6 EMA Time Windows

Analysis Window Label	Week 4	Week 5	Week 6	…	Week 12	…	Week 16
	EMA						
Study Day	22 to Last assessment before first dose in Period 3(1)	First assessment after first dose in Period 3(1) to 35	36 to 42	… (2)	119 to 126	… (2)	106 to 112
(1) Latest assessment prior to intake of first study medication. Use date and time, if available. (2) Go on in 7 days steps.							

- For analysis and reporting: all patients entering Period 3 will be included as per the population definitions in the section 4.1.
- Summaries will use the time windows as above and analysis flags as defined below.
- Analyses will have 5 treatment arms, per randomization in Period 3: “pbo -> ralmi150”, “pbo -> ralmi45”, “risp -> risp”, “ralmi45 -> ralmi45”, and “ralmi150 -> ralmi150”.
- Analysis:
  - ANAFLAG = ‘Y’ if (1) the assessment is in time window AND (2) the assessment is within 4 days after the last dose of study drug.
  - Percentage of answers based on total questions per patient and time window will be calculated. Individual percentages per time window, treatment arm and question will be summarized (mean, median, etc).

As a starting point, questions 1 and 2 will be combined into a patient status (home alone, home with someone, away) and the percentage of each status per patient and time window will be calculated. The patient percentages will be summarized per time window and treatment group for Period2 and Period 3.

Futher analyses may be conducted depending on the number of patients participating in EMA questions.

QSCAT = EMA BP41743 VERSION

4.5.4.11 Feedback questions

To assess patients' perception of changes relative to their condition and relevance and ease of understanding of the PRO instruments used in the study patients are asked two sets of questions once at the end of hospitalization (Week 4 visit). In the first set, patients are asked if they have experienced changes in relation to their condition. If they respond yes, they will be asked to further describe this change. Responses will be captured as free text and closed questions.

In the second set of questions, patients are asked to provide their feedback on the following PRO instruments (ReQoL-20, BCIS, VAGUS, SUMD-9) from an ease of understanding and relevance (ReQoL-20) perspective. These question uses a 5-point Likert scale ranging from "strongly agree" to "strongly disagree" plus a "no opinion" option. The assessment should take approximately 5-10 minutes to administer.

The assessment will not be performed in non-English speaking countries without linguistic validated translation. This applies also to patients who do not speak English as a first language but are living in an English-speaking country. Validated translations of the ReQoL-20 were available in other study languages.

Non-freetext questions will be summarized by randomized treatment arm.

QSCAT=BP4173 FEEDBACK QUESTIONNAIRE

4.5.4.12 Premorbid Adjustment Scale (PAS)

Premorbid Adjustment Scale (PAS) assesses functioning across four developmental stages: childhood (up to 11 years), early adolescence (12–15 years), late adolescence (16–18 years) and adulthood (19 years and beyond); and five domains: sociability/ withdrawal, peer relationships, scholastic performance, adaptation to school and socio-sexual functioning, in addition 9 items general scale that assesses, the level of best functioning achieved by the individual, as well as items related to characteristics of illness onset, energy level, education and independence (see Appendix 11).

PAS is administered by raters and assesses life periods up to 1 year before the onset of psychotic illness and consists of up to 17 items (depending on disease onset), and each item is assessed on a 0-6 Likert scale, where lower numbers indicate normal, healthy functioning and higher numbers suggest pathologic development.

The PAS is administered as part of Day 14 assessments.

The ratings received for each item in a section are summed and expressed as total score divided by the possible score. The possible score indicates the highest score obtainable by adding the maximum score for all items completed. Thus, if a subject receives ratings of 2, 3, 3, and 2 for the four items in the childhood section, the total score for that section is 10. The possible score is 24 (6+6+6+6), and the total score

divided by the possible score is .42. When no information is available for a particular item, the item is not scored. The score for the section then is expressed as total score/possible score for the items rated. For example, if only three out of four of the items in the preceding example are scored, possible score becomes 18 (6+6+6) instead of 24. If the patient received the same ratings as in the previous example, except for one undatable last item, the total section score would be 8 (2+3+3). In this case, total score/possible score is 8/18 or .44.

An overall score for the whole scale will be calculated by averaging the subscale scores for all the subscales rated for the patient. An average is preferred to a total score in order to avoid bias that would occur in cases in which the sum of a few highly scored subscales would result in the same score as the sum of several moderately or low-scored subscales, when age of onset of illness or lack of information leads to some subscales being left out.

The PAS total average score wil be summarized for the EAP by treatment group.

To evaluate relationship between the premorbid functioning and treatment response, PANSS Total Score up to Week 4 and change from baseline will be summarized and analyzed descriptively by subgroups defined by the median total average PAS score in the EAP at baseline.

The primary analysis for the PANSS Total Score at Week 4 and the analysis for the PANSS Total Score at Week 12 will be applied to the subgroups.

QSCAT = PAS-SI

4.5.4.13 PANSS, CGI-S and CGI-I at Week 48

Changes from baseline in the PANSS total and factor scores, CGI-S and CGI-I at Week 48. Analysis by the following groups: risperidone, RO6889450 45 mg, RO6889450 150 mg, placebo/ RO6889450 45 mg, placebo/RO6889450 150 mg

To observe the effect of treatment with two doses of RO6889450 (45 mg and 150 mg) up to 48 weeks.

4.5.5 Additional Analyses

4.5.5.1 Local vs Central PANSS Assessment

Analysis of local versus central PANSS assessment for Japanese patients will be described in a separate document.

4.5.5.2 WASI-II/WAIS-IV

The Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II) is an intelligence test designed to estimate IQ in individuals. The WASI-II will be administered according to standard instructions, as part of Day 14 assessments.

The Full-Scale Intelligence Quotient (FSIQ) score of the four-subtest form will be derived based on the total combined performance on the Vocabulary, Similarities, Block Design, and Matrix Reasoning subtests. A Verbal Comprehension Index (VCI) (Vocabulary and Similarities subtests) and a Perceptual Reasoning Index (Block Design, Matrix Reasoning subtests) will also be derived.

The assessment will not be performed in non-English speaking countries without linguistic validated translation. This applies also to patients who do not speak English as a first language but are living in an English-speaking country. If validated translations become available, they may be used. In Japan, the Wechsler Adult Intelligence Scale – Fourth edition (WAIS-IV) will be used as an equivalent scale.

The following composite scores of the WASI-II will be summarized by randomized treatment group in the EAP: VCI, PRI, FSIQ-2 and FSIQ-4.

QSCAT=WASI-E2, ZDCAT = WAIS-E4 US ENGLISH VERSION

4.5.5.3 WRAT4/JART

The Wide Range Achievement Test 4 (WRAT-4, Wilkinson et al 2006) measures basic reading skills. The test covers ages from 5 to 75 years old and takes approximately 15-30 minutes to administer. The WRAT-4-reading test (or an equivalent test in non-English speaking countries, if available) will be administered according to standard instructions, as part of Day 14 assessments. The age-corrected standard score obtained will be used as pre-morbid IQ estimate. The assessment will not be performed in non-English speaking countries without linguistic validated translation. This applies also to patients who do not speak English as a first language but are living in an English-speaking country. If validated translations become available, they may be used. Equivalent scales may be used, if available. In Japan, the Japanese Adult Reading Test (JART) will be used as an equivalent scale.

The Word Reading Standard Score of the WRAT4 will be summarized by treatment group in the EAP.

QSCAT = WRAT4, ZDCAT = JART 25

4.5.5.4 PANSS IC

The PANSS-Informant Checklist (PANSS-IC) is an informant questionnaire designed to supplement the PANSS by collecting information about the participant's symptoms and behaviors during the past seven days from the informant.

The information is meant to be gathered from an informant such as a caregiver or from a treating clinician or site personnel during the inpatient stay who has had significant contact with the participant during the reference period. During the interview, the informant will be asked for their observations about the participant's symptoms and

behaviors, this information may be used to inform ratings of fourteen PANSS items (i.e., Positive = P1, P3, P4, P5, P6, P7; Negative = N2, N4 and General = G5-G6, G7, G8, G14, G16). For each item, it will be assessed if the symptom is present or not, subsequent questions will then assess the frequency, severity or interference of the symptom. Collecting informant data is particularly helpful for subjects who are unwilling or unable to accurately report their symptoms during the interview. The checklist does not provide any direct study data but is simply used to assist the independent rater in rating the PANSS. However, the questions informing negative items might be scored as displayed in Appendix 20. and summarized by treatment group and time interval.

RSCAT = PANSS-IC V2019

4.6 PHARMACOKINETIC AND EXPOSURE-RESPONSE ANALYSES

The objective of the PK review is to determine the dose-exposure relationship of RO6889450 and if indicated explore the relationship between plasma exposure of RO6889450 and effect or exposure of RO6889450 or M5 and safety signals.

Plasma concentrations of RO6889450 and, if applicable, RO6889450-derived metabolite(s) will be summarized descriptively by treatment arm per time points: the number of non-missing values, arithmetic mean, geometric mean, coefficient of variation, standard deviation, minimum and maximum will be reported.

Population PK analyses using nonlinear mixed effects modelling will be performed to analyze the sparse dose-plasma concentration-time data of RO6889450 If deemed necessary, data may be pooled with data from other studies with RO6889450 (and derived metabolite(s) if available and applicable) in order to improve the parameter estimates of the model.

AUC_{ss}, C_{max} of RO6889450 and, if feasible, of RO6889450-derived metabolite(s) at week 4, as well as other PK parameter as appropriate will be estimated.

Population PK and exposure-response described in the next section will be performed by the pharmacometrician.

4.6.1 Pharmacodynamic Analyses

An exploratory graphical analysis of the relationship between pharmacokinetic exposure and efficacy based on the pharmacokinetic population will be performed by the pharmacometrician. The analysis will initially focus on the primary endpoint PANSS Total score up to 4 weeks, but other (secondary) efficacy parameters may also be investigated (e.g. PANSS-PSFS and PANSS-NSFS) as approporiate. In addition, the data up to 12 weeks treatment will also be evaluated.

For the exploratory graphical exposure-efficacy analyses, (model based) Cave,ss will be used either as a continuous covariate or as grouping variable. Other exposure metrics,

such as cumulative Cave may also be investigated. Graphical displays will include (but are not limited to) efficacy outcome measure vs. exposure by visit, and efficacy outcome measure vs. time, with trend lines split by exposure category (e.g. placebo, Low, Medium and High Tertile of Cave,ss). The effect of subpopulations (e.g., sex, region) and PANSS Total score at baseline, will also be investigated.

If warranted after review of initial graphical displays, a model-based approach may be considered to quantify the exposure-effect relationship for PANSS Total (or other efficacy metric as indicated by the graphical analysis).

If appropriate based on the initial read-out of the data, an exposure-response anlaysis may also be performed for identified safety signals as well as investigating the risk of drop out from the trial.

Results from pharmacometric analyses may be reported in a document separate from the clinical study report.

4.7 SAFETY ANALYSES

The safety analysis will be conducted to compare the safety and the tolerability of treatment with RO6889450 (45mg, 150 mg), or risperidone with placebo. Safety assessments included monitoring and recording Aes, including SAEs, measurement of protocol-specified safety laboratory assessments, measurement of protocol-specified vital signs, ECGs, and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

All safety analyses will be based on the safety analysis population grouped according to the treatment assigned at randomization.

If not otherwise stated, all safety data will be explored for the initial 4 weeks double-blind treatment period (period 2) and, as available, separately for the 8 weeks double-blind period (period 3) and the 48 weeks long-term safety extension period.

Four treatment groups will be analysed for period 2:

- placebo,
- RO6889450 45mg,
- RO6889450 150mg,
- risperidone.

Five treatment groups will be analysed in period 3 and the 48 weeks long-term safety extension:

- placebo-> RO6889450 45mg,
- placebo-> RO6889450 150mg,

- RO6889450 45mg,
- RO6889450 150mg.
- Risperidone

4.7.1 Definition of Time Windows

Table 7 Analysis Time Windows for Double Blind Treatment Period 2

Applicable to all patients

Analysis Window Label	Baseline	Day 3	Day 7	Day 14	Day 21	Day 28
Planned Study Day	**1**	**3**	**7**	**14**	**21**	**28**
C-SSRS						
Study Day	≤ 1(1)	NA	2 to 10(2)	11 to 17	18 to 24	≥ 25(3)
Laboratory, Body Weight, ESRS-A						
Study Day	≤ 1(1)	NA	NA	2 to 21	NA	≥ 22(3)
ECG						
Study Day	≤ 1(1)	NA	2 to 10(2)	2 to 21	NA	≥ 22(3)
Vital Signs						
Study Day	≤ 1(1)	2 to 5	6 to 10(2)	11 to 17	18 to 24	≥ 25(3)

(1) Latest assessment prior to intake of first study medication. Use date and time, if available.
(2) May include assessments on day 1 if AFTER time of first study medication.
(3) Includes any assessments on that study day or later and prior to the date of first dose in the double blind extension treatment period (Period 3).

- For analysis and reporting: all patients entering Period 2 will be included as per the population definitions in the section 4.1.
- Summaries will use the time windows as above and analysis flags as defined below and only include the time windows shown in the table. Hence summaries will not include “screening” or “follow-up”.
- Listings will include the analysis window label as above as well as the label which was assigned in the database. All values, also duplicates per window, will be included in listings.
- All analyses will have 4 treatment arms, as per randomization in Period 2.
- The analysis dataset will contain all assessment results. An analysis flag will be created to indicate the values that will enter the respective stats analysis and associated summary tables:
  - ANAFLAG = ‘Y’ if the assessment (1) is in time window AND (2) the assessment is within 4 days after the last dose of study drug. If more than one assessment is in the same time window after applying (1) and (2) the assessment that is closest to planned study day (see above) will be selected.

Table 8 Analysis Time Windows for Double Blind Extension Period 3

Applicable to all patients randomized to Period 3

Analysis Window Label	Period 3 Baseline	Day 35	Day 42	Day 49	Day 56	Day 70	Day 84
Laboratory, ESRS-A							
Study Day	Last assessment before first dose in Period 3[(2)]	NA	NA	NA	First assessment after first dose in Period 3[(2)] to 70	NA	≥70[(2)]
C-SSRS							
Study Day	Last assessment before first dose in Period 3[(1)]	First assessment after first dose in Period 3[(1)] to 38	39 to 45	46 to 52	53 to 63	64 to 77	≥78[(2)]
ECG							
Study Day	Last assessment before first dose in Period 3[(1)]	NA	First assessment after first dose in Period 3[(2)] to 49	NA	50 to 63	NA	≥64[(2)]
Vital Signs, Body Weight							
Study Day	Last assessment before first dose in Period 3[(1)]	NA	First assessment after first dose in Period 3[(2)] to 49	NA	50 to 63	64 to 77	≥78[(2)]

(1) Use date and time, if available.
(2) Includes any assessments on that study day or later and either (1) within 4 days after last dose for patients not entering the long-term safety extension period or (2) up to study day 126 for patients entering the long-term safety extension period.

- For analysis and reporting: all patients entering Period 3 will be included as per the population definitions in the section 4.1.
- The analysis dataset will contain analysis flag as defined in Table 7**Fehler! Verweisquelle konnte nicht gefunden werden.**.
- All analyses will have 5 treatment arms, per randomization in Period 3: “pbo -> ralmi150”, “pbo -> ralmi45”, “risp -> risp”, “ralmi45 -> ralmi45”, and “ralmi150 -> ralmi150”.
- Separate listings, summary tables and analyses will be created for these patients.

Table 9 Analysis Time Windows for Long-Term Safety Extension

Applicable to all patients entering the Long-Term Safety Extension

Analysis Window Label	Week 24	Week 36	Week 48
Laboratory Values, ECG, Vital Signs, Body Weight, C-SSRS, ESRS-A			
Study Day	127 to 210	211 to 294	≥295(1)
(1) As drug intake is not recorded for the long-term extension study, the day of last dose of study drug intake cannot be assessed. Therefore, any assessments reported with the Follow-up folder will not be included.			

Separate listings, summary tables and analyses will be created for these patients.

4.7.2 Exposure of Study Medication

Exposure of randomized study medication will be summarized for the initial 4 weeks double-blind treatment period (period 2) and, as available, for the 8 weeks double-blind period (period 3):

- Duration of treatment (days) in period 2, which will be calculated from the first day of randomized double-blind study medication intake as recorded in the eCRF to the last day of study medication intake in the initial 4 weeks double-blind treatment period (period 2) as recorded in the eCRF, i.e., last dosing date in period 2 minus first dosing date inpriod 2 plus 1 day.

- Duration of treatment (days) in period 3, which will be calculated from the first day of randomized double-blind study medication intake after end of period 3 as recorded in the AiCure app to the last day of dosing as recorded in the AiCure app, i.e., last dosing date in period 3 minus first dosing date in period 3 plus 1 day.

- Number of doses over the intital 4-weeks double-blind treatment period (period 2) derived from the number of days at which randomized double-blind treatment was taken as recorded in the eCRF.

- Number of doses over the period 3 derived from the number of days at which randomized double-blind treatment was taken as recorded in the AiCure app.

- Total cumulative dose (mg) over the intital 4-weeks double-blind treatment period (period 2) as recorded in the eCRF.

- Total cumulative dose (mg) over period 3 as recorded in the AiCure app.

- Extent of compliance with randomized double-blind RO6889450 (%). Treatment compliance for each participant will be calculated as cumulative actually taken dose during the intital 4-weeks double-blind treatment period (period 2) divided by the

planned dose. The planned dose is the cumulative planned dose over 28 days, i.e., 150mg×28 days or 45mg×28 days.

4.7.3 Adverse Events

The original terms recorded on the eCRF by the Investigator for Aes will be assigned by the Sponsor to a standardized term (the “preferred term”) based on MedDRA. All data displays of AE will be performed using the system organ class and preferred terms. All Aes will be presented as frequency tables by arm with numbers and percentage of participants experiencing Aes.

AEs will be summarized separately

(1) for the 4-weeks double-blind treatment period (Period 2) including all patients who received at least one study medication in Period 2 and Aes from day of first onset of study medication in Period 2 until the day before first study medication intake in the 8-weeks double-blind extension treatment period (Period 3) if the patient received study medication in Period 3, or until the last day of study medication intake in Period 2 plus 4 days if the patient did not receive study medication in Period 3. Aes will be displayed by the four randomized treatment groups (placebo, RO6889450 45 mg, RO6889450 150 mg, risperidone),

(2) for Period 3 including all patients who received at least one study medication in Period 3 and Aes from the first day of study medication intake in Period 3 until the last day of study medication intake in Period 3 plus 4 days. Aes will be displayed by the two placebo/ RO6889450 groups (placebo/45 mg RO6889450, placebo/150 mg RO6889450) and the three randomized active treatment arms (RO6889450 45 mg, RO6889450 150 mg, risperidone),

(3) combined for Period 2 and Period 3 including all patients who received at least one active study medication (RO6889450 45 mg, RO6889450 150 mg, risperidone) in Period 2 or Period 3. Patients who switched from placebo to RO6889450 45 mg or RO6889450 150 mg will be added to the respective treatment arm. Aes from the first day of active study medication intake in Period 2 or Period 3 until the last day of study medication intake in Period 3 plus 4 days. For patients who switched from placebo to RO6889450 45 mg or RO6889450 150 mg only Aes from the day of first RO6889450 will be included. Aes will be displayed by the three active treatment arms (RO6889450 45 mg, RO6889450 150 mg, risperidone),

(4) for the 36-Week Safety Extension Phase including all all patients who received at least one active study medication (RO6889450 45 mg, RO6889450 150 mg, risperidone) in the 36-Week Safety Extension Phase. Aes will be displayed by the two placebo/ RO6889450 groups (placebo/45 mg RO6889450, placebo/150

mg RO6889450) and the three randomized active treatment arms (RO6889450 45 mg, RO6889450 150 mg, risperidone),

(5) for the follow-up period including all patients with at least one dose of study medication in Period 2 or Period 3 or the 36-Week Safety Extension Phase and Aes from day 5 after the last treatment until 28 days later. Aes will be displayed by 6 arms: placebo (only), placebo/45 mg RO6889450, placebo/150 mg RO6889450, RO6889450 45 mg, RO6889450 150 mg, risperidone.

Table 10 Adverse Event Time Windows

Study Period	Patients Included	Time Window
Follow-up	All treated	Day 5 after the last treatment until 28 days later
36-Week Safety Extension Phase	All treated in the 36-Week Safety Extension Phase	First day of study medication intake in the in the 36-Week Safety Extension Phase until the last day of study medication intake in in the 36-Week Safety Extension Phase plus 4 days.
Period 3 double-blind 8 weeks extension treatment period	All treated in Period 3	First day of study medication intake in Period 3 until the last day of study medication intake in Period 3 plus 4 days.
Period 2 double-blind 4 weeks treatment period	All treated in Period 2	Day of first onset of study drug in Period 2 until the day before first study medication intake in Period 3, or until the last day of study medication intake in Period 2 plus 4 days if the was patient did receive treatment in Period 3.
Baseline Sign and Symptoms	All treated	Before first study drug intake

For output templates please refer to Appendix 7.

Intensity and relationship to study treatment will be summarized as assigned by the investigator.

In the summary table of Aes by intensity, if a participant has more than one occurrence of an event, the event with the most severe intensity will be counted. If the intensity of an AE is missing, then the AE will be included only in the total number of events column and not in the count of participants with the event by intensity.

In the summary table of Aes by relationship to trial treatment, if a participant has more than one occurrence of an event, the most closely related event will be counted. If the relationship of an AE is missing, then the AE will be included only in the total number of events column and not in the count of participants with the event by relationship.

All SAEs and Aes that led to death, and Aes that led to withdrawal of study treatment will also be summarized by treatment arm.

Abuse liability Aes will be summarized. MedDRA Baskets and/or preferred terms to be included in that summary are provided in Appendix 8

AE summaries by study periods will be produced as displayed in the following table:

Type of AE summary	Period 2	Period 3	Period 2+3	FU
AE summary	x	x	x	x
SAE summary	x	x	-	-
By relationship	x	x	-	-
By greatest intensity	x	x	-	-
Leading to discontinuation of treatment	x	x	-	-
Leading to interruption of treatment	x	x	-	-
Abuse liability Aes	x	x	-	-

The following rules will be applied for AEs with missing onset or end dates:

- Events that are missing both, onset and end dates, will be considered as emerging from treatment, given the participant had at least one dose of study medication.
- If the onset date is missing and the end date is on or after the first dosing date, then the event will be considered as emerging from treatment.
- If the end date is missing and the onset date is on or after the first dosing date of a specific period, then the event will be considered as emerging from treatment.
- If the end date is missing and the most extreme intensity is worse than the initial intensity and the onset date is before the first dosing date of a specific period, then the event will be considered as emerging from treatment.
- If the onset or end dates are missing, the duration will be set to missing.

The analysis will be based on the safety analysis population grouped according to the treatment assigned at randomization.

4.7.4 Clinical Laboratory Tests

A central laboratory designated by the Sponsor will be used for all laboratory testing required during the study except for dipstick urinalysis, urine dipstick alcohol test, drugs of abuse, urine pregnancy test and COVID-19 test (when not performed centrally). The central laboratory should be used for all laboratory testing whenever possible (including unscheduled and follow-up laboratory testing, if needed).

The Investigator will review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF.

For this IA only the following laboratory parameters will be analysed:

- Lipids: cholesterol, low-density lipoproteins (LDL) cholesterol, high-density lipoproteins (HDL) cholesterol, triglycerides
- Clinical chemistry: blood glucose (fasting), HbA1c, ALT, ALP, AST, CRP, creatinine, total and direct bilirubin

Outputs for the following laboratory parameters will be prepared for review in case of need:

- Clincial chemistry: sodium, potassium, chloride, bicarbonate, fasting glucose, glycated hemoglobin, urea, protein, albumin, phosphate calcium, urate, lactate dehydrogenase.
- Haematology: leucocytes, erythrocytes, hemoglobin, hematocrit, platelets, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes).
- Coagulation: INR, aPTT, PT.
- Urinalysis: specific gravity, dipstick: pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase and any performed microscopy.

Chemistry and lipids as well the other laboratory parameters are assessed at Screening (day -7 to -3), Day 1 (Baseline), Day 14, Day 28/EOT Period 2, Day 56, Day 84/EOT Period 3, Day 112 (FU if patients do not participate in the 36-Week Safety Extension Phase). If patients participate in the 36-Week Safety Extension Phase additional assessments are done at Week 24 (Day 168), Week 36 (Day 252), Week 48 (Day 336) and Week 52 (Day 364, FU).

Chemistry, lipids and other laboratory parameters assessments will be assigned to analysis study days according to section 4.7.1.

Laboratory results from central laboratory q2labsolutions that are below the lower limit of quantification (LLOQ) or or above the upper limit of quantification (ULOQ) will be reported as character results of “<[LLOQ]” or “>[ULOQ]”. Numeric values will be derived as LLOQ/2 for values below LLOQ and as ULOQ for values above ULOQ.

Clinical laboratory data are stored on the database in the units in which they were reported. For analysis laboratory data will be converted using the International System of Units (SI units; Système International d’Unités). Laboratory data not reported in SI units

will be converted to SI units before processing and will be transformed to common reference range using Roche Safety Lab Standardisation.

Summary statistics for converted values and changes from baseline at each assessment time will be presented for EAP (Period 2) and EAPP3 (Period 3). Baseline is the patient's last observation prior to initiation of randomized double-blind study treatment in Period 2.

The number of patients with a laboratory value abnormality in the direction specified (low/high) among patients during randomzed double-blind treatment without this abnormality at baseline will be summarized.

Mean (+/- SEM) plots will be presented by scheduled time point and randomized treatment arm.

The analysis will be based on the safety analysis population grouped according to the treatment assigned at randomization.

4.7.5 Electrocardiograms (ECG) data analysis

Sites will be provided with ECG equipment by the central ECG analysis vendor. ECG recordings will be electronically transferred to a central ECG analysis vendor.

Triplicate ECGs are required at screening, where the three individual ECG tracings should be obtained as closely as possible in succession, but no more than two minutes apart. The full set of triplicates should be completed in less than five minutes. At all other visits, single ECGs are collected. Any clinically relevant changes or abnormalities occurring during the study should be recorded in the AE section of the eCRF. For this IA only QTcF values will be analyzed.

Twelve-lead ECG recording will be obtained at Screening (day -7 to -3), Day 7, Day 14, Day 28/EOT Period 2, Day 42, Day 56, Day 84/EOT Period 3, Day 112 (FU if patients do not participate in the 36-Week Safety Extension Phase). If patients participate in the 36-Week Safety Extension Phase additional assessments are done at Week 24 (Day 168), Week 36 (Day 252), Week 48 (Day 336) and Week 52 (Day 364, FU).

ECG assessments will be assigned to analysis study days according to section 4.7.1.

Summary statistics for actual heart rate QTcF values and changes from baseline at each assessment time will be presented. Baseline is the patient's last observation prior to initiation of randomized double-blind study treatment.

QTcF intervals will be classified into categories ≤450 msec, >450-≤480 msec, >480-≤500 msec and >500 msec, change from baseline will be classified into categories ≤30 msec, >30-≤60 msec, >60 msec; both will be summarized by scheduled time point.

Mean (+/- SEM) plots will be presented by scheduled time point and randomized treatment arm. ECG parameter shift tables from baseline to highest post-baseline value will be provided for Period 2 and Period 3.

The analysis will be based on the safety analysis population grouped according to the treatment assigned at randomization.

4.7.6 Concomitant Medications

Concomitant therapy includes any medication, e.g., prescription drugs, over-the-counter [OTC] drugs, approved dietary and herbal supplements, nutritional supplements and any nonmedication interventions (e.g., individual psychotherapy, cognitive behavioural therapy, smoking cessation therapy, and rehabilitative therapy). As a general rule, no new concomitant medications are permitted, with the exception of medications to treat Aes.

The original terms (the “verbatim term”) recorded on the participants’ eCRF by the investigator will be assigned to a standardized term (the “preferred term”) and Anatomical Therapeutic Chemical (ATC) classification using WHODrug Global B3 Format dictionary. Analyses will use preferred terms and grouped by ATC2 (pharmacological or therapeutic properties) levels. Note: If a generic is assigned multiple classes ATC Class paths in WHODrug, it may be listed multiple times.

Previous/Concomitant medications (started before first randomized double-blind treatment intake), concomitant medications (started after first randomized double-blind treatment intake) and medications to treat Aes will be presented by treatment arm in summary tables. Multiple occurrences of a medication in an individual (i.e., same coded term) will be counted only once in summary tables.

The analysis will be based on the safety analysis population grouped according to the treatment assigned at randomization.

4.7.7 Vital Signs, Body Weight and BMI

Orthostatic vital signs are vital signs taken when the patient moves from supine to standing position.

Systolic blood pressure, diastolic blood pressure and heart rate are assessed in supine as well as standing position at Screening (day -7 to -3), Day 1 (Baseline), Day 3, Day 7, Day 14, Day 21, Day 28/EOT Period 2, Day 42, Day 56, Day 70, Day 84/EOT Period 3, Day 112 (FU if patients do not participate in the 36-Week Safety Extension Phase). If patients participate in the 36-Week Safety Extension Phase additional assessments are done at Week 24 (Day 168), Week 36 (Day 252), Week 48 (Day 336) and Week 52 (Day 364, FU).

Blood pressure and heart rate assessments will be assigned to analysis study days according to section 4.7.1.

Body weight is assessed at Screening (day -7 to -3), Day 1 (Baseline), Day 14, Day 28/EOT Period 2, Day 42, Day 56, Day 70, Day 84/EOT Period 3, Day 112 (FU if patients do not participate in the 36-Week Safety Extension Phase). If patients participate in the 36-Week Safety Extension Phase additional assessments are done at Week 24 (Day 168), Week 36 (Day 252), Week 48 (Day 336) and Week 52 (Day 364, FU).

Body weight assessments will be assigned to analysis study days according to to section 4.7.1.

BMI is calculated as weight (kg) / height $(m)^2$ (height as measured at baseline).

Summary statistics for values and changes from baseline at each assessment time will be presented. Baseline is the patient's last observation prior to initiation of randomized double-blind study treatment. Blood pressure and heart rate will be presented in units as collected (mmHg and beats/min), while body weight will be converted to kg.

Orthostatic vital signs are vital signs taken when the patient moves from supine to standing position. The definition of Postural Orthostatic Tachycardia (POT) is a heart rate > 120 bpm on standing or an increase in heart rate by 30 bpm from a resting heart rate without clinically significant orthostatic hypotension. To support assessment of POT, orthostatic systolic and diastolic blood pressure and heart rate will be calculated as standing minus supine systolic and diastolic blood pressure and heart rate, respectively. Patients with a heart rate > 120 bpm in standing position or an increase in heart rate by 30 bpm from a supine heart rate will be listed.

Mean (+/- SEM) plots will be presented by scheduled time point and randomized treatment arm.

The analysis will be based on the safety analysis population grouped according to the treatment assigned at randomization.

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

The C-SSRS is a tool used to assess the lifetime suicidality of a participant (C-SSRS baseline) as well as new instances of suicidality (C-SSRS since last visit). It incorporates a structured interview to prompt recollection of suicidal ideation, including the intensity of the ideation, behavior, and attempts with actual/potential lethality.

The "baseline" version will be completed at the Screening visit (day -7 to -3) and a "since last visit" version will be completed at subsequent visits at Day 1, Day 7, Day 14, Day 21, Day 28/EOT Period 2, Day 35, Day 42, Day 49, Day 56, Day 70, Day 84/EOT Period

3, Day 112 (FU if patients do not participate in the 36-Week Safety Extension Phase). If patients participate in the 36-Week Safety Extension Phase additional assessments are done at Week 24 (Day 168), Week 36 (Day 252), Week 48 (Day 336) and Week 52 (Day 364, FU).

C-SSRS assessments will be assigned to analysis study days according to section 4.7.1.

The items of the C-SSRS will be listed. The number and percentage of patients with suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent based on the C-SSRS during treatment will be summarized (see Appendix 9).

The analysis will be based on the safety analysis population grouped according to the treatment assigned at randomization.

QSCAT = C-SSRS BASELINE/SCREENING VERION and C-SSRS SINCE LAST VISIT

4.7.9 Extrapyramidal Symptom Rating Scale, Abbreviated Version (ESRS-A)

The presence and severity of extrapyramidal symptoms are evaluated using ESRS-A. The reliability and validity of the ESRS have been demonstrated in antipsychotic-induced movement disorders. The scale is organized into two main components: (1) an assessment of specific symptoms of Parkinsonism, dyskinesia, akathisia, and dystonia (2) the Clinician's Global Impression (CGI) of these symptoms. All are evaluated on a scale of 0 (absent) to 5 (extreme).

The assessments will be carried out at the Screening visit (day -7 to -3), and subsequent visits Day 14, Day 28/EOT Period 2, Day 56, Day 84/EOT Period 3, Day 112 (FU if patients do not participate in the 36-Week Safety Extension Phase). If patients participate in the 36-Week Safety Extension Phase additional assessments are done at Week 24 (Day 168), Week 36 (Day 252), Week 48 (Day 336) and Week 52 (Day 364, FU).

ESRS-A assessments will be assigned to analysis study days according to section 4.7.1.

The movement related rating scales (ESRS-A) will be summarized for the total score of each domain (i.e., Parkinsonism, Akathisia, Dystonia, Dyskinesia) and the associate CGIS score by treatment group using descriptive statistics at each scheduled assessment visit. Change from baseline will be summarized by timepoint using descriptive statistics.

The analysis will be based on the safety analysis population grouped according to the treatment assigned at randomization.

QSCAT = ESRSA

4.8 MISSING DATA HANDLING

Generally, in summaries, all data from the respective analysis population regardless of completeness by Week 4 will be included; participants who have taken the study medication or have visited the sites only partially will be included in the summaries. No imputation will be applied for missing data will be applied.

For all rating scales, if any item score contributing to the total/factor/subscale score is missing, then the total/factor/subscale will be set to missing, unless specified otherwise.

4.9 PATIENT DATA LISTINGS

Listings will only be prepared if a CSR is written.

5. REFERENCES

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APPENDIX 1 PROTOCOL SYNOPSIS

PROTOCOL TITLE:	**A PHASE II, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL GROUP, PLACEBO-CONTROLLED TRIAL OF THE EFFICACY AND THE SAFETY OF RO6889450 (RALMITARONT) VS. PLACEBO IN PATIENTS WITH AN ACUTE EXACERBATION OF SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER.**
SHORT TITLE	**EFFECT OF RO6889450 VERSUS PLACEBO IN PATIENTS WITH AN ACUTE EXACERBATION OF SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER**
PROTOCOL NUMBER:	BP41743
VERSION:	4
TEST PRODUCT:	RO6889450
PHASE:	II

RATIONALE

RO6889450 is a novel compound and a partial agonist of the trace amine-associated receptor 1 (TAAR1) for the treatment of schizophrenia. RO6889450 is currently in Phase II clinical development.

TAAR1 is a class A G protein coupled receptor (GPCR). It is expressed in the amygdala, hypothalamus, subiculum, and rhinal cortices as well as areas of the brain where modulation of dopaminergic (ventral tegmental area) and serotonergic (dorsal raphe nucleus) neuronal activity occurs. TAAR1 partial agonists have been shown to modulate dopaminergic, serotonergic, and glutamatergic neurotransmission, and have demonstrated anti-psychotic, anti-addictive, stress response, and glucose-regulating activity in nonclinical models. By targeting overlapping brain circuits that are implicated in psychotic and affective symptoms, and reward processing, as well as brain and peripheral circuits that regulate energy homeostasis, RO6889450 represents a potential novel therapy for the treatment of psychotic and affective disorders, including schizophrenia and schizoaffective disorder.

In schizophrenic patients, the F-DOPA signal is increased indicating an abnormal increase in presynaptic dopamine synthesis capacity. Elevated dopamine synthesis capacity, as measured by [18F]-DOPA, is seen in people with schizophrenia and correlates with the degree of psychosis in patients who are treatment responsive. In rodents, the F-DOPA signal was significantly decreased by RO6889450, which provides initial evidence that RO6889450 may normalize a key abnormality of the dopamine system in patients with schizophrenia. These results indicate a potential utility of RO6889450 in the treatment of patients with acute exacerbation of schizophrenia. Recently, results of a Phase II trial with the investigational product SEP-363856, characterized as a TAAR1 and 5HT1a agonist, have shown improvement in patients with acute exacerbation of schizophrenia *at 4* weeks. A *6-month open-label extension period following the 4-week study was associated with continued improvement as assessed by the Positive and Negative Syndrome Scale (PANSS) total score and Clinical Global Impression Severity (CGI-S) with minimal effects on metabolic parameters and extrapyramidal symptoms. In addition, negative symptoms continued to show improvement during a 26-week, open-label treatment as assessed by the Brief Negative Symptom Scale total score and the Marder PANSS negative symptom factor score.*

This Phase II study will be conducted to further investigate and confirm whether the administration of RO6889450 as a monotherapy treatment in patients with an acute exacerbation of schizophrenia can improve the symptoms of schizophrenia. *The 36-Week Safety Extension Phase of this study will aim to evaluate long-term safety, tolerability, and selected effectiveness outcomes.*

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To compare the effect of 4-week treatment with two doses of RO6889450 (45 mg and 150 mg) vs. placebo in participants with acute symptoms of schizophrenia or schizoaffective disorder.	• Change from baseline at Week 4 in the Positive and Negative Syndrome Scale (PANSS) total score.
Secondary	
• To compare the effect of two doses of RO6889450 (45 mg and 150 mg) with placebo on symptoms of schizophrenia or schizoaffective disorder as assessed with PANSS.	• Proportion of participants with at least 20% or 50% improvement from baseline on PANSS total score. • Changes from baseline in the PANSS factor scores and proportion of participants with at least 20% or 50% improvement from baseline in the PANSS factor scores.
• To compare the effect of two doses of RO6889450 (45 mg and 150 mg) with placebo on: Clinical Global Impression Severity (CGI-S) and improvement (CGI-I).	• Change from baseline (CGI-S and CGI-S MTS scores) • CGI-I and CGI-I MTS scores
• To compare the effect of two doses of RO6889450 (45 mg and 150 mg) with placebo on time-to-readiness for discharge from inpatient unit.	• Time from first randomized treatment intake to readiness for discharge as assessed by the Readiness for Discharge Questionnaire (RDQ) or actual discharge or censoring if the participant discontinues the study early.

Objectives	Endpoints
• To compare the safety and tolerability of 4 weeks of treatment with two doses of RO6889450 (45 mg and 150 mg) vs. placebo.	• Incidence, nature, and severity of adverse events (Aes). • Incidence, nature, and severity of serious Aes (SAEs). • Incidence, nature, and severity of treatment discontinuations due to Aes. • Change from baseline in standing vital signs recordings. • Change from baseline in electrocardiogram (ECG) intervals: heart rate, PQ (PR), QRS, QT, RR and QTcF along with information on T- and U-waves. • Incidence of laboratory abnormalities based on hematology, clinical chemistry, and urinalysis test results. • Change from baseline in Columbia-Suicide Severity Rating Scale (C-SSRS) and Extrapyramidal symptom rating scale, abbreviated (ESRS-A).
• To observe the effect of treatment of two doses of RO6889450 (45 mg and 150 mg) up to 12 weeks.	• Proportion of participants with at least 20% or 50% improvement from baseline on PANSS total score. • Changes from baseline in the PANSS factor scores and proportion of participants with at least 20% or 50% improvement from baseline in the PANSS factor scores. • CGI-S and CGI-S MTS. • CGI-I and CGI-I MTS.
• To observe the safety and tolerability of extended treatment with two doses of RO6889450 (45 mg and 150 mg) up to 12 weeks.	• Incidence, nature, and severity of Aes. • Incidence, nature, and severity of SAEs. • Incidence, nature, and severity of treatment discontinuations due to Aes. • Change from baseline in standing vital signs recordings. • Change from $screening$ in ECG intervals: heart rate, PQ (PR), QRS, QT, RR and QTcF along with information on T- and U-waves • Incidence of laboratory abnormalities based on hematology, clinical chemistry, and urinalysis test results. • Change from baseline in C-SSRS and ESRS-A.

Objectives	Endpoints
• To evaluate the pharmacokinetics (PK) of RO6889450 and RO6889450-derived metabolite(s).	• Concentration per time point. • AUC_{ss} of RO6889450 and, if feasible, RO6889450- derived metabolite(s) at Week 4. • C_{max} of RO6889450 and, if feasible, RO6889450-derived metabolite(s) at Week 4. • Other PK parameters as appropriate.
Exploratory	
• To evaluate the changes in Sleep, Mood, Well-being, Cognitive Functioning and Treatment Expectancy.	• Smartphone App Questionnaire.
• To assess the changes in ReQoL.	• Change in ReQoL from baseline, proportion of patients with 10 points improvement or more.
• To compare the effect of two doses of RO6889450 (45 mg and 150 mg) with placebo on: Patient Global Impression – Change (PGI-C).	• PGI-C.
• To assess the relationship between the levels of inflammatory biomarkers and cognitive subtype.	• Differences in levels of inflammatory biomarkers between subgroups of patients defined by pre-morbid and current IQ estimate (Wide Range Achievement Test [WRAT-4] and Wechsler Abbreviated Scale of Intelligence – Second Edition [WASI-II]).
• To evaluate the change in the level of depression in schizophrenia measured by Calgary Depression Scale for Schizophrenia (CDSS) up to 48 weeks.	• Calgary Depression Scale for Schizophrenia.
• To evaluate the changes in the level of insight into mental disorder.	• Scale to Assess Unawareness of Mental Disorder (SUMD). • VAGUS insight into Psychosis Scale. • Beck Cognitive Insight Scale (BCIS).
• To explore the changes in nicotine addiction measured by Fagerström Test for Nicotine Dependence.	• Fagerström Test for Nicotine Dependence.
• To explore the effects of RO6889450 on levels and patterns of social and general activity and psychotic symptoms	• Ecological Momentary Assessment
• To assess patients perception of changes relative to their condition and relevance and ease of understanding of the PRO instruments used in the study	• Feedback questions
• To evaluate relationship between the premorbid functioning and treatment response	• Premorbid Adjustment Scale (PAS)

Objectives	Endpoints
• *To observe the effect of treatment with two doses of RO6889450 (45 mg and 150 mg) up to 48 weeks*	• *Changes from baseline in the PANSS total and factor scores at Week 48. Analysis by the following groups: risperidone, RO6889450 45 mg, RO6889450 150 mg, placebo/RO6889450 45 mg, placebo/RO6889450 150 mg.* • *CGI-S* • *CGI-I*
• *To observe the safety and tolerability of long-term treatment with RO6889450 up to 48 weeks*	• *Incidence, nature, and severity of Aes.* • *Incidence, nature, and severity of SAEs.* • *Incidence, nature, and severity of treatment discontinuations due to Aes.* • *Change from baseline in standing vital signs recordings.* • *Change from screening in ECG intervals: heart rate, PQ (PR), QRS, QT, RR, and QTcF along with information on T- and U-waves* • *Incidence of laboratory abnormalities based on hematology, clinical chemistry, and urinalysis test results.* • *Change from baseline in C-SSRS and ESRS-A.*

OVERALL DESIGN

This is a Phase II, multi-center, randomized, double-blind, parallel group, placebo-controlled study in participants with an acute exacerbation of schizophrenia or schizoaffective disorder.

Study Design

Participants who are experiencing an exacerbation of their schizophrenia, starting no later than 8 weeks prior to the screening visit, will be included.

After eligibility is confirmed during the screening period (Study Period 1), approximately 280 participants will be randomized outside Japan (United States [US] and rest of the world [ROW]) in equal proportions (approximately 70 per group) to one of the following treatments: 150 mg QD of RO6889450, 45 mg QD of RO6889450, placebo, or risperidone 4 mg QD (titration period: 2 mg of risperidone on Day 1, 4 mg of risperidone from Day 2) in a double-blind fashion for 4 weeks. In addition to these 280 participants, approximately 28 participants will be recruited in Japan.

Outside Japan randomization will be based on region (North America, Eastern Europe, and Asia), baseline PANSS total (80-95 and 96 and above), duration of the disease (≤ 5 years and > 5 years), and sex. In Japan randomization will be stratified according to baseline PANSS total (80-95 and 96 and above). Participants must remain as inpatients throughout Study Period 1 and during the 4 weeks of the double-blind treatment period (Study Period 2).

After completion of the 4-week Study Period 2, the participants may enter a double-blind extension period (Study Period 3) if agreed between Investigator and participant based on clinical status.

Participants treated with risperidone, or 150 mg QD of RO6889450, or 45 mg QD of RO6889450 during the Study Period 2 will continue with their respective treatments in the Study Period 3, while participants assigned to placebo will be randomized to either 150 mg QD or 45 mg QD of RO6889450 in a blinded fashion. Outside Japan randomization will be based on region (North America, Eastern Europe, and Asia), baseline PANSS total (80-95 and 96 and above), duration of the disease (≤ 5 years and > 5 years), and sex. In Japan randomization will be stratified according to baseline PANSS total (80-95 and 96 and above). At the beginning of the Study Period 3, participants will be discharged from the hospital or may remain inpatient for the first weeks if required according to the clinical judgment of the Investigator. If the participant must remain in the hospital beyond the first weeks of Study Period 3 according to the clinical judgment of the Investigator, the Investigator will need to obtain approval from the Sponsor. For Japan, due to regional differences in health care, Sponsor approval is not required.

After completion of Study Period 3, participants may be offered continuation in the optional 36-Week Safety Extension Phase if they meet additional inclusion criteria. Participants will continue to receive the same treatments as those they received during Study Period 3, in a double-blind fashion.

The assessment of the primary endpoint (PANSS) will be performed by trained centralized raters independent from the investigational sites. Participants who discontinue study medication during Study Period 2 are required to complete the Study Period 2 EOT visit as soon as possible after the last dose of study drug (if possible, PANSS assessment should be performed before rescue medications are taken). These participants are also required to return to the clinic 4 weeks after the first dose of study drug (at the end of the 4-week Study Period 2) for Week 4 early termination visit (ETV). Participants will also be asked to return for the follow-up visit (4 weeks after the last dose of study drug).

Treatment Groups and Duration

The investigational medicinal product (IMP) will be one of the following: 150 mg QD of RO6889450, 45 mg QD of RO6889450, placebo, or risperidone 4 mg QD (titration period: 2 mg of risperidone on Day 1, 4 mg of risperidone from Day 2) in a double-blind fashion for 4 weeks *in* Study Period 2*,* 8 weeks *in* Study Period 3*, and 36 weeks in the 36-Week Safety Extension Phase.*

Length of Study

The total duration of the study for each participant will be approximately 17 weeks *(or 53 weeks if participating in the 36-Week Safety Extension Phase)* divided as follows:

- Study Period 1: Screening: approximately 3 to 7 days (1 week: inpatient).
- Study Period 2: Double-blind treatment period: 28 days (4 weeks: inpatient).
- Study Period 3: Double-blind extension treatment period: 56 days (8 weeks). At the beginning of the extension period, participants will be discharged from the hospital or may remain inpatient for the first weeks if required according to the clinical judgment of the Investigator.
- *36-Week Safety Extension Phase (optional): 36 weeks. Participants, who have completed Study Period 3 and in the opinion of the Investigator may benefit from the prolonged treatment, may enter 36-Week Safety Extension Phase if they meet additional eligibility criteria. Participants with worsening of their psychiatric or medical status that would preclude their safe participation in the 36-Week Safety Extension Phase or their ability to comply with the required procedures will not be eligible for the 36-Week Safety Extension Phase of this study.*
- Study Period 4: Safety follow-up*/Follow-up Period for 36-Week Safety Extension Phase*: 28 days (4 weeks). *Mandatory follow-up assessments for all participants 4 weeks after the last dose of study drug.*
- End of study visit: 1 day

Participants must be observed/treated on an inpatient basis from Day -3 (at the latest) until Day 28. Participants will be discharged on Day 28 of the Study Period 2 once all planned study activities are done. The inpatient period can be extended into the double-blind extension treatment period (Study Period 3) if deemed necessary by the Investigator.

At the Investigator's discretion and upon Sponsor notification, a day pass may be granted to participants that need to temporarily leave the hospital during the inpatient periods. Urine drug screen and alcohol test need to be performed on the return of participant to the hospital.

End of Study

The end of the study is defined as the date of the last participant, last visit (LPLV) in the study.

PARTICIPANT POPULATION

The participants in this study will be patients diagnosed with an acute exacerbation of schizophrenia or schizoaffective disorder between 18 to 45 years of age, inclusive, who fulfill all of the given inclusion criteria.

Inclusion/Exclusion Criteria

Inclusion Criteria

Informed Consent

1. Able and willing to provide written informed consent and to comply with the study protocol according to the International Council for Harmonisation (ICH) and local regulations. Alternatively, if applicable, a legally authorized representative must be able to consent for the participant according to ICH and local regulations.

Age

2. Participant must be 18 to 45 years of age inclusive, at the time of signing the informed consent.

Type of Participants and Disease Characteristics

3. Participants with a DSM-5 diagnosis of schizophrenia or schizoaffective disorder as confirmed by the Mini International Neuropsychiatric Interview (MINI).
4. Disease duration $\leq$ 10 years.
5. Have a recent acute exacerbation of schizophrenia (or a psychotic exacerbation of schizoaffective disorder) of no more than 8 weeks before screening visit and no current signs of apparent lack of treatment response. Note: For exacerbations that started between 8 weeks and 3 months an exception can be authorized upon the discussion with the Medical Monitor if well-documented medical history is available that rules out a potential lack of treatment response.
6. At the time of screening, the participant needs to be either hospitalized or requiring inpatient psychiatric care according to clinical judgment *for the treatment of the acute exacerbation*. If the participant has been hospitalized for the current exacerbation, the hospitalization has to be of a maximum of 1 week prior to screening. For hospitalization between 1 and 2 weeks, an exception can be authorized upon the discussion with the Medical Monitor.
7. In previous exacerbations and hospitalizations, the subject has shown a pattern of response to appropriate antipsychotic treatment.

8. Medically stable over a period of 3 months (non-psychiatric conditions) prior to screening visit and not expected to require hospitalization or change of treatment for non-psychiatric conditions for the duration of the study.
9. Screening and baseline CGI-S ≥ 4 (moderate or worse).
10. Screening and baseline PANSS total score ≥ 80.
11. Based on screening and baseline PANSS, a score of ≥ 4 (moderate or worse) on 2 or more of the following items: delusions, conceptual disorganization, unusual thought content, hallucinatory behavior, or suspiciousness/persecution.

Weight

12. Body mass index (BMI) between 18 and 35 kg/m^2 inclusive.

Sex

13. Male and female participants:

1. A female is eligible to participate if she is not pregnant (see Appendix 5, negative serum pregnancy test at screening), not breastfeeding, and at least one of the following conditions applies:

    a) Women of non-childbearing potential (WONCBP), as defined in Appendix 5.

    b) Women of childbearing potential (WOCBP), who agree to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive methods during the treatment period and for at least 28 days after the last dose of study drug.

    The following are acceptable contraceptive methods: bilateral tubal occlusion/ligation, male sexual partner who is sterilized, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices and copper intrauterine devices, male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide (see Appendix 5).

The contraception and abstinence requirements are intended to prevent exposure of an embryo to the study treatment. The reliability of sexual abstinence for female enrollment eligibility needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of preventing drug exposure.

Inclusion Criteria for the Optional 36-Week Safety Extension Phase

Participants who, according to clinical judgment of the Investigator, may benefit from prolonged treatment and meet the following additional inclusion criteria, may be eligible for participation in the 36-Week Safety Extension Phase:

A. Completion of the 12-week treatment (Study Periods 2 and 3).

B. Able and willing to provide written informed consent for the 36-Week Safety Extension Phase and to comply with the study protocol according to the ICH and local regulations. Alternatively, if applicable, a legally authorized representative must be able to consent for the participant according to ICH and local regulations.

C. Female participants of childbearing potential must have a negative urine pregnancy test at the Week-12 visit and be willing to remain abstinent or continue the use of contraceptive methods as described in Inclusion Criterion 13.

D. *No signs or symptoms of worsening of the psychiatric or medical status that would preclude the patient from the participation in the 36-Week Safety Extension Phase or affect their ability to comply with the study requirements.*

Exclusion Criteria

General exclusions

2. Has been inpatient for > 2 weeks or have any other hospitalization for acute exacerbation of schizophrenia or schizoaffective disorder within the prior 8 weeks or signs of lack of response to antipsychotic treatment.
3. Disease duration longer than 10 years.
4. Is currently an inpatient on an involuntary basis.
5. Subject answers “yes” to “Suicidal Ideation” Item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation with specific plan and intent) or any suicidal behavior on the C-SSRS assessment within one month from Screening or between Screening and Baseline (i.e., since last visit). Significant risk of suicide or harming himself / herself or others according to the Investigator’s judgment.
6. Lifetime history of homicidal behavior.
7. Moderate to severe substance use disorder within six months (excluding nicotine) as defined by DSM-5.
8. Other current DSM-5 diagnosis (e.g., bipolar disorder, major depressive disorder).

9. **Medical conditions**

10. A prior or current general medical condition that might be impairing cognition or other psychiatric functioning (e.g., migraine headaches requiring prophylaxis treatment, head trauma, dementia, seizure disorder, stroke; or neurodegenerative, inflammatory, infectious, neoplastic, toxic, metabolic, or endocrine conditions).
11. Positive result at screening for hepatitis B surface antigen (HbsAg), hepatitis C virus (HCV, untreated), or human immunodeficiency virus (HIV)-1 or -2. HCV participants who have been successfully treated and who test negative for HCV RNA, may be considered eligible for entry into the study.
12. Tardive dyskinesia that is moderate to severe or requires treatment.
13. History of neuroleptic malignant syndrome.

14. Clinically significant abnormalities in laboratory safety test results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis), including:
    15. a) Aspartate aminotransferase (AST), OR alanine aminotransferase (ALT) 2 × upper limit of normal (ULN), OR total bilirubin > 1.5 ULN with the exception of known Gilbert syndrome.
    16. b) Serum creatinine > 1.5 ULN.

NOTE: In case of uncertain or questionable results, tests performed during screening may be repeated before randomization to confirm eligibility or may be accepted if they are, in the opinion of the Investigator and the Medical Monitor, not clinically significant.

17. Average triplicate QTcF interval greater than 450 msec for males and 470 msec for females or other clinically significant abnormality on screening ECG based on centralized reading.

Prior/Concomitant Therapy

18. Participants for whom risperidone is contraindicated or who have a documented history of lack of response or intolerance to risperidone or paliperidone or participants with known hypersensitivity to risperidone, paliperidone, or to any excipients in Risperdal.
19. Participant treated with a long acting injectable antipsychotic (LAI) or other antipsychotics that cannot be washed-out during the screening period. See a list of specific medications in Section 6.5.
20. History of electroconvulsive therapy (ECT).
21. Participant treated with clozapine within 12 months of screening visit or participants treated with clozapine at 200 mg/day or above at any time; low dose (<200mg/day) use for insomnia or dyskinesia 12 months prior to screening visit may be permitted if approved by the Sponsor (or designee; Section 6.5).
22. Participant currently receiving a psychotropic or other medication used as a psychotropic, which cannot be discontinued during the screening period.
23. Positive urine drug screen for amphetamines, methamphetamines, opiates, buprenorphine, methadone, cocaine and barbiturates. In case of positive urine drug screen for cannabinoids (including cannabidiol), the participant may be allowed to enter the study if approved by Medical Monitor (mild cannabis use disorder or sporadic use of cannabis are considered eligible for entry into the study).
24. Diagnosis of COVID-19 infection (confirmed or presumptive) 4 weeks prior to Screening or during Screening. Participants can be re-screened after 4 weeks of full recovery in addition to Investigator and/or institutional approval to enroll.

Prior/Concurrent Clinical Study Experience

25. Participant has previously received RO6889450.
26. Participant received an investigational drug within 28 days or five times the half-life of the investigational drug (whichever is longer) prior to the first study drug administration (study Day 1).

NUMBER OF PARTICIPANTS

Approximately 280 participants will be randomized (70 per group: RO6889450 150 mg QD; RO6889450 45 mg QD; risperidone 4 mg QD; and placebo) outside Japan (US and ROW). In addition to these 280 participants, approximately 28 participants will be recruited in Japan.

Outside Japan randomization will be based on region (North America, Eastern Europe, and Asia), baseline PANSS total (80-95 and 96 and above), duration of the disease (≤ 5 years and > 5 years), and sex. In Japan randomization will be stratified according to baseline PANSS total (80-95 and 96 and above). Participants must remain as inpatients at a minimum during the screening period and during Study Period 2.

CONCOMITANT MEDICATIONS

Any medication (prescription and over-the-counter [OTC]) taken within 28 days of study screening and any non-pharmacological interventions (e.g., individual psychotherapy, cognitive behavioral therapy, smoking cessation therapy, and rehabilitative therapy) will be recorded on the appropriate electronic case report form (eCRF).

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Anti-psychotic medication

All anti-psychotics are prohibited in the study during Study Periods 2 and 3*, the 36-Week Safety Extension Phase,* and with a minimum washout period of 72 hours before the initiation of study medication. Washout periods for a specific anti-psychotic medication are provided in the table below.

Rescue anti-psychotic treatment

If the clinical state of the participant would require treatment with an anti-psychotic other than the study medication, in the judgment of the Investigator, an antipsychotic should be prescribed and the participant will be immediately withdrawn from the study drug. Investigators should make a reasonable effort to complete a final assessment including efficacy endpoints before starting antipsychotic medication. The reasons for use of rescue medication should be documented in detail.

Anti-psychotic and rescue medication

Type of medication	Timelines and instructions
Antipsychotic medication • asenapine • chlorpromazine • fluphenazine • haloperidol • iloperidone • loxapine • molindone • olanzapine • pericyazine • perospirone • perphenazine • prochlorperazine • quetiapine • trifluoperazine • thiothixene • ziprasidone • zuclopenthixol	Permitted as prior medication and during the screening period, but prohibited within the 72 hours prior to the first dose of study medication*, during* Study *Periods* 2 and 3*, and the 36-Week Safety Extension Phase* (blinded treatment).
• risperidone • paliperidone	Permitted as prior medication and during the screening period, but prohibited within the 72 hours prior to the first dose of study medication*, during* Study Periods 2 and 3*, and the 36-Week Safety Extension Phase* (blinded treatment). Participant excluded if there is a history of lack of response or intolerance to risperidone or paliperidone.
• aripiprazole. 2 weeks • blonanserin, 3 weeks • brexpiprazole. 3 weeks • cariprazine. 15 weeks • aripiprazole LAI (Abilify Maintena®). 2 months • aripiprazole lauroxil (Aristada®). 4 months • fluphenazine deconate. 2 months • haloperidol decanoate. 2 months • olanzapine LAI. 2 months	Permitted as prior medication if had been stopped before the indicated wash out periods prior to screening visit. Note: Single doses (before reaching steady state) of aripiprazole, brexpiprazole and blonanserin administered to control current exacerbation can be authorized upon the discussion with the Medical Monitor.
• paliperidone palmitate (Invega Sustenna®, Invega Trinza®). 6 months • risperidone LAI (Risperdal Consta®). 1 month	Permitted as prior medication if had been stopped before the indicated wash out periods prior to screening visit. Participants excluded if there is a history of lack of response or intolerance to risperidone or paliperidone.
• clozapine	Excluded any use in previous 12 months before screening, and any lifetime use at doses of 200 mg/day or greater.

Non anti-psychotic concomitant medication

Permitted Therapy

Non-psychoactive medications, including over-the-counter medications, that are required to treat pre-existing conditions or adverse events (Aes) that occur during the study may be used at the discretion of the Investigator.

All therapy and/or medication administered to manage Aes should be recorded on the AE eCRF. For further information regarding the management of specific Aes see Appendix 2.

Non-prohibited medications used for the treatment of stable medical conditions other than schizophrenia (e.g., hypertension, diabetes, oral contraceptives, hormone replacement therapy) are allowed during the study.

Agents designed to prevent pregnancy: intrauterine device in place, oral contraceptives, dermal contraceptives, and injectable or implantable hormonal agents are permitted from enrollment until the end of the treatment period.

Concomitant therapy includes any medication, e.g., prescription drugs, OTC drugs, *vaccines (including those against COVID-19),* approved dietary and herbal supplements, nutritional supplements and any non-pharmacological interventions (e.g., individual psychotherapy, group therapy, cognitive behavioral therapy, smoking cessation therapy, and rehabilitative therapy) used by a participant from 28 days prior to screening until the follow-up visits. All concomitant medications should be reported to the Investigator and recorded in the eCRF.

Prohibited Therapy

All medications (prescription and OTC) taken within 28 days of study screening and any non-pharmacological interventions (e.g., individual psychotherapy, cognitive behavioral therapy, smoking cessation therapy, and rehabilitative therapy) will be recorded on the appropriate eCRF.

As a general rule, no new concomitant medication or therapies will be permitted, with the exception of medications to treat pre-existing conditions or Aes, unless the rationale for exception is discussed and clearly documented between the Investigator and the Sponsor.

Specific prohibited medications are provided in the table below.

Prohibited Therapies

Type of medication	Timelines and instructions
Illegal substance use (including legal cannabis) : opiates, amphetamine, barbiturate, cocaine, cannabis, cannabidiol, or hallucinogen	From enrollment until the end of the treatment period
All psychotropic medications including anxiolytic, antidepressants, mood stabilizer, hypnotic, sedative medication and St John's wort except those listed in Section 6.5.2.1 permitted therapy and Table 3 restricted therapy.	From enrollment until the end of the treatment period. Must be discontinued during the screening period, regardless of the indication for which they have been prescribed.

Treatment with sedating anti-histamines (such as promethazine or diphenhydramine)	Should not be initiated during the treatment period, nor should the dose be changed for those participants who were already on treatment at the time of randomization.
Participants receiving treatment for tardive dyskinesia (e.g., valbenazine or deutetrabenazine) are excluded.	From enrollment until the end of the treatment period.
The following strong CYP3A4 inducers are prohibited: carbamazepine, aprepitant, phenytoin.	From enrollment until the end of the treatment period.
The following strong P-gp inducers are prohibited: verapamil, apalutamide.	From enrollment until the end of the treatment period.
Clinically relevant substrates of P-gp, including quinidine and loperamide	From enrollment until the end of the treatment period.

Restricted Therapy

The list of restricted therapies is provided in the table below.

Restricted Therapies

Type of medication	Timelines and instructions
Medication for extrapyramidal symptoms (EPS) • benztropine: up to 4 mg/day (up to 2 mg single dose), • or biperiden up to 6 mg/day (up to 2 mg single dose), • or trihexyphenidyl up to 6 mg/day (up to 3 mg single dose) • propanolol (up to 60 mg/day)	Initiation and dose increase of anticholinergic medications should only happen to treat emergent EPS related Aes. Treatment should be limited to a 7-day period. A prescription may be renewed if necessary after reevaluation. Continuation of previous treatment may be allowed if the patient has been on a stable dose for at least 28 days prior to the screening period and the Investigator considers it clinically required after consultation with the Sponsor or Medical monitor.
Lorazepam or equivalent benzodiazepine • Total dose $\leq$ 6 mg/day of lorazepam during screening and the first week of the trial • Total dose $\leq$ 4 mg/day lorazepam from Week 2 until the end of the Study Period 3. • Total dose $\leq$ 3 mg/day of alprazolam during screening and the first week of the trial • Total dose $\leq$ 2 mg/day of alprazolam from Week 2 until the end of the Study Period 3 • Total dose $\leq$ 90 mg/day of oxazepam during screening and the first week of the trial • Total dose $\leq$ 60 mg/day of oxazepam from Week 2 until the end of the Study Period 3.	Benzodiazepine use is permitted provided the patient has been receiving a stable dose for at least 3 months and the total dose for all uses is < 6mg/day of lorazepam. Initiation and/or dose increase of lorazepam or equivalent benzodiazepine should only happen to treat emergent anxiety, akathisia, agitation, or sleep disorders, and only within the maximum dose described in the left column. Lorazepam or equivalent benzodiazepine treatment should not be administered within 12 hours prior to PANSS assessments.
Hypnotic or sedative medication • zolpidem tartrate up to 10 mg/day, • or chloral hydrate up to 2 g/day, • or zaleplon up to 10 mg/day, • or zopiclone up to 7.5 mg/day	Hypnotic or sedative medication is preferred treatment for sleep disorders rather than lorazepam and equivalent benzodiazepines. Routine use is allowed to treat sleep disorders if the patient takes a stable restricted dose for at least 3 months prior to the screening period, and only within the maximum dose described in the left column. Initiation and/or dose increase of hypnotic should only happen to treat emergent sleep disorders, and only within the maximum dose described in the left column. Hypnotic or sedative medications should not be administered within 12 hours prior to PANSS assessments.

APPENDIX 2 SCHEDULE OF ACTIVITIES STUDY BP41743

Schedule of Activities *without 36-Week Extension Safety Phase*

	Period 1	Period 2							Period 3						Period 4
		Double-blind Treatment Period (4 weeks)							Double-blind Extension Treatment Period (8 weeks)						Follow-up Period (4 weeks)
Visit Name/Study Week	Screening[a]	Baseline	1	1	2[s]	3	4[b,s] Period 2 EOT	4[b] ETV	5	6	7	8[s]	10	12[b,s] Period 3 EOT	16[b,s,ee]
Study Day	-7 to -3	1	3	7	14	21	28	28	35	42	49	56	70	84	112
Visit window (± days)[x]		± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 2	± 2	± 2	± 2	± 3	± 3	± 3
Written Informed Consent	X														
Inclusion/Exclusion criteria	X	X													
Eligibility Assessment Form	X														
Randomization		X					(X)[r]								
Demographics	X														
FTND[c,v]	X	X			X		X					X		X	X
Psychiatric/Medical History[bb]	X														
Mini International Neuropsychiatric Interview (MINI)	X														
Physical Exam[d, bb]	X						X							X	X
12 lead ECG[bb]	X			X	X		X			X		X		X	X
Vitals (supine and standing)[bb]	X	X	X	X	X	X	X			X		X	X	X	X
Weight and waist circumference[bb,cc]	X	X			X		X			X		X	X	X	X
Previous and Concomitant Medications[bb]	X	X		X	X	X	X		X	X	X	X	X	X	X
Alcohol Test[bb,y]	X	X			X		X			X		X		X	X
Viral serology[bb]	X														
Blood Chemistry[e,bb]	X	X			X		X					X		X	X
Hematology[e,bb]	X	X			X		X					X		X	X
Coagulation[e,bb]	X	X			X		X					X		X	X
Lipids[e,bb]	X	X			X		X					X		X	X
Urinalysis[e,bb]	X	X			X		X					X		X	X
Prolactin[f, bb]	X						X							X	X

	Period 1	Period 2							Period 3						Period 4
		Double-blind Treatment Period (4 weeks)							Double-blind Extension Treatment Period (8 weeks)						Follow-up Period (4 weeks)
Visit Name/Study Week	Screening[a]	Baseline	1	1	2[s]	3	4[b,s] Period 2 EOT	4[b] ETV	5	6	7	8[s]	10	12[b,s] Period 3 EOT	16[b,s,ee]
Study Day	-7 to -3	1	3	7	14	21	28	28	35	42	49	56	70	84	112
Visit window (± days)[x]		± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 2	± 2	± 2	± 2	± 3	± 3	± 3
Urine drug screen[bb]	X						X							X	X
Pregnancy Test[g bb]	X	X					X							X	
PK samples[h,bb]				X	X		X			X		X		X	
Plasma[i,bb]		X					X							X	
Clinical genotyping[j,bb]		X													
COVID-19 test[bb, w]	X														
Mandatory Inpatient Hospitalization[k]	X	X		X	X	X	X		OPTIONAL[k]						
PANSS[l, v,]	X	X		X	X	X	X	X				X		X	X
PANSS-Informant Checklist[v]	X	X		X	X	X	X	X				X		X	X
CGI-S[v]	X	X		X	X	X	X	X	X	X	X	X	X	X	X
CGI-S MTS[v]	X	X		X	X	X	X	X	X	X	X	X	X	X	X
CGI-I[v]				X	X	X	X	X	X	X	X	X	X	X	X
CGI-I MTS[v]				X	X	X	X	X	X	X	X	X	X	X	X
PGI-C[v]				X	X	X	X			X		X		X	X
CDSS[v]		X					X							X	X
ESRS-A[v]	X				X		X					X		X	X
C-SSRS[v]	X	X		X	X	X	X		X	X	X	X	X	X	X
Adverse events[v,bb]	X[z]	X		X	X	X	X		X	X	X	X	X	X	X
Readiness for Discharge Questionnaire (RDQ)				X	X	X	X								
ReQoL[q, v]		X			X		X					X		X	X
IMP Dispensing[m,aa]		X			X		X			X		X	X		
Administration of study drug[o]		←							↔					→	
Phone Call[n]								←						→	
Study Treatment Accountability[v ,bb]									X	X	X	X	X	X	

	Period 1	Period 2							Period 3						Period 4
		Double-blind Treatment Period (4 weeks)							Double-blind Extension Treatment Period (8 weeks)						Follow-up Period (4 weeks)
Visit Name/Study Week	Screening[a]	Baseline	1	1	2[s]	3	4[b,s] Period 2 EOT	4[b] ETV	5	6	7	8[s]	10	12[b,s] Period 3 EOT	16[b,s,ee]
Study Day	-7 to -3	1	3	7	14	21	28	28	35	42	49	56	70	84	112
Visit window (± days)[x]		±1	±1	±1	±1	±1	±1	±1	±2	±2	±2	±2	±3	±3	±3
Medication Adherence App[t]						←		→	←						→
Assessment of Sleep, Mood, Well-being and Cognitive Functioning and Treatment Expectancy[p]	←						→	→						→	
WASI-II[q,]					X										
WRAT-4[q]					X										
PAS					X										
SUMD-9[v]		X					X							X	X
EMA[u]					←		→	←							→
Feedback questions[q,v]							X								
VAGUS-SR[v]		X					X							X	X
VAGUS-CR[v]		X					X							X	X
BCIS[v]		X					X							X	X

Schedule of Activities for the 36-Week Safety Extension Phase (Optional)

	36-Week Safety Extension Phase				Follow-up Period for 36-Week Safety Extension Phase [b,s]
Visit Name	Additional Assessments at Week 12 (Additional to Period 3 EOT)	Week 24	Week 36	Week 48 / 36-Week Safety Extension EOT	
Study Week	12	24	36	48	52
Study Day	84	168	252	336	364
Visit window (± days)[x]	±3	±7	±7	±7	±3
Written Informed Consent	X[dd]				
Inclusion criteria for extension phase	X				
Physical Exam[d, bb]		X	X	X	X
12 lead ECG[bb]		X	X	X	X
Vitals (supine and standing)[bb]		X	X	X	X
Weight and waist circumference[bb,cc]		X	X	X	X
Previous and Concomitant Medications[bb]		X	X	X	X
Alcohol Test[bb,y]		X	X	X	X
Blood Chemistry[e,bb]		X	X	X	X
Hematology[e,bb]		X	X	X	X
Coagulation[e,bb]		X	X	X	X
Lipids[e,bb]		X	X	X	X
Urinalysis[e,bb]		X	X	X	X
Prolactin[f, bb]		X	X	X	X
Urine drug screen[bb]		X	X	X	X
Pregnancy Tests[g bb]		X	X	X	
PK samples[h,bb]		X	X	X	
Plasma[i,bb]		X	X	X	
Safety Samples (plasma and serum)[bb,ff]	X	X	X	X	
PANSS[l, v]		X	X	X	X
PANSS-Informant Checklist[v]		X	X	X	X
CGI-S[v]		X	X	X	X
CGI-I[v]		X	X	X	X
CDSS[v]		X	X	X	X

	36-Week Safety Extension Phase				Follow-up Period for 36-Week Safety Extension Phase [b,s]
Visit Name	Additional Assessments at Week 12 (Additional to Period 3 EOT)	Week 24	Week 36	Week 48 / 36-Week Safety Extension EOT	
Study Week	12	24	36	48	52
Study Day	84	168	252	336	364
Visit window (±days)[x]	±3	±7	±7	±7	±3
ESRS-A[v]		X	X	X	X
C-SSRS[v]		X	X	X	X
ReQoL[q, v]		X	X	X	X
Adverse events[v,bb]		X	X	X	X
IMP Dispensing[m,aa]	X	X	X		
Administration of study drug[o]	←				→
Phone Call[n]	←				
Study Treatment Accountability[v ,bb]		X	X	X	
Smartphone apps: EMA and Assessment of Sleep, Mood, Well-being and Cognitive Functioning and Treatment Expectancy[p,u]	← Up to Week 16 →				

Footnotes for Schedule of Activities Table 1 and Table 2

a Screening period can be extended up to 10 days upon Medical monitor approval and only in the case of delay in availability of laboratory results.

B EOT, End of Treatment; ETV, Early termination visit.

During Study Period 2: If a participant voluntarily withdraws from the study or is withdrawn by the Investigator, the participant will be asked to complete Study Period 2 EOT visit as soon as possible after the last dose of study drug. This may be sooner than Day 28. Participant will also be asked to return to the clinic 4 weeks after the first dose of study drug (at the end of the 4-week Study Period 2) for Week 4 ETV to complete assessments of the primary and secondary efficacy outcomes. Participants will also be asked to return for the follow-up visit (4 weeks after the last dose of study drug).

During Study Period 3: If a participant voluntarily withdraws from the study or is withdrawn by the Investigator, the participant should return to complete Study Period 3 EOT visit as soon as possible after the last dose of study drug. This may be sooner than Day 84. Participant will also be asked to return for the follow-up visit assessments (4 weeks after the last dose of study drug).

During 36-Week Safety Extension Phase: If a participant voluntarily withdraws from the study or is withdrawn by the Investigator, the participant should return to complete the 36-Week Safety Extension EOT visit as soon as possible after the last dose of study drug. The participant will also be asked to return for the follow-up visit assessments (4 weeks after the last dose of study drug).

For the participants who discontinue study treatment prematurely, if the EOT visit for Study Period 2 and 3*, and the 36-Week Safety Extension Phase* falls into the windows of planned visit, only missing assessments need to be completed (see Section **Fehler! Verweisquelle konnte nicht gefunden werden.** And **Fehler! Verweisquelle konnte nicht gefunden werden.** Of the protocol).

C FTND (Fagerström Test for Nicotine Dependence) excludes cigar, snuff, oral, and vaping (e-cigarette) users.

D Height at screening only.

E All study-required laboratory assessments, with the exception of dipstick urinalysis, urine dipstick alcohol test, drugs of abuse, urine pregnancy test and COVID-19 test (when not performed centrally), will be performed by a central laboratory. Microscopic urinalysis if deemed necessary to be performed centrally (see Appendix 4 of the protocol).

F Prolactin results will be kept blinded to participants and Investigators.

G All women of childbearing potential (including those who have had a tubal occlusion) will have a blood pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test.

H Pre-dose at Week 1 and 2; pre-dose, 1, 2 (± 0.5) and 6 hours (±0.5) post-dose at Week 4; one sample pre-dose at Weeks 6, 8, 12 visits. PK sampling at Week 4 should be performed within two days before the Day 28 visit. During outpatient period of the study, PK samples should be taken (if possible) as the last assessment after all other assessments have been completed. Additional PK samples will be taken at the time of treatment discontinuation and in case of overdose.

I Plasma samples for the exploratory biomarker assessments will be processed centrally.

j Whole blood samples will be collected for clinical genotyping and will be processed centrally (see Section **Fehler! Verweisquelle konnte nicht gefunden werden.** of the protocol). Any other time point can be used if blood volume limits are exceeded at a particular visit day.

Footnotes for Schedule of Activities Table 1 and Table 2 (cont.)

k Participants must be observed/treated on an inpatient basis from Day -3 (at the latest) until Day 28. Participants will be discharged on Day 28 of Study Period 2 once all planned study activities are done. The inpatient period can be extended into the blinded extension treatment period if deemed necessary by the Investigator (see Section **Fehler! Verweisquelle konnte nicht gefunden werden.** of the protocol).

l Done by centralized raters.

m IMP dispensing (see Section **Fehler! Verweisquelle konnte nicht gefunden werden.** of the protocol).

n Phone calls by a case manager at the minimum once weekly are mandatory. *During the 36-Week Safety Extension Phase, phone calls by a case manager once a month are mandatory.* More frequent phone calls are encouraged. *Follow-up phone calls will be made approximately 7, 14, and 21 days after the last dose of study drug or after early termination (see Section* ***Fehler! Verweisquelle konnte nicht gefunden werden.*** of the protocol*).*

o Study drug – two tablets (one each from Bottle A and B) and two capsules (from Bottle C) except for Day 1 when only one capsule should be taken – is administered once daily, at bedtime, without food and swallowed whole with fluid. Ideally, no food should be consumed for at least 2.5 hours before and after the dosing.

p The Assessment of Sleep, Mood, Well-being and Cognitive Functioning and Treatment Expectancy is optional but strongly recommended. In total up to 28 questionnaires for assessment of Sleep, Mood, Well-being and Cognitive Functioning and Treatment Expectancy will be presented on the smartphone as part of AiCure app at selected time points that will appear as random to the participant. During Study Period 2 and for Japanese patients during Study Period 3 and Study Period 4, the questions will be captured on Medavante Virgil platform. *Participants continuing in the 36-Week Safety Extension Phase will have the option to continue using this smartphone app for the first 4 weeks (Weeks 13-16).*

q This assessment will not be performed in non-English speaking countries without linguistic validated translation. This applies also to patients who do not speak English as a first language but are living in an English speaking country. If validated translations become available, they may be used. Equivalent scales may be used, if available.

r After completion of the 4-week Study Period 2, the participants may be re-randomized into a double-blind extension period (Study Period 3) if agreed between Investigator and participant based on clinical status. Randomization numbers will remain unchanged.

s The study visit can be split over 2 days within visit window.

t The use of medication adherence platform via a smartphone app in Japan may not be required.

u EMA is optional but strongly recommended. EMA will be performed 3 times throughout the day, 5 days a week (not at the visit day). Assessments between Day 21 and Day 28 will be for training purpose and less frequent. EMA will not be performed in Japan. *Participants continuing in the 36-Week Safety Extension Phase will have the option to continue using this smartphone app for the first 4 weeks (Weeks 13-16).*

v If onsite visits are not permitted due to local restrictions, (e.g., due to travel restrictions for COVID-19) this assessment can be performed remotely if confirmed by the Sponsor, for visits subsequent to the Period 2 EOT visit. The scope of the assessment remains the same. Source documentation should detail if the assessment has been performed remotely.

Footnotes for Schedule of Activities Table 1 and Table 2 (cont.)

w Unless performed locally within 2 weeks and available documentation can be provided.

x In exceptional situations (i.e., COVID-19 outbreak), the visit may be split between two days.

y Alcohol test will be performed using a urine dipstick test.

z Serious Adverse Event (SAE) only.

aa If onsite visits during study Period 3 *and the 36-Week Safety Extension Phase* are not permitted due to local restrictions, (e.g., due to travel restrictions for COVID-19) study drug can be shipped from sites directly to a patient if approved by Sponsor and relevant health authorities, if applicable. This must be confirmed and documented in the participan''s source file.

bb If the post Period 2 EOT visit study assessments and procedures cannot be administered because the visit cannot take place (e.g., due to travel restriction due to an outbreak of COVID-19), the Home HealthCare System can be used. The scope of the assessment remains the same. Source documentation should detail if the assessment has been performed remotely.

cc For anthropometric measurements of weight and waist circumference the use of the same weighing scale and tape measure throughout the study is recommended.

dd Informed consent form for the 36-Week Safety Extension Phase must be signed prior to initiation of any procedures related to the 36-Week Safety Extension Phase.

ee Only for participants who completed Study Period 3 but did not enter the optional 36-Week Safety Extension Phase.

ff Safety blood samples will be taken and may be analyzed if needed, to investigate any new clinical safety signal.

APPENDIX 3 PANSS SYMPTOM FACTORS

Factor	Original PANSS item number	PANSS item name
Negative symptoms	N1	Blunted affect
	N2	Emotional withdrawal
	N3	Poor rapport
	N4	Passive/apathetic social withdrawal
	N6	Lack of spontaneity and flow of conversation
	G7	Motor retardation
	G16	Active social avoidance
Disorganized thought/cognition	P2	Conceptual disorganization
	N5	Difficulty in abstract thinking
	G5	Mannerisms and posturing
	G10	Disorientation
	G11	Poor attention
	G13	Disturbance of volition
	G15	Preoccupation
Positive symptoms	P1	Delusions
	P3	Hallucinatory behavior
	P5	Gandiosity
	P6	Suspiciousness
	N7	Stereotyped thinking
	G1	Somatic concern
	G9	Unusual thought content
	G12	Lack of judgment and insight
Uncontrolled hostility/excitement	P4	Excitement
	P7	Hostility
	G8	Uncooperativeness
	G14	Poor impulse control
Anxiety/depression	G2	Anxiety
	G3	Guilt feelings
	G4	Tension
	G6	Depression

PANSS symptom factors based on “Marder” PANNS factor analysis published in J Clin Psych 58:12, December 1997 p538 [Marder 1997].

Expressive Deficit: N01 + N03 + N06 + G07 (Khan)

Avolition: N01 + N02 + N04 + G16

APPENDIX 4 UNCORRELATED PANSS SCORE MATRIX (UPSM) FOR GENERATING TRANSFORMED PANSS FACTOR SCORES

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

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

APPENDIX 5 CGI-S AND CGI-I QUESTIONS

Clinical Global Impression

Clinical Global Impression – Severity of Illness Scale (CGI-S)

Circle the appropriate number for item below.

SEVERITY OF ILLNESS

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

0 = Not assessed	4 = Moderately ill
1 = Normal, not at all ill	5 = Markedly ill
2 = Borderline mentally ill	6 = Severely ill
3 = Mildly ill	7 = Among the most extremely ill patients

Clinical Global Impression – Improvement Scale (CGI-I)

Circle the appropriate number for item below.

GLOBAL IMPROVEMENT

Rate total improvement whether or not, in your judgment, it is due entirely to drug treatment. Compared to his condition at baseline (prior to randomization), how much has patient changed?

0 = Not assessed	4 = No change
1 = Very much improved	5 = Minimally worse
2 = Much improved	6 = Much worse
3 = Minimally improved	7 = Very much worse

Adapted from Guy W. ECDEU Assessment manual for Psychopharmacology, US Department of Health, Education, and Welfare publication (ADM) 76-338, Rockville, MD; National Institute of Mental Health, 1976.

Clinical Global Impression Most Troubling Symptoms – Severity of Illness Scale (CGI-S MTS)

1–- SYMPTOM NOT PRESENT

2–- PRESENCE OF SYMPTOM QUESTIONABLE

3–- PRESENT TO A MINOR DEGREE

4–- PRESENT TO A MODEST DEGREE

5–- PRESENT TO A SIGNIFICANT DEGREE

6–- PRESENT TO A SEVERE DEGREE

7–- PRESENT TO AN EXTREME DEGREE

Clinical Global Impression Most Troubling Symptoms – Improvement Scale (CGI-I MTS)

1 – VERY MUCH IMPROVED

2 – MUCH IMPROVED

3 – MINIMALLY IMPROVED

4 – NO CHANGE

5 – MINIMALLY WORSE

6 – MUCH WORSE

7 – VERY MUCH WORSE

APPENDIX 6 FAGERSTÖM TEST OF NICOTINE DEPENDENCE SCORING

How Long After Waking For First	0 = After 60 minutes 1 = 31-60 minutes 2 = 6-30 minutes 3 = Within 5 minutes
Difficult to Refrain	0 = No 1 = Yes
Hardest Cigarette to Give Up	1 = The first in the morning 0 = Any other
No. of Cigarettes per Day	0 = 10 or less 1 = 11-20 2 = 21-30 3 = 31 or more
More Just After Awakening	0 = No 1 = Yes
Smokes When ill and Bedbound?	0 = No 1 = Yes

APPENDIX 7 ADVERSE EVENT TEMPLATES

Adverse Events During Period 2

MedDRA System Organ Class MedDRA Preferred Term	Placebo (N=xx)	RO6889450 45MG QD (N=xx)	RO6889450 150MG QD (N=xx)	Risperidone 4MD QD (N=xx)
Total number of patients with at least one adverse event	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Overall total number of events	xx	xx	xx	xx
Gastrointestinal disorders				
Total number of patients with at least one adverse event	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Total number of events	x	x	x	x
Vomiting	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)
Nausea	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)

...

Investigator text for aEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. Only treatment emergent aEs are displayed. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of""Total number of event"" rows, multiple occurrences of the same AE in an individual are counted separately. Data which has been collected during Periods 2 is included.

Notes:

- Period 2: 4 week in-patient period
- Period 3: 8 weeks out-patient period
- N in the column headings is the number of patients who received at least one treatment in Period 2.
- Treatment emergent aEs are those with start date between first treatment in Period 2 and the day before first treatment in the 8-weeks double-blind extension treatment period (Period 3) if the patient received treatment in Period 3, or the last day of treatment in Period 2 + 1 day if the patient did not receive treatment in Period 3.

Adverse Events During Period 3

MedDRA System Organ Class MedDRA Preferred Term	Placebo P2/ RO6889450 45MG QD P3 (N=xx)	Placebo P2/ RO6889450 150MG QD P3 (N=xx)	RO6889450 45MG QD P2/3 (N=xx)	RO6889450 150MG QD P2/3 (N=xx)	Risperidone 4MD QD P2/3 (N=xx)
Total number of patients with at least one adverse event	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Overall total number of events	xx	xx	xx	xx	xx
Gastrointestinal disorders					
Total number of patients with at least one adverse event	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Total number of events	x	x	x	x	x
Vomiting	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)
Nausea	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)

...
Investigator text for aEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of""Total number of event"" rows, multiple occurrences of the same AE in an individual are counted separately. Data which has been collected during Period 3 is included.

Notes:

- Period 3: 8 weeks out-patient period
- N in the column headings is the number of patients who received at least one treatment in Period 3.
- aEs with start date between first treatment in Period 3 and last treatment in Period 3 + 1 day will be included.

Adverse Events During Period 2 and 3

MedDRA System Organ Class MedDRA Preferred Term	RO6889450 45MG QD P2/3 (N=xx)	RO6889450 150MG QD P2/3 (N=xx)	Risperidone 4MD QD P2/3 (N=xx)
Total number of patients with at least one adverse event	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Overall total number of events	xx	xx	xx
Gastrointestinal disorders			
Total number of patients with at least one adverse event	x (xx.x%)	x (xx.x%)	x (xx.x%)
Total number of events	x	x	x
Vomiting	x (x.x%)	x (x.x%)	x (x.x%)
Nausea	x (x.x%)	x (x.x%)	x (x.x%)

...
Investigator text for aEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. Only treatment emergent aEs are displayed. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of""Total number of event"" rows, multiple occurrences of the same AE in an individual are counted separately. Data which has been collected during Periods 2 and 3 is included.

Notes:

- Period 2: 4 week in-patient period
- Period 3: 8 weeks out-patient period
- N in the column headings is the number of patients who received at least one treatment in Period 2 or Period 3.
- Treatment emergent aEs are those with start date between first treatment in Period 2 and last treatment in Period 3 + 1 day.

Adverse Events During Period 2 and 3

MedDRA System Organ Class MedDRA Preferred Term	Placebo (N=xx)	Placebo P2/ RO6889450 45MG QD P3 (N=xx)	Placebo P2/ RO6889450 150MG QD P3 (N=xx)	RO6889450 45MG QD P2/3 (N=xx)	RO6889450 150MG QD P2/3 (N=xx)	Risperidone 4MD QD P2/3 (N=xx)
Total number of patients with at least one adverse event	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Overall total number of events	xx	xx	xx	xx	xx	xx
Gastrointestinal disorders						
Total number of patients with at least one adverse event	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Total number of events	x	x	x	x	x	x
Vomiting	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)
Nausea	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)

...
Investigator text for aEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of""Total number of event"" rows, multiple occurrences of the same AE in an individual are counted separately. Data which has been collected during Follow-up is included.

Notes:

- Follow-up: after last dose of treatment in Period 2 (if the patient did not enter Period 3) or in Period 3 + 28 days.
- N in the column headings is the number of patients who received at least one treatment in Period 2 or Period 3.
- Treatment emergent aEs are those with start date after last treatment in Period 2 (if the patient did not enter Period 3) or in Period 3 until 28 days later.

APPENDIX 8 ABUSE LIABILITY MEDDRA TERMS

Drug abuse and dependence SMQ wide

Drug withdrawal SMQ wide

Plus these additional PTs:

- Euphoric mood
- Elevated mood
- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Thinking abnormal
- Hallucination
- Inappropriate affect
- Somnolence
- Mood disorders and disturbances
- Psychosis
- Aggression
- Confusion
- Disorientation
- Drug Tolerance
- Habituation
- Drug withdrawal syndrome
- Substance related disorders

Based on MedDRA version 24.0

APPENDIX 9 PATIENTS WITH SUICIDAL IDEATION, SUICIDAL BEHAVIOR, AND SELF-INJURIOUS BEHAVIOR WITHOUT SUICIDAL INTENT BASED ON THE C-SSRS DURING TREATMENT

Events during treatment	Drug Name N=xx n (%)	Comparator Name N=xx n (%)
Suicidal Ideation (1-5)	x (%)	x (%)
1) Wish to be dead	x (%)	x (%)
2) Non-specific active suicidal thoughts	x (%)	x (%)
3) Active suicidal ideation with any methods (not plan) without intent to act	x (%)	x (%)
4) Active suicidal ideation with some intent to act, without specific plan	x (%)	x (%)
5) Active suicidal ideation with specific plan and intent	x (%)	x (%)
Suicidal Behavior (6-10)	x (%)	x (%)
6) Preparatory acts or behavior	x (%)	x (%)
7) Aborted attempt	x (%)	x (%)
8) Interrupted attempt	x (%)	x (%)
9) Non-fatal suicide attempt	x (%)	x (%)
10) Completed suicide	x (%)	x (%)
Suicidal Ideation or Behavior (1-10)	x (%)	x (%)
Self-injurious behavior without suicidal intent	x (%)	x (%)

Notes: N = number of enrolled patients with at least one post-baseline C-SSRS assessment. In this table, n and (%) refer to the number and percent of patients who experience the event at least once during treatment. For the composite endpoint of suicidal ideation (1-5), n and (%) refer to the number and percent of patients who experience any one of the five suicidal ideation events at least once during treatment. For the composite endpoint of suicidal behavior (6-10), n and (%) refer to the number and percent of patients who experience any one of the five suicidal behavior events at least once during treatment. For the composite endpoint of suicidal ideation or behavior (1-10), n and (%) refer to the number and percent of patients who experience any one of the ten suicidal ideation or behavior events at least once during treatment.

			Suicidal Ideation					Suicidal Behavior					
Patient	Trt	Visit	1	2	3	4	5	6	7	8	9	10	Self-Inj Beh wo SI
xxxx			Y	Y	Y	N	Y	N	N	N	N	N	N

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

Only patients with suicidal ideation, suicidal behavior, or self-injurious behavior without suicidal intent are displayed. For patients with suicidal ideation, suicidal behavior, or self-injurious behavior without suicidal intent at any time, data from all visits are displayed. Self-Inj Beh wo SI = Self-injurious Behavior without Suicidal Intent.

APPENDIX 10 ASSESSMENT OF SLEEP, MOOD, WELL-BEING AND COGNITIVE FUNCTIONING, AND ASSUMED TREATMENT ASSIGNMENT

Sleep (treatment period)

"How did you sleep last night?"

Mood & Well-being (treatment period)

"How are you feeling today?"

"How is your energy level today?"

Cognitive Functioning (treatment period)

"How is your concentration and memory today?"

Treatment Expectation (baseline visit only)

"Do you expect that the study drug will help you?"

Treatment Expectation (treatment period)

"Do you think the drug is helping you?"

Treatment Expectation (Day 84 ±2)

"Do you think you were taking placebo or study drug?"

Placebo ☐

Study drug ☐

APPENDIX 11 PREMORBID ADJUSTMENT SCALE (PAS)

Appendix: Premorbid Adjustment Scale

Childhood (up through age 11)

1. Sociability and withdrawal

0 Not withdrawn, actively and frequently seeks out social contacts.

1

2 Mild withdrawal, enjoys socialization when involved, occasionally seeks opportunities to socialize.

3

4 Moderately withdrawn, given to daydreaming and excessive fantasy, may passively allow self to be drawn into contact with others but does not seek it.

5

6 Unrelated to others, withdrawn and isolated. Avoids contacts.

2. Peer relationships

0 Many friends, close relationships with several.

1

2 Close relationships with a few friends (one or two), casual friendships with others.

3

4 Deviant friendship patterns: friendly with children younger or older only, or relatives only, or casual relationships only.

5

6 Social isolate, no friends, not even superficial relationships.

3. Scholastic performance

0 Excellent student.

1

2 Good student.

3

(cont on next pages)

4 Fair student.

5

6 Failing all classes.

4. Adaptation to school

0 Good adaptation, enjoys school, no or rare discipline problems, has friends at school, likes most teachers.

1

2 Fair adaptation, occasional discipline problem, not very interested in school, but no truancy, or rare. Has friends in school, but does not often take part in extracurricular activities.

3

4 Poor adaptation, dislikes school, frequent truancy, frequent discipline problem.

5

6 Refuses to have anything to do with school—delinquency or vandalism directed against school.

Adolescence (Early, ages 12–15)

1. Sociability and withdrawal

0 Not withdrawn.

1

2 Mild withdrawal, enjoys socialization when involved, occasionally seeks opportunities to socialize.

3

4 Moderately withdrawn, given to daydreaming and excessive fantasy, may passively allow self to be drawn into contact with others, but does not seek it.

5

6 Unrelated to others, withdrawn and isolated. Avoids contact.

2. Peer relationships

0 Many friends, close relationships with several.

1

2 Close relationships with a few friends (one or two), casual friendships with others.

3

4 Deviant friendship patterns: friendly with children younger or older only, or relatives only, or casual relationships only.

5

6 Social isolate, no friends, not even superficial relationships.

3. Scholastic performance

0 Excellent student.

1

2 Good student.

3

4 Fair student.

5

6 Failing all classes.

4. Adaptation to school

0 Good adaptation, enjoys school, no or rare discipline problems, has friends at school, likes most teachers.

1

2 Fair adaptation, occasional discipline problem, not very interested in school, but no truancy, or rare. Has friends in school, but does not often take part in extracurricular activities.

3

4 Poor adaptation, dislikes school, frequent truancy, frequent discipline problem.

5

6 Refuses to have anything to do with school—delinquency or vandalism directed against school.

5. Social-sexual aspects of life during early adolescence

0 Started dating, showed a "healthy interest" in the opposite sex, may have gone "steady," may include some sexual activity.

1 Attachment and interest in others, may be same-sex attachments, may be a member of a group, interested in the opposite sex, although may not have close, emotional relationship with someone of the opposite sex, "crushes" and flirtations.

2 Consistent deep interest in same-sex attachments with restricted or no interest in the opposite sex.

3 Casual same-sex attachments, with inadequate attempts at relationships with the opposite sex. Casual contacts with both sexes.

4 Casual contacts with the same sex, no interest in the opposite sex.

5 A loner, no or rare contacts with either boys or girls.

6 Antisocial, avoids and avoided by peers. (Differs from above in that an active avoidance of others rather than passive withdrawal is implied.)

Adolescence (Late, ages 16–18)

1. Sociability and withdrawal

0 Not withdrawn.

1

2 Mild withdrawal, enjoys socialization when involved, occasionally seeks opportunities to socialize.

3

4 Moderately withdrawn, given to daydreaming and exces-

sive fantasy, may passively allow self to be drawn into contact with others, but does not seek it.

5

6 Unrelated to others, withdrawn and isolated. Avoids contact.

2. Peer relationships

0 Many friends, close relationships with several.

1

2 Close relationships with a few friends (one or two), casual friendships with others.

3

4 Deviant friendship patterns: friendly with children younger or older only, or relatives only, or casual relationships only.

5

6 Social isolate, no friends, not even superficial relationships.

3. Scholastic performance

0 Excellent student.

1

2 Good student.

3

4 Fair student.

5

6 Failing all classes.

4. Adaptation to school

0 Good adaptation, enjoys school, no or rare discipline problems, has friends at school, likes most teachers.

1

2 Fair adaptation, occasional discipline problem, not very interested in school, but no truancy, or rare. Has friends in school, but does not often take part in extracurricular activities.

3

4 Poor adaptation, dislikes school, frequent truancy, frequent discipline problem.

5

6 Refuses to have anything to do with school—delinquency or vandalism directed against school.

5. Social aspects of sexual life during adolescence and immediately beyond

0 Always showed a "healthy interest" in the opposite sex, dating, has gone "steady," engaged in some sexual activity (not necessarily intercourse).

1 Dated regularly. Had only one friend of the opposite sex with whom the patient went "steady" for a long time. (Includes sexual aspects of a relationship, although not necessarily intercourse; implies a twosome, pairing off into couples, as distinguished from below.)

2 Always mixed closely with boys and girls. (Involves membership in a crowd, interest in and attachment to others, no couples.)

3 Consistent deep interest in same-sex attachments with restricted or no interest in the opposite sex.

4 Casual same-sex attachments with inadequate attempts at adjustment to going out with the opposite sex. Casual contacts with boys and girls.

5 Casual contacts with same sex with lack of interest in opposite sex. Occasional contacts with the opposite sex.

6 No desire to be with boys and girls, never went out with opposite sex.

Adulthood (Age 19 and above)

1. Sociability and withdrawal

0 Not withdrawn, actively and frequently seeks out social contact.

1

2 Mild withdrawal, enjoys socialization when involved, occasionally seeks opportunities to socialize.

3

4 Moderately withdrawn, given to daydreaming and excessive fantasy, may passively allow self to be drawn into contact with others but does not seek it.

5

6 Unrelated to others, withdrawn and isolated. Avoids contacts.

2. Peer relationships

0 Many friends, close relationships with several.

1

2 Close relationships with a few friends (one or two), casual friendships with others.

3

4 Deviant friendship patterns: friendly with children younger or older only, or relatives only, or casual relationships only.

5

6 Social isolate, no friends, not even superficial relationships.

3. Aspects of adult social-sexual life.

a. Married, presently or formerly:

0 Married, only one marriage (or remarried as a result of death

of spouse), living as a unit, adequate sexual relations.

1 Currently married with history of low sexual drive, periods of difficult sexual relations, or extramarital affair.

1 Married, more than one time, currently remarried. Adequate sexual relations during at least one marriage.

2 Married, or divorced and remarried, with chronically inadequate sex life.

2 Married, and apparently permanently separated or divorced without remarriage, but maintained a home in one marriage for at least 3 years.

3 Same as above, but: divorce occurred over 3 years ago, and, while married, maintained a home for less than 3 years.

b. Never married, over 30:

2 Has been engaged one or more times or has had a long-term relationship (at least 2 years) involving heterosexual or homosexual relations, or apparent evidence of a love affair with one person, but unable to achieve a long-term commitment such as marriage.

3 Long-term heterosexual or homosexual relationship lasting over 6 months but less than 2 years. (If stable, long-lasting homosexual relationship, over 2 years, score as "3.")

4 Brief, or short-term dating experiences (heterosexual or homosexual) with one or more partners, but no long-lasting sexual experience with a single partner.

5 Sexual and/or social relationships rare or infrequent.

6 Minimal sexual or social interest in either men or women, isolated.

c. Never married, age 20–29:

0 Has had at least one long-term love affair (minimum of 6 months) or engagement, even though religious or other prohibitions or inhibitions may have prevented actual sexual union. May have lived together.

1 Has dated actively, had several "boyfriends" or "girlfriends," some relationships have lasted a few months, but no long-term relationships. Relationships may have been "serious," but a long-term commitment such as marriage was not understood to be an eventuality.

3 Brief, short-term dating experiences or "affairs" with one or more partners, but no long-lasting sexual experiences with a single partner.

4 Casual sexual or social relationships with persons of either sex with no deep emotional bonds.

5 Sexual and/or social relationships rare or infrequent.

6 Minimal sexual or social interest in either men or women, isolated.

General

1. Education

0 Completed college and/or graduate school, or professional school (Law, for example).

1 Completed high school and some college or vocational training school or business school (such as secretarial or computer programming schools).

2 Completed high school.

3

4 Completed eighth grade.

5

6 Did not get beyond fifth grade.

2. During a period of 3 years up to 6 months before first hospitalization or onset of first episode, patient was employed for pay or functioning in school

0 All the time.

1

2 Half the time.

3

4 Briefly, about 25 percent of the time.

5

6 Never.

3. Within a period of a year up to 6 months before first hospitalization or first episode change in work or school performance occurred

0 Abruptly.

1

2 Within 3 months.

3

4 Within 6 months.

5

6 Imperceptibly, difficult or not possible to determine onset of deterioration.

4. During a period of 3 years up to 6 months before first hospitalization or first episode, frequency of job change, if working, or interruption of school attendance was

0 Same job held, or remained in school.

1

2 Job change or school interruption occurred two to three times.

3

4 Kept the same job more than 8 months but less than a year, or remained continuously in school for the same period.

5

6 Less than 2 weeks at a job or in school.

5. Establishment of independence

0 Successfully established residence away from family home, financially independent of parents.

2 Made unsuccessful attempts to establish independent residence, lives in parents' home, but pays parents room and board, otherwise financially independent.

4 Lives in parents' home, receiving an allowance from parents which patient budgets to pay for entertainment, clothes, etc.

6 Made no attempt to leave home or be financially independent.

6. Global assessment of highest level of functioning achieved in patient's life

0 Fully able to function successfully in and take pleasure from (1) school or job; (2) friends; (3) intimate sexual relationships; (4) church, hobbies, etc. Enjoys life and copes with it well.

2 Able to function well in and enjoys some spheres of life, but has a definite lack of success in at least one area.

4 Minimum success and pleasure in three areas of life.

6 Unable to function in or enjoy any aspect of life.

7. Social-personal adjustment

0 A leader or officer in formally designated groups, clubs, organizations, or athletic teams in senior high school, vocational school, college, or young adulthood. Involved in intimate, close relationship with others.

1 An active and interested participant, but did not play a leading role in groups of friends, clubs, organizations, or athletic teams, but was involved in close relationships with others also.

2 A nominal member, but had no involvement in or commitment to, groups of friends, clubs, organizations, etc. Had close relationships with a few friends.

3 From adolescence through early adulthood had a few casual friends.

4 From adolescence through early adulthood had no real friends, only superficial relationships.

5 From adolescence through early adulthood (i.e., after childhood), quiet, seclusive, preferred to be by self, minimal efforts to maintain any contact at all with others.

6 No desire to be with peers or others. Either asocial or antisocial.

8. Degree of interest in life

0 Keen, ambitious interest in some of the following: home, family, friends, work, sports, art, pets, gardening, social activities, music, and drama.

2 Moderate degree of interest in several activities including social gatherings, sports, music, and opposite sex.

4 Mild interest in a few things such as job, family, quiet social gatherings. The interest is barely sustaining.

6 Withdrawn and indifferent toward life interests of average individual. No deep interests of any sort.

9. Energy level

0 Strong drive, keen, active, alert interest in life. Liked life and had energy enough to enjoy it. Outgoing and adequate in meeting life.

2 Moderately adequate drive, energy, interest, as described above.

4 Moderately inadequate energy level. Tended toward submissive, passive reactions. Showed some potential to face life's problems, but would rather avoid them than expend the necessary energy.

6 Submissive, inadequate, passive reactions. Weak grasp on life, does not go out to meet life's problems, does not participate actively, but passively accepts his lot without having the energy to help self.

APPENDIX 12 CALGARY DEPRESSION SCALE FOR SCHIZOPHRENIA (CDSS)

Calgary Depression Scale for Schizophrenia (CDSS)

Interviewer: Ask the first question as written. Use follow up probes or qualifiers at your discretion. Time frame refers to last two weeks unless stipulated. N.B. The last item, # 9, is based on observations of the entire interview.

I. DEPRESSION: How would you describe your mood over the last two weeks? Do you keep reasonably cheerful or have you been very depressed or low spirited recently? In the last two weeks how often have you (own words) every day? All day?

0. **Absent**
1. **Mild** - Expresses some sadness or discouragement on questioning.
2. **Moderate** - Distinct depressed mood persisting up to half the time over last 2 weeks: present daily.
3. **Severe** - Markedly depressed mood persisting daily over half the time interfering with normal motor and social functioning.

II. HOPELESSNESS: How do you see the future for yourself? Can you see any future? Or has life seemed quite hopeless? Have you given up or does there still seem some reason for trying?

0. **Absent**
1. **Mild** - Has at times felt hopeless over the last 2 weeks but still has some degree of hope for the future.
2. Moderate - Persistent, Moderate sense of hopelessness over the last 2 weeks. Can be persuaded to acknowledge possibility of things being better.
3. **Severe** - Persisting and distressing sense of hopelessness.

III. SELF DEPRECIATION: What is your opinion of your self compared to other people? Do you feel better, not as good, or about the same as others? Do you feel inferior or even worthless?

0. **Absent**
1. **Mild** - Some inferiority; not amounting to feeling of worthlessness.
2. **Moderate** - Subject feels worthless, but less than 50% of the time.
3. **Severe** - Subject feels worthless more than 50% of the time. May be challenged to acknowledge otherwise.

IV. GUILTY IDEAS OF REFERENCE: Do you have the feeling that you are being blamed for something or even wrongly accused? What about? (Do not include justifiable blame or accusation. Exclude delusions of guilt.)

0. **Absent**
1. **Mild** - Subject feels blamed but not accused less than 50% of the time.
2. **Moderate** - Persisting sense of being blamed, and/or occasional sense of being accused.
3. **Severe** - Persistent sense of being accused. When challenged, acknowledges that it is not so.

V. PATHOLOGICAL GUILT: Do you tend to blame yourself for little things you may have done in the past? Do you think that you deserve to be so concerned about this?

0. **Absent**
1. **Mild** - Subject sometimes feels over guilty about some minor peccadillo, but less than 50% of time.
2. **Moderate** - Subject usually (over 50% of time) feels guilty about past actions the significance of which s/he exaggerates.
3. **Severe** - Subject usually feels s/he is to blame for everything that has gone wrong, even when not his/her fault.

VI. MORNING DEPRESSION: When you have felt depressed over the last 2 weeks have you noticed the depression being worse at any particular time of day?

0. **Absent** - No depression.
1. **Mild** - Depression present but no diurnal variation.
2. **Moderate** - Depression spontaneously mentioned to be worse in a.m.
3. **Severe** - Depression markedly worse in a.m., with impaired functioning which improves in p.m.

VII. EARLY WAKENING: Do you wake earlier in the morning than is normal for you? How many times a week does this happen?

0. **Absent** - No early wakening.
1. **Mild** - Occasionally wakes (up to twice weekly) 1 hour or more before normal time to wake or alarm time.
2. **Moderate** - Often wakes early (up to 5 times weekly) 1 hour or more before normal time to wake or alarm.
3. **Severe** - Daily wakes 1 hour or more before normal time.

VIII. SUICIDE: Have you felt that life wasn't worth living? Did you ever feel like ending it all? What did you think you might do? Did you actually try?

0. **Absent**
1. **Mild** - Frequent thoughts of being better off dead, or occasional thoughts of suicide.
2. **Moderate** - Deliberately considered suicide with a plan, but made no attempt.
3. **Severe** - Suicidal attempt apparently designed to end in death (i.e.: accidental discovery or inefficient means).

IX. OBSERVED DEPRESSION: Based on interviewer's observations during the entire interview. The question "Do you feel like crying?" used at appropriate points in the interview, may elicit information useful to this observation.

0. **Absent**
1. **Mild** - Subject appears sad and mournful even during parts of the interview, involving affectively neutral discussion.
2. **Moderate** - Subject appears sad and mournful throughout the interview, with gloomy monotonous voice and is tearful or close to tears at times.
3. **Severe** - Subject chokes on distressing topics, frequently sighs deeply and cries openly, or is persistently in a state of frozen misery if examiner is sure that this is present.

APPENDIX 13 THE ABBREVIATED VERSION OF THE SCALE TO ASSESS UNAWARENESS IN MENTAL DISORDER IN SCHIZOPHRENIA (SUMD-9)

1. Awareness of mental disorder: In the most general terms, does the subject believe that he or she has a mental disorder?

2. Awareness of the consequences of mental disorder: What is the subject's belief regarding the reason(s) he or she has been unemployed, evicted, hospitalized, etc.?

3. Awareness of the effects of drugs: Does the subject believe that medications have diminished the severity of his or her symptoms (if applicable) ?

4. Awareness of hallucinatory experiences: Does the subject believe that he or she experiences hallucinations as such? Rate his or her ability to interpret this experience as primarily hallucinatory.

5. Awareness of delusional ideas: Does the subject believe that he or she experiences delusions as such, that is, as internally produced erroneous beliefs ? Rate his or her awareness of the implausibility of the belief if applicable.

6. Awareness of disorganized thoughts: Does the subject believe that his or her communications are disorganized?

7. Awareness of blunted affect: >Rate the subject's awareness of his or her affect as communicated by his or her expressions, voice, gestures, etc. Do not rate his or her evaluation of his or her mood.

8. Awareness of anhedonia: Is the subject aware that his or her behaviour reflects an apparent decrease in experiencing pleasure while participating in activities normally associated with such feelings?

9. Awareness of lack of sociality: Is the subject aware that he or she shows no interest in social relationships?

APPENDIX 14 VAGUS SELF-REPORT VERSION (VAGUS-SR)

	Yes	No
A) Have you ever had visions or seen things that others can't see?	☐	☐
B) Have you ever feared that someone, some force or entity was after you or out to hurt you?	☐	☐
C) Have you ever received special messages just for you from the newspaper, TV, radio, or other device?	☐	☐
D) Have you ever received special messages just for you from strangers on the street?	☐	☐
E) Have you ever had any special gifts or abilities?	☐	☐
F) Could you ever read minds?	☐	☐
G) Have you ever felt that others could read your thoughts?	☐	☐
H) Have you ever felt that your thoughts were broadcast for others to hear?	☐	☐
I) Have you ever had a special relationship with God beyond the average person?	☐	☐
J) Have you ever communicated with spiritual beings, such as angels or demons?	☐	☐
K) Have you ever communicated with aliens?	☐	☐
L) Have you ever felt excessively guilty? Or that you had done something very bad?	☐	☐
M) Have you ever felt that your thoughts or actions were controlled by some outside force?	☐	☐
N) Have you ever felt that you were possessed?	☐	☐
O) Have you ever had the sense that something had changed about your body?	☐	☐
P) Have you ever felt that your body or some part of your body was diseased or dying?	☐	☐
Q) Other: _____	☐	☐

Choose the most intense unusual or unique experience from above.

Write the corresponding letter here _____.

Indicate the extent to which you agree or disagree at the present moment with each of the following statements by circling the appropriate number, keeping in mind your most intense experience.

1) My unusual or unique experiences are due to my mental illness.

0----------1----------2----------3----------4----------5----------6----------7----------8----------9----------10

Strongly Disagree | Moderately Disagree | Slightly Disagree | Unsure | Slightly Agree | Moderately Agree | Strongly Agree

2) My unusual or unique experiences are REAL regardless of what other people think about them. (e.g. doctors, family, friends, etc.)

0----------1----------2----------3----------4----------5----------6----------7----------8----------9----------10

Strongly Disagree | Moderately Disagree | Slightly Disagree | Unsure | Slightly Agree | Moderately Agree | Strongly Agree

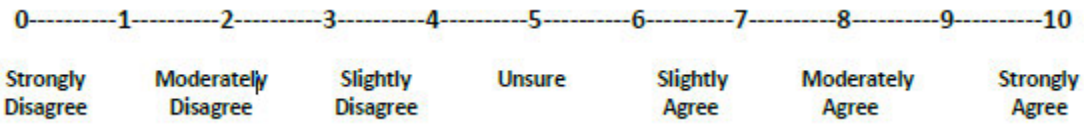
Indicate if you have ever had the following unusual or unique experience by reading the question and marking ☒ either Yes or No.

	Yes	No
Have you ever heard voices or sounds that others can't hear?	☐	☐

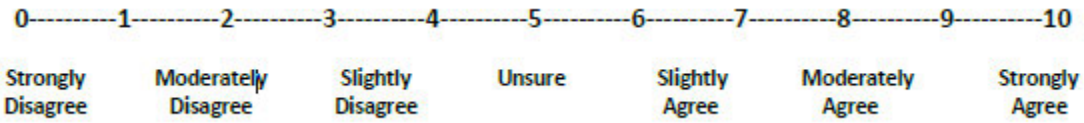
If 'NO,' please go to the next page.

If 'YES' to the above indicate the extent to which you agree or disagree at the present moment with each of the following statements by circling the appropriate number.

3) The voices other people can't hear are REAL regardless of what my doctor, family or friends believe.



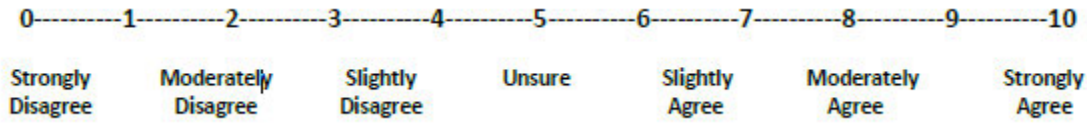
4) My mental illness has caused me to hear voices that other people cannot hear.



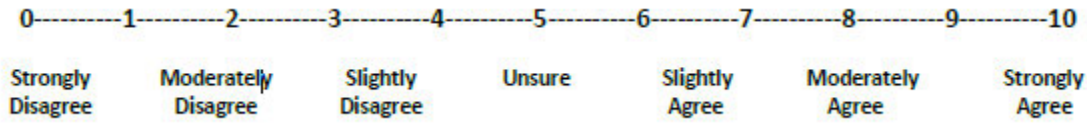
PLEASE GO TO THE NEXT PAGE

Please indicate the extent to which you agree or disagree at the present moment with each of the following statements by circling the appropriate number.

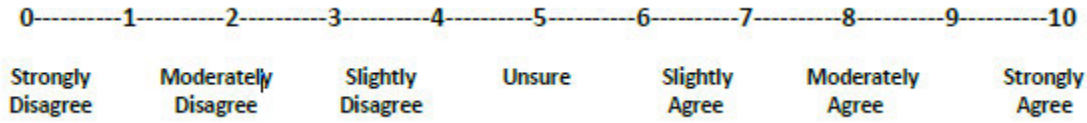
5) I truly believe I have a mental disorder/illness (e.g. Schizophrenia, Schizoaffective Disorder, Bipolar Disorder, Depression with Psychosis, etc.).



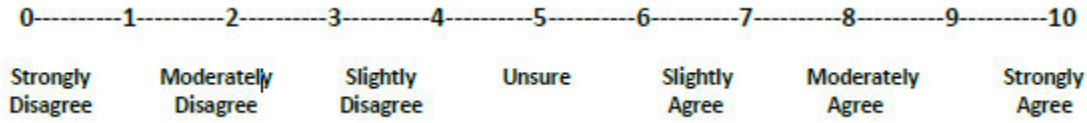
6) I definitely NEED treatment with an antipsychotic medication.



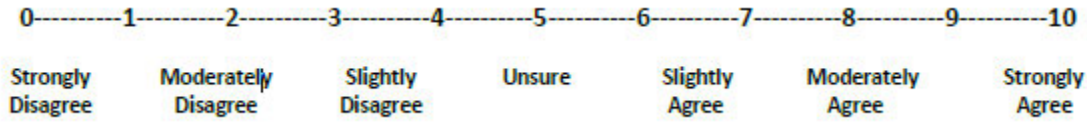
7) I have always been mentally healthy.



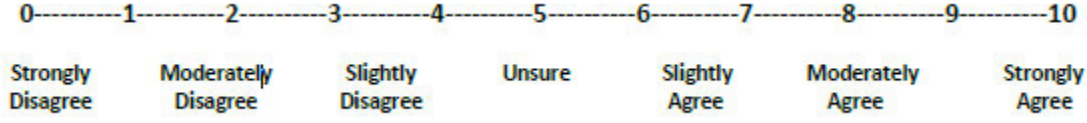
8) I should stop or avoid taking antipsychotic medication.



9) My unusual or unique experiences have led to negative consequences in my life (e.g. hospitalization, work, family or social problems).



10) Antipsychotic medications have lessened the intensity of my unusual or unique experiences.
☐ Not Applicable as I have never taken antipsychotic medication before.



APPENDIX 15 VAGUS-SR SCORING SHEET

Awareness Category	Calculation	Score [1]
Illness Awareness	Q5___ + (10 – Q7___) ÷ total # of responses___	
Symptom Attribution	Q1___ + (10 - Q2___) + (10 - Q3___) + Q4___ ÷ total # of responses___ * *Exclude questions indicated as N/A	
Awareness of Need for Treatment	Q6___ + (10 – Q8___) + Q10___ ÷ total # of responses___ * *Exclude questions indicated as N/A	
Awareness of Negative Consequences	Q9___	
	Subtotal (sum of scores)	
VAGUS-SR Total Score	Subtotal ÷ 4 [2]	

[1] The score for each Awareness Category should be left blank if NO items were completed for that category.

[2] The Total Score calculation should be the Subtotal ÷ 4 or the number of Awareness Categories for which a score could be calculated.

APPENDIX 16 VAGUS CLINICIAN RATED VERSION (VAGUS-CR)

Read the initial statement (italics) to the participant or patient and then ask the following questions in order to gather information to complete the related VAGUS-CR Insight Scale.

*"I am interested in your own understanding of your unusual or unique experiences **at the present moment**. I am **NOT** interested in what others may wish you to believe about your experiences."*

Describe your unusual or unique experiences. For example,

		Yes	No
A)	Have you ever heard voices or sounds that others can't hear?	☐	☐
B)	Have you ever had visions or seen things that others can't see?	☐	☐
C)	Have you ever feared that someone, some force or entity was after you or out to get you or hurt you?	☐	☐
D)	Have you ever received special messages just for you from the TV, radio, newspaper or any other device?	☐	☐
E)	Have you ever received special messages just for you from strangers on the street?	☐	☐
F)	Have you ever had any special gifts or abilities?	☐	☐
G)	Could you ever read minds?	☐	☐
H)	Have you ever felt that others could read your thoughts or that your thoughts were broadcast for others to hear?	☐	☐
I)	Have you ever had a special relationship with God beyond the average person?	☐	☐
J)	Have you ever communicated with spiritual beings, such as angels or demons or aliens?	☐	☐
K)	Have you ever felt excessively guilty or that you had done something very bad?	☐	☐
L)	Have you ever felt that some outside force controlled your thoughts or actions?	☐	☐
M)	Have you ever felt that you were possessed?	☐	☐
N)	Have you ever felt that your body or some part of your body was diseased, rotting, or dying?	☐	☐
O)	Other: _____	☐	☐

2) How do you explain your unusual or unique experiences? At the present moment, what do you believe the cause is for these experiences?

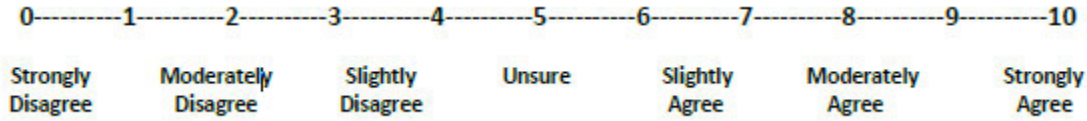
3) Do you currently believe you have a mental illness or a psychiatric disorder, such as Schizophrenia, Bipolar Disorder or Depression with psychosis, etc.? Please elaborate.

4) Do you think your unusual or unique experiences require treatment? Do you NEED antipsychotic medication? Please elaborate.

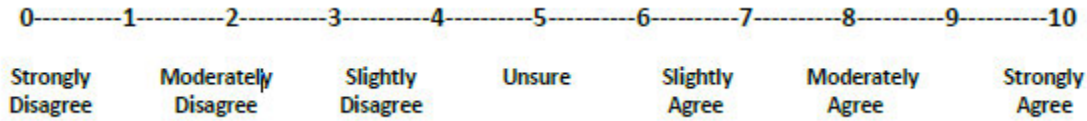
5) Have you experienced any negative consequences as a result of your unusual or unique experiences?
Or as a result of your emotional or psychiatric problems? (e.g. hospitalization, occupational or social dysfunction).

Please indicate the extent to which you agree or disagree at the present moment with each of the following statements regarding the participant or patient you are rating below. Circle the appropriate number for each statement. Base your answers on the structured interview.

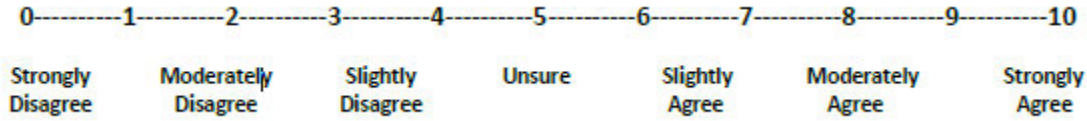
1) The subject believes he/she has a mental disorder/illness (e.g. Schizophrenia, Schizoaffective Disorder, Bipolar Disorder, Depression with Psychosis, etc.).



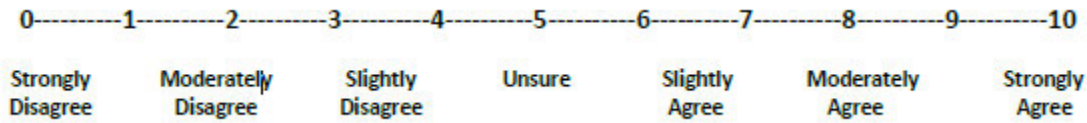
2) The subject is aware the auditory hallucinations (past or present) are due to his/her mental illness.
□ Not applicable as the participant has never had auditory hallucinations.



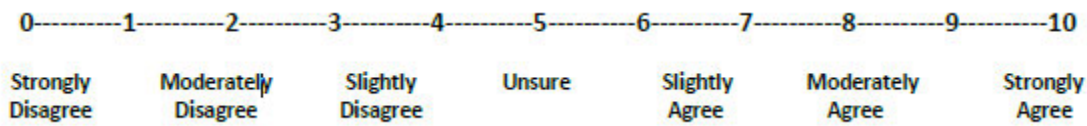
3) The subject is aware that the delusions (past or present) are due to his/her mental illness.



4) The subject believes that he/she should discontinue or avoid taking an antipsychotic medication.



5) The subject believes that his/her mental illness has led to negative consequences in his/her life (e.g. hospitalization, work, family or social dysfunction).



APPENDIX 17 VAGUS-CR SCORING SHEET

Awareness Category	Calculation	Score [1]
Illness Awareness	Q1___	
Symptom Attribution	Q2___ + Q3___ ÷ total # of responses___ * *Exclude questions indicated as N/A	
Need for Treatment Awareness	10 – Q4___	
Awareness of Negative Consequences	Q5___	
	Subtotal (sum of scores)	
VAGUS-CR Total Score [2]	Subtotal ÷ ____	

[1] The score for each Awareness Category should be left blank if NO items were completed for that category.

[2] The Total Score calculation should be the Subtotal ÷ 4 or the number of Awareness Categories for which a score could be calculated.

APPENDIX 18 BECK COGNITIVE INSIGHT SCALE (BCIS)

				BCIS
Instructions: Below is a list of sentences about how people think and feel. Please read each sentence in the list carefully. Indicate how much you agree with each statement by placing an **X** in the corresponding space in the column next to each statement.				
	Do Not Agree at All	Agree Slightly	Agree a Lot	Agree Completely
1. At times, I have misunderstood other people's attitudes towards me.				
2. My interpretations of my experiences are definitely right.				
3. Other people can understand the cause of my unusual experiences better than I can.				
4. I have jumped to conclusions too fast.				
5. Some of my experiences that have seemed very real may have been due to my imagination.				
6. Some of the ideas I was certain were true turned out to be false.				
7. If something feels right, it means that it is right.				
8. Even though I feel strongly that I am right, I could be wrong.				
9. I know better than anyone else what my problems are.				
10. When people disagree with me, they are generally wrong.				
11. I cannot trust other people's opinion about my experiences.				
12. If somebody points out that my beliefs are wrong, I am willing to consider it.				
13. I can trust my own judgment at all times.				
14. There is often more than one possible explanation for why people act the way they do.				
15. My unusual experiences may be due to my being extremely upset or stressed.				

Scoring & Interpretation of the Beck Cognitive Insight Scale (BCIS)

The BCIS is comprised of two subscales: self-**reflectiveness** and **self-certainty**. The total score for each scale is the sum of the item scores that comprise it (see below). **The BCIS composite index** is calculated as self-reflectiveness minus self-certainty. Poorer cognitive insight is indexed by lower scores on the self-reflectiveness subscale, higher self-certainty scores, and lower BCIS composite index scores.

Step 1. Score every item on the BCIS from “0” to “3” according to the following rule:

- “Do Not Agree at All” = 0
- “Agree Slightly” = 1
- “Agree a Lot” = 2
- “Agree Completely” = 3

Step 2. Calculate self-reflectiveness subscale: sum items 1, 3, 4, 5, 6, 8, 12, 14, and 15.

Step 3. Calculate self-certainty subscale: sum items 2, 7, 9, 10, 11, and 13.

Step 4. Calculate BCIS composite index: self-reflectiveness minus self-certainty.

APPENDIX 19 EMA

Roche PB41743 Questions and Answers

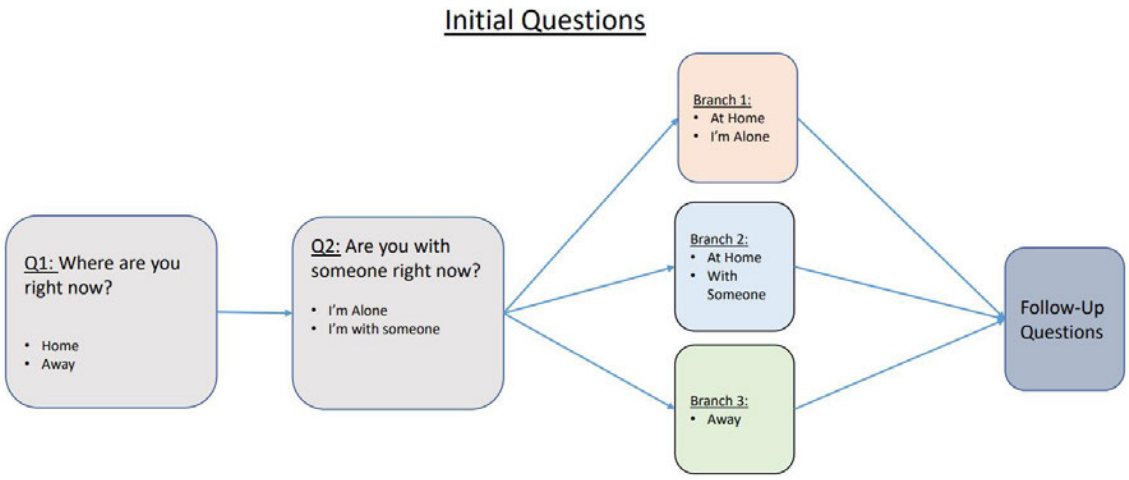
Overview:

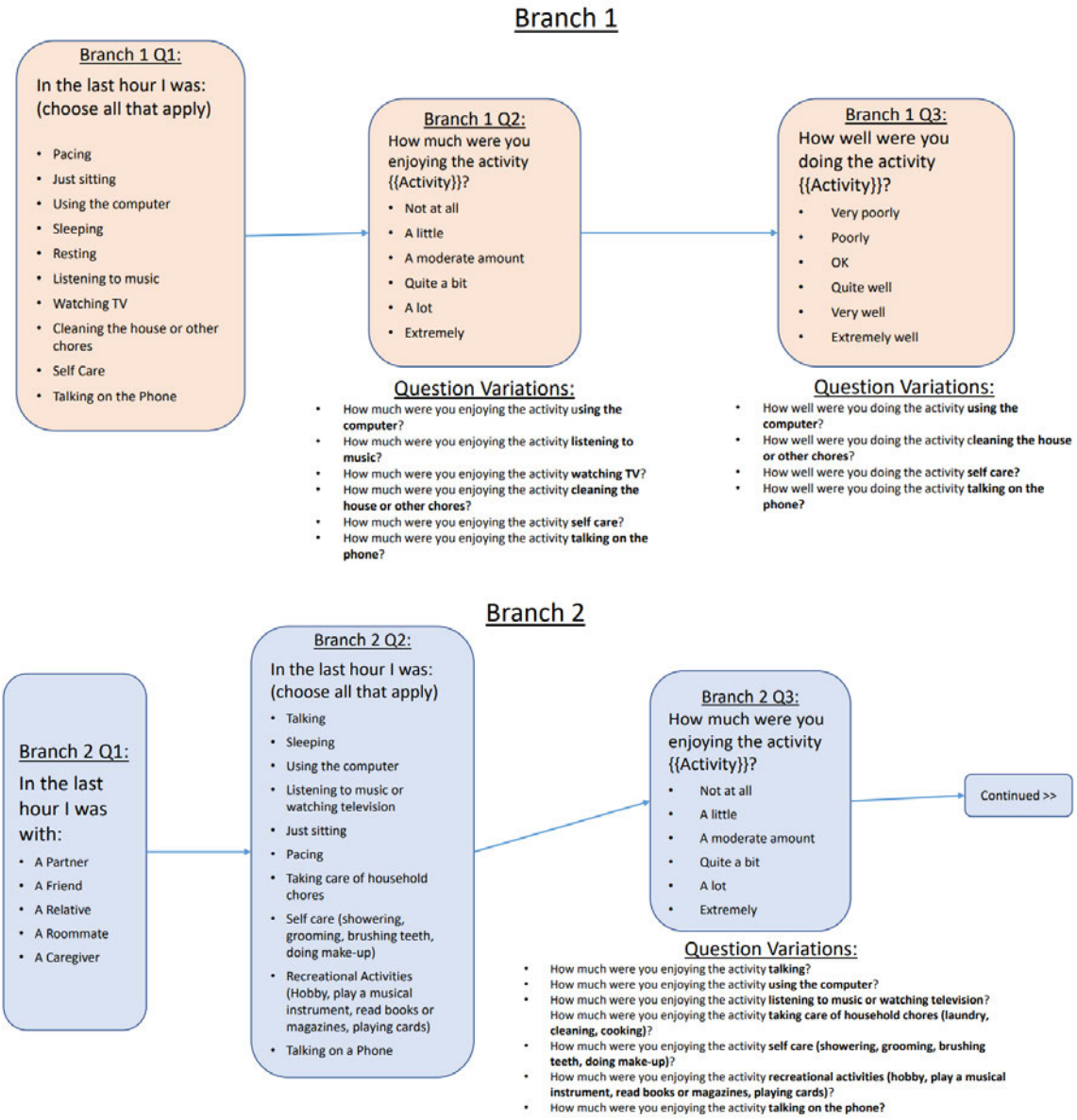
• The questions utilize branching logic based upon the first two questions. There are three possible branches based upon the first two questions:

- Branch 1: Home Alone
- Branch 2: Home with Someone
- Branch 3: Away

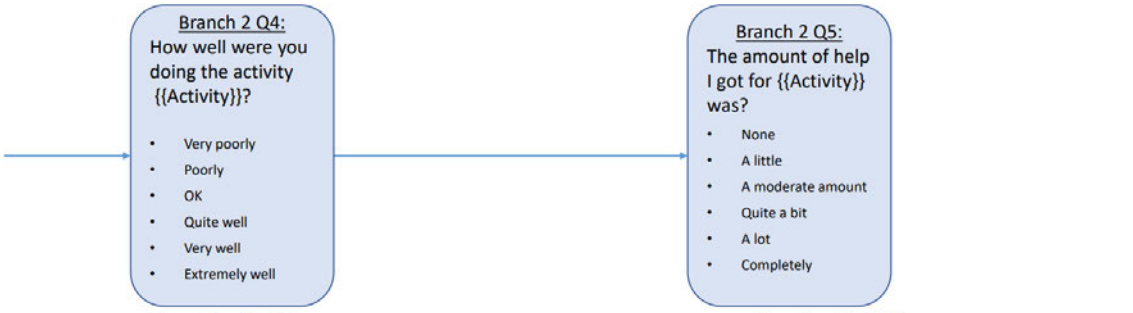
• Within each branch there are certain questions that have multiple variations based upon the answers selected in a previous question. For example, within Branch 1, the Questions for 2 and 3 are dependent on the answers selected in Question 1. For each answer selected for Question 1, Question 2 and 3 will be repeated with the activity selected in Question 1 being substituted for {{Activity}} in Question 2 and 3. So if a subject selects “Just Sitting” and “Pacing” for Question 1, Questions 2 and 3 will be asked twice, once for the activity “Just Sitting” and once for the activity “Pacing”.

• When a subject completes all the questions for a branch they will be asked the three Follow-Up Questions.




Branch 1
Branch 1 Q1:
In the last hour I was: (choose all that apply)
Pacing
Just sitting
Using the computer
Sleeping
Resting
Listening to music
Watching TV
Cleaning the house or other chores
Self Care
Talking on the Phone
Branch 1 Q2:
How much were you enjoying the activity {{Activity}}?
Not at all
A little
A moderate amount
Quite a bit
A lot
Extremely
Question Variations:
How much were you enjoying the activity using the computer?
How much were you enjoying the activity listening to music?
How much were you enjoying the activity watching TV?
How much were you enjoying the activity cleaning the house or other chores?
How much were you enjoying the activity self care?
How much were you enjoying the activity talking on the phone?
Branch 1 Q3:
How well were you doing the activity {{Activity}}?
Very poorly
Poorly
OK
Quite well
Very well
Extremely well
Question Variations:
How well were you doing the activity using the computer?
How well were you doing the activity cleaning the house or other chores?
How well were you doing the activity self care?
How well were you doing the activity talking on the phone?
Branch 2
Branch 2 Q1:
In the last hour I was with:
A Partner
A Friend
A Relative
A Roommate
A Caregiver
Branch 2 Q2:
In the last hour I was: (choose all that apply)
Talking
Sleeping
Using the computer
Listening to music or watching television
Just sitting
Pacing
Taking care of household chores
Self care (showering, grooming, brushing teeth, doing make-up)
Recreational Activities (Hobby, play a musical instrument, read books or magazines, playing cards)
Talking on a Phone
Branch 2 Q3:
How much were you enjoying the activity {{Activity}}?
Not at all
A little
A moderate amount
Quite a bit
A lot
Extremely
Continued >>
Question Variations:
How much were you enjoying the activity talking?
How much were you enjoying the activity using the computer?
How much were you enjoying the activity listening to music or watching television?
How much were you enjoying the activity taking care of household chores (laundry, cleaning, cooking)?
How much were you enjoying the activity self care (showering, grooming, brushing teeth, doing make-up)?
How much were you enjoying the activity recreational activities (hobby, play a musical instrument, read books or magazines, playing cards)?
How much were you enjoying the activity talking on the phone?

Branch 2 Continued



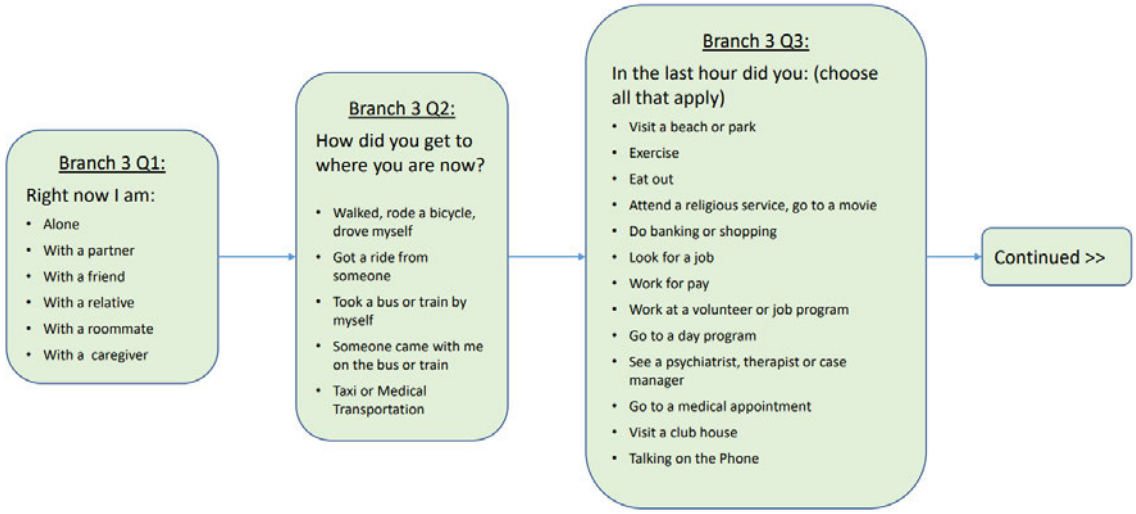
Question Variations:

- How well were you doing the activity **using the computer**?
- How well were you doing the activity **taking care of household chores (laundry, cleaning, cooking)**?
- How well were you doing the activity **self care (showering, grooming, brushing teeth, doing make-up)**?
- How well were you doing the activity **recreational activities (hobby, play a musical instrument, read books or magazines, playing cards)**?
- How well were you doing the activity **talking on the phone**?

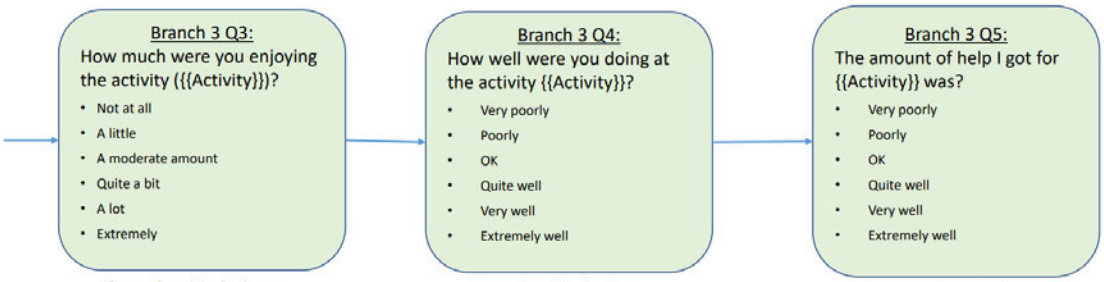
Question Variations:

- The amount of help I got for **using the computer** was?
- The amount of help I got for **listening to music or watching television** was?
- The amount of help I got for **taking care of household chores (laundry, cleaning, cooking)** was?
- The amount of help I got for **self care (showering, grooming, brushing teeth, doing make-up)** was?
- The amount of help I got for **recreational activities (hobby, play a musical instrument, read books or magazines, playing cards)** was?
- The amount of help I got for **talking on the phone** was?

Branch 3



Branch 3 (Continued)



Question Variations:

- How much were you enjoying the activity **visit a beach or park**?
- How much were you enjoying the activity **exercise**?
- How much were you enjoying the activity **eating out**?
- How much were you enjoying the activity **attend a religious service, go to a movie**?
- How much were you enjoying the activity **do banking or shopping**?
- How much were you enjoying the activity **look for a job**?
- How much were you enjoying the activity **work for pay**?
- How much were you enjoying the activity **work at a volunteer or job program**?
- How much were you enjoying the activity **go to a day program**?
- How much were you enjoying the activity **see a psychiatrist, therapist or case manager**?
- How much were you enjoying the activity **go to a medical appointment**?
- How much were you enjoying the activity **visit a club house**?
- How much were you enjoying the activity **talking on the phone**?

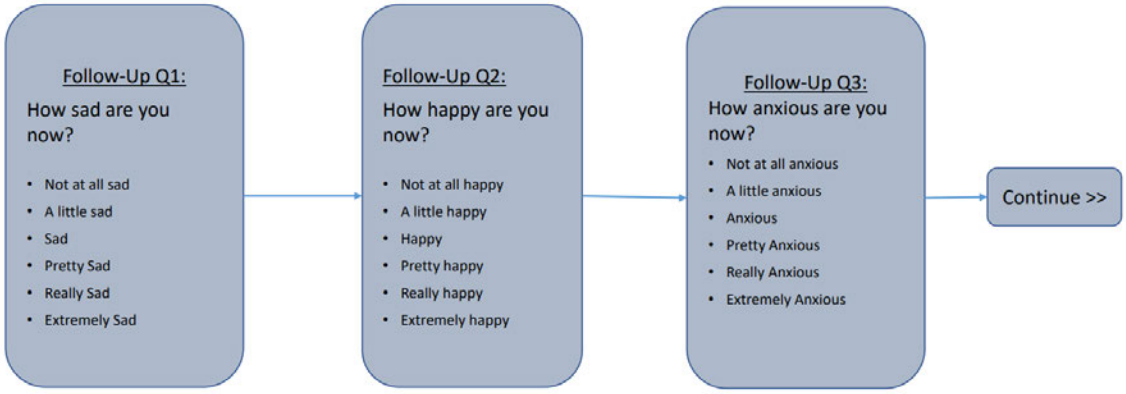
Question Variations:

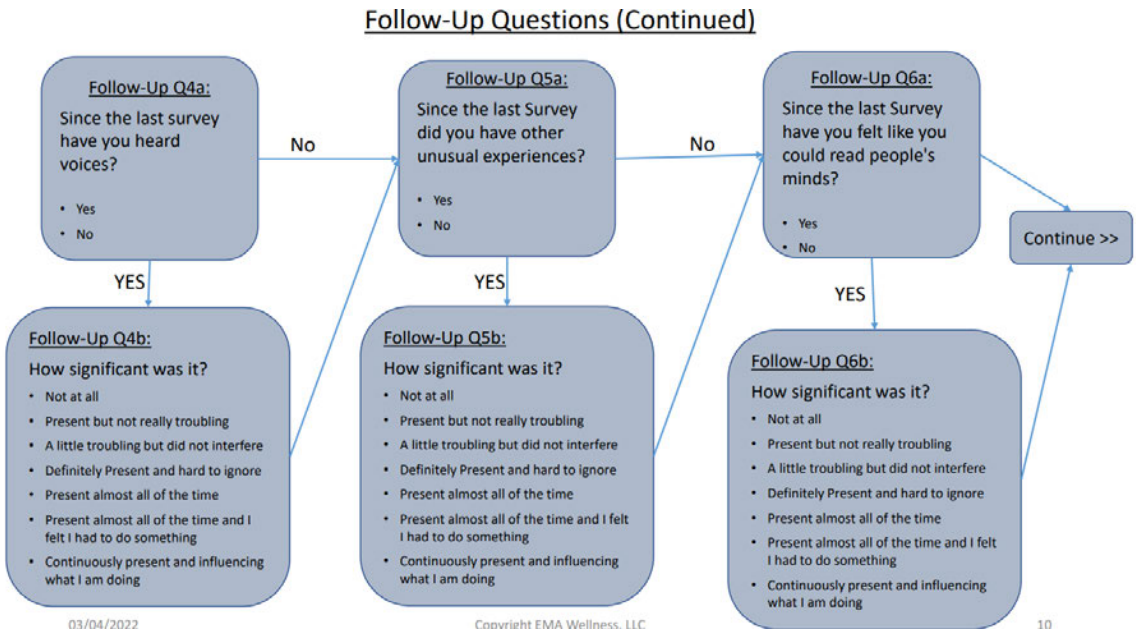
- How well were you doing the activity **visit a beach or park**?
- How well were you doing the activity **exercise**?
- How well were you doing the activity **do banking or shopping**?
- How well were you doing the activity **look for a job**?
- How well were you doing the activity **work for pay**?
- How well were you doing the activity **work at a volunteer or job program**)?
- How well were you doing the activity **talking on phone**?

Question Variations:

- The amount of help I got for **visiting a beach or park** was?
- The amount of help I got for **exercise** was?
- The amount of help I got for **eating out** was?
- The amount of help I got for **attending a religious service, or going to a movie** was?
- The amount of help I got for **doing banking or shopping** was?
- The amount of help I got for **looking for a job** is ?
- The amount of help I got for **working for pay** was?
- The amount of help I got for **working at a volunteer or job program** was?
- The amount of help I got for **going to a day program** was?
- The amount of help I got for **seeing a psychiatrist, therapist or case manager** was?
- The amount of help I got for **going to a medical appointment** was?
- The amount of help I got for **visiting a club house** was?
- The amount of help I got for **talking on phone** was?

Follow-Up Questions




Follow-Up Questions (Continued)
Follow-Up Q4a:
Since the last survey have you heard voices?
• Yes
• No
No
Follow-Up Q5a:
Since the last Survey did you have other unusual experiences?
• Yes
• No
No
Follow-Up Q6a:
Since the last Survey have you felt like you could read people's minds?
• Yes
• No
Continue >>
YES
Follow-Up Q4b:
How significant was it?
• Not at all
• Present but not really troubling
• A little troubling but did not interfere
• Definitely Present and hard to ignore
• Present almost all of the time
• Present almost all of the time and I felt I had to do something
• Continuously present and influencing what I am doing
YES
Follow-Up Q5b:
How significant was it?
• Not at all
• Present but not really troubling
• A little troubling but did not interfere
• Definitely Present and hard to ignore
• Present almost all of the time
• Present almost all of the time and I felt I had to do something
• Continuously present and influencing what I am doing
YES
Follow-Up Q6b:
How significant was it?
• Not at all
• Present but not really troubling
• A little troubling but did not interfere
• Definitely Present and hard to ignore
• Present almost all of the time
• Present almost all of the time and I felt I had to do something
• Continuously present and influencing what I am doing
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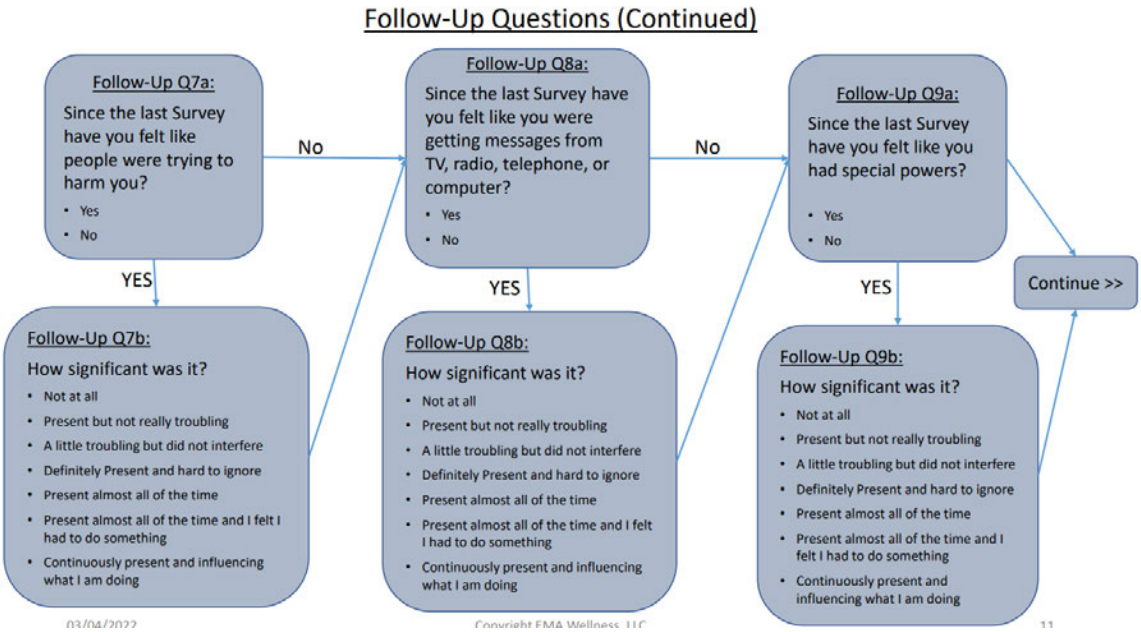
Follow-Up Questions (Continued)
Follow-Up Q7a:
Since the last Survey have you felt like people were trying to harm you?
• Yes
• No
No
Follow-Up Q8a:
Since the last Survey have you felt like you were getting messages from TV, radio, telephone, or computer?
• Yes
• No
No
Follow-Up Q9a:
Since the last Survey have you felt like you had special powers?
• Yes
• No
Continue >>
YES
Follow-Up Q7b:
How significant was it?
• Not at all
• Present but not really troubling
• A little troubling but did not interfere
• Definitely Present and hard to ignore
• Present almost all of the time
• Present almost all of the time and I felt I had to do something
• Continuously present and influencing what I am doing
YES
Follow-Up Q8b:
How significant was it?
• Not at all
• Present but not really troubling
• A little troubling but did not interfere
• Definitely Present and hard to ignore
• Present almost all of the time
• Present almost all of the time and I felt I had to do something
• Continuously present and influencing what I am doing
YES
Follow-Up Q9b:
How significant was it?
• Not at all
• Present but not really troubling
• A little troubling but did not interfere
• Definitely Present and hard to ignore
• Present almost all of the time
• Present almost all of the time and I felt I had to do something
• Continuously present and influencing what I am doing
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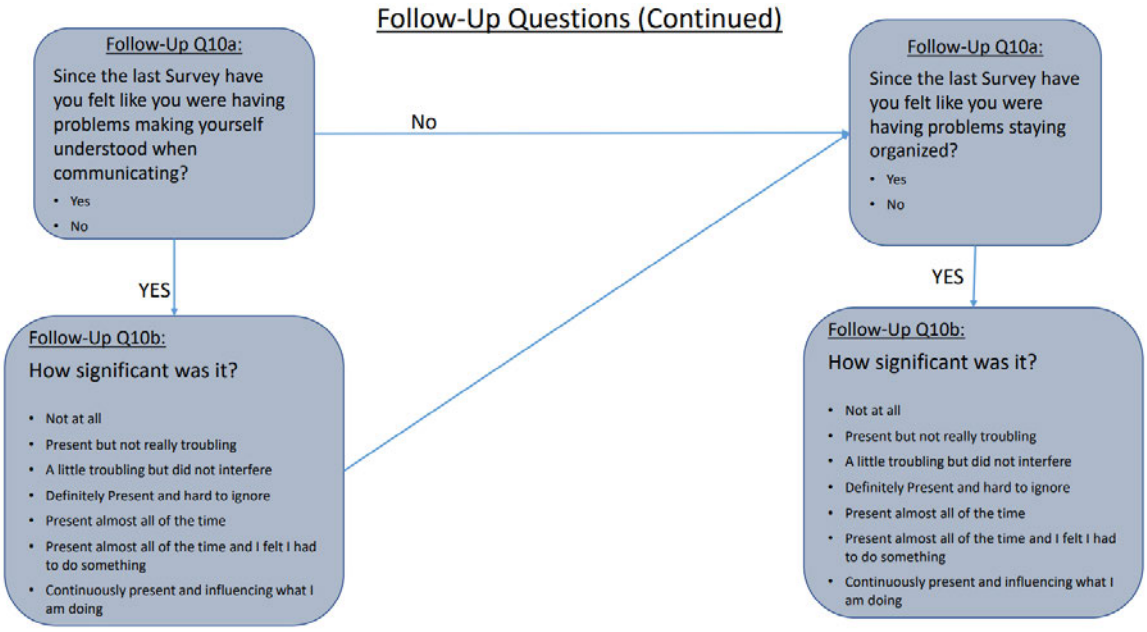
Follow-Up Questions (Continued)
Follow-Up Q10a:
Since the last Survey have you felt like you were having problems making yourself understood when communicating?
• Yes
• No
No
Follow-Up Q10a:
Since the last Survey have you felt like you were having problems staying organized?
• Yes
• No
YES
YES
Follow-Up Q10b:
How significant was it?
• Not at all
• Present but not really troubling
• A little troubling but did not interfere
• Definitely Present and hard to ignore
• Present almost all of the time
• Present almost all of the time and I felt I had to do something
• Continuously present and influencing what I am doing
Follow-Up Q10b:
How significant was it?
• Not at all
• Present but not really troubling
• A little troubling but did not interfere
• Definitely Present and hard to ignore
• Present almost all of the time
• Present almost all of the time and I felt I had to do something
• Continuously present and influencing what I am doing

APPENDIX 20 PANSS IC NEGATIVE QUESTIONS SCORING

N2. Emotional Withdrawal

Lack of interest in, involvement with, and affective commitment to life's events.

Did the patient seem emotionally distant, withdrawn, or uninterested in activities and events in the past 7 days? (1)

- ◯ YES
- ◯ NO

To what degree did the patient appear withdrawn or uninterested in life events and activities?

- (1) ◯ Lacks initiative and occasionally shows lack of interest in surrounding events
- (2) ◯ Usually emotionally distanced from surroundings and events but can be engaged with encouragement
- (3) ◯ Clearly detached emotionally from persons and events and resists attempts to engage; can be involved in communication briefly; tends to personal needs alone or with minimal assistance
- (4) ◯ Severe lack of interest and emotional commitment; engages in limited conversation; frequently neglects personal needs or requires supervision to complete them
- (5) ◯ Patient is almost totally withdrawn, uncommunicative; neglects personal needs

N4. Passive/Apathetic Social Withdrawal

Diminished social involvement due to apathy, indifference, or lack of interest.

Has the patient shown little interest in socializing with others due to passivity, apathy, lack of energy and/or lack of motivation in the past 7 days? (1)

- ◯ YES
- ◯ NO

In the past 7 days, to what degree did the patient display a lack of interest in social activities or activities of daily living?

- (1) ◯ Usually engages with others only when approached first by them or when prompted; shows occasional interest in social activities
- (2) ◯ Attends most activities in a disinterested or mechanical way; recedes to the background
- (3) ◯ Spends little time with others, passively participates in a few activities but shows no interest or initiative
- (4) ◯ Apathetic and isolates from others, occasionally neglects personal needs and has very few social contacts
- (5) ◯ Extremely apathetic, isolated, and does not tend to personal needs