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: Protocol Version 5: 06-Oct-2021

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**
PROTOCOL NUMBER:	BP41743
VERSION:	5
EUDRACT NUMBER:	2019-003788-23
IND NUMBER:	[redacted]
TEST PRODUCT:	RO6889450
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 20 October 2019
DATE AMENDED:	Version 2: 16 April 2020 Version 3: 17 September 2020 Version 4: 3 June 2021 Version 5: See electronic date stamp below

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
06-Oct-2021 09:58:03	Company Signatory	[redacted]

PROTOCOL ACCEPTANCE FORM

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**
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SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please keep the signed original form in your study files, and return a copy to your local Site Monitor.

PROTOCOL AMENDMENT, VERSION 5
RATIONALE

Protocol BP41743 has been amended to allow:

- enrollment of participants without prior approval by the Medical Monitor/Sponsor;
- safety monitoring of vasculitis during 36-Week Safety Extension Phase.

Changes to the protocol, along with a rationale for each change:

- The schedule of the activities (SoA) without 36-Week Safety Extension Phase (Table 1 in Section 1.3) has been amended to replace Eligibility Assessment Form by Eligibility Checklist Form (ECF) to remove the approval of eligibility by Medical Monitor. The SoA for the 36-Week Safety Extension Phase has been updated to include the Samples for vasculitis monitoring (Table 2 in Section 1.3).
- Footnotes for SoA Table 1 and Table 2 have been updated as follows:
    - Footnote “e” has been amended to inform that the Erythrocyte sedimentation rate (ESR) samples will be processed locally.
    - Footnote “h” has been amended to provide clarity on the timing of the PK sampling during the 36-Week Safety Extension Phase.
    - Footnotes “v”, “x”, “aa”, and “bb" have been updated to allow the following being used in the exceptional situation beyond COVID-19 pandemic: assessments being performed remotely (Footnote “v”), study visit being split over 2 days (Footnote “x”), study drug being shipped directly from site to patient (Footnote “aa”), and the Home HealthCare system (Footnote “bb”). It has been also added that the Home HealthCare system will not be used in Japan as the services are not provided by the selected vendor in Japan (Footnote “bb”).
    - Footnote “gg” has been added to provide information on the tests that are to be performed as part of the vasculitis monitoring.
- Section 2.3 (Benefit/Risk Assessment) has been amended to add a statement to clarify the impact of the COVID-19 pandemic on the benefit/risk assessment of this study protocol.
- Section 3 (Objectives and Endpoints) Table 3 has been amended to add clarification on the time points of the secondary analysis planned and that both PANSS total and factor scores changes from baseline will be assessed up to week 12.
- Section 5.1 (Inclusion Criteria) has been amended to
    - remove the possibility to enroll subjects with the duration of exacerbation at screening longer than 8 weeks (Inclusion criterion 5);
    - remove the possibility to enroll subjects with hospitalization duration at screening longer than 7 days, except for in exceptional situations (e.g., delay due to the administrative procedures) where the maximum may be

10 days prior to screening (prior discussion with the Medical Monitor is recommended) (Inclusion criterion 6);

- add Inclusion criterion E for the 36-Week Safety Extension Phase specifying the requirement for no clinically significant abnormality in laboratory assessments performed for evaluation of the confirmed or suspected presence of vasculitis.

- Section 5.2 (Exclusion Criteria) has been amended to:
  - limit the hospitalization duration for current exacerbation of schizophrenia to 1 week at screening visit or in exceptional situations (e.g., delay due to the administrative procedures) to 10 days (Exclusion criterion 1);
  - remove Medical Monitor approval requirement for the decision made for the laboratory results at screening (Exclusion criterion 12);
  - remove Medical Monitor approval requirement for the use of low doses of clozapine (< 200 mg/day) to treat insomnia or dyskinesia more than 12 months prior to screening visit. Further clarification has been provided that any use of clozapine (any dose regimen/ any indication) is prohibited within 12 months prior to screening visit (Exclusion criterion 17).
  - remove the possibility to enroll subjects with regular use of cannabis (including cannabidiol) meeting criteria for substance use disorder for cannabis in case of positive urine drug screen (only sporadic use of cannabis is allowed) (Exclusion criterion 19).
- Section 5.5 (Screen Failures) has been amended to remove Sponsor/Medical Monitor approval requirement for the decision on subject re-screening. Potential re-screenings should be discussed with the Medical Monitor/delegate.
- Section 6.4 (Treatment Compliance) has been amended to allow the use of direct site-to-patient drug delivery in the exceptional situation beyond COVID-19 pandemic upon Sponsor/Medical Monitor approval. Further clarification has been added that compliance below 80% on a weekly basis should be brought to the Sponsor's attention.
- Section 7.1 (Discontinuation of study treatment) has been amended to add the condition indicating confirmed presence of vasculitis as requirement for discontinuation of the participant entering the 36-Week Safety Extension Phase from the study treatment. In addition, the participant may be discontinued if vasculitis is suspected.
- Section 8 (Study Assessments and Procedures) has been amended to allow the use of remote assessments and use of the Home HealthCare system in the exceptional situation beyond COVID-19 pandemic upon Sponsor/Medical Monitor approval. It has been also added that the Home HealthCare system will not be used in Japan as the services are not provided by the selected vendor in Japan.
- Section 8.2.1 (Physical Examination) has been amended to add that the Investigators should pay special attention to clinical signs of rash, myalgia, arthritis,

and fever, and report those as adverse events (AEs) as part of the evaluation of a confirmed or suspected presence of vasculitis.

- Section 8.2.4 (Clinical Safety Laboratory Assessments) has been amended to provide the details on tests for vasculitis monitoring.
- Section 8.2.7 (Psychiatric/Medical History and Demographic Data) has been amended to:
    - remove Medical Monitor/Sponsor approval requirement for eligibility during screening.
    - replace the Eligibility Assessment Form with the ECF.
    - require completion and submission to the Clinical Research Organization (CRO) electronic Protocol Inquiry Platform (ePIP) system of the ECF during screening for documentation and monitoring purposes.
- Section 8.7 (Pharmacodynamics and Biomarker Samples) has been amended to add the requirement for mandatory blood sample collection for the assessment of suspected vasculitis.
- Section 8.10.1 (Screening and Pre-treatment Assessments) has been amended to remove the requirement of Eligibility Assessment Form submission and Medical Monitor/Sponsor approval prior to randomization. Instead, an ECF should be completed and submitted to the CRO ePIP system during screening as per guidance provided in the protocol for documentation and monitoring purposes.
- Section 8.10.2 (Assessment during Treatment) has been amended to provide clarification of the order of assessments.
- Section 9.2 (Sample size determination) has been amended to allow an increase of a number of randomized participants in case of an unexpectedly high proportion of participants not completing initial 4 weeks of treatment (i.e., more than 25%).
- Section 9.4.2 (Efficacy Analyses) Table 7 has been amended to clarify that both total and factor PANSS score changes from baseline will be assessed.
- Section 9.4.3 (Safety Analyses) Table 8 has been amended to clarify that tabular summaries will be used to present clinical laboratory test results.
- Appendix 4:
    - has been amended to provide information on which tests for vasculitis monitoring are to be performed locally.
    - Table 1 (Laboratory Assessments) has been amended to include a list of tests to be performed for vasculitis monitoring
- Appendix 6 Table 1 has been amended to
    - remove Medical Monitor approval requirement for the use of single doses of aripiprazole, brexpiprazole, and blonanserin administered to control current exacerbation.
    - Add clarification that the indicated washout periods are relative to the first dose of study drug.

    - Add clarification that all antipsychotics are prohibited during Study Periods 2 and 3, and the 36-Week Safety Extension Phase.
- Appendix 6 Table 3 has been amended to
    - remove Medical Monitor/Sponsor approval requirement for continuation of previous treatment for extrapyramidal symptoms 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.

Additional minor changes have been made to improve clarity and consistency. Substantial new information appears in *Book Antiqua italics*. This amendment represents cumulative changes to the original protocol.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	*Anti-nuclear antibodies*
ANCA	*Anti-neutrophil cytoplasmic antibodies*
anti-dsDNA	*Anti-double-stranded DNA*
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BCIS	Beck Cognitive Insight Scale
BP	Blood pressure
CDSS	Calgary Depression Scale for Schizophrenia
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression Severity
C_{max}	Maximum concentration
CNS	Central nervous system
COA	Clinical outcome assessments
COVID-19	Corona virus pandemic: the name designation refers to COVI for the acronym of coronavirus, D for the word disease, and 19 for the year of the outbreak
CRO	*Clinical Research Organization*
CRP	*C-reactive protein*
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common terminology criteria for adverse events
CTM	*Clinical Team Manager*
CYP	Cytochrome
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECF	*Eligibility Checklist Form*
ECG	Electrocardiogram
ECT	Electroconvulsive therapy
eCOA	Electronic clinical outcome assessment
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	Ecological Momentary Assessment
ePIP	*Electronic Protocol Inquiry Platform*

Abbreviation	Definition
EPS	Extrapyramidal symptoms
ESR	*Erythrocyte sedimentation rate*
ESRS-A	Extrapyramidal symptom rating scale, abbreviated
EOT	End of Treatment
ETV	Early Termination Visit
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
FTND	Fagerström Test for Nicotine Dependence
GPCR	G protein coupled receptor
HBsAg	Hepatitis B surface antigen
HBcAb	Total hepatitis B core antibody
HCV	Hepatitis C virus
HDL	High-density lipoproteins
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IND	Investigational New Drug (application)
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive response technology
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LDH	Lactate dehydrogenase
LDL	Low-density lipoproteins
LPLV	Last participant, last visit
MAD	Multiple-ascending dose
MTS	Most troubling symptoms
MTD	Maximum tolerated dose
NGS	Next generation sequencing
NSAESI	Non-serious adverse event of special interest
OTC	Over-the-counter
PANSS	Positive and Negative Syndrome Scale
PAS	Premorbid Adjustment Scale
PD	Pharmacodynamic

Abbreviation	Definition
PK	Pharmacokinetic
PRO	Patient-reported outcome
POT	Postural orthostatic tachycardia
QD	Once daily
QRS	QRS complex
QT	QT interval
QTc	QT corrected for heart rate
QTcF	QT corrected for heart rate using the Fridericia's correction factor
RBC	Red blood cell
RBR	Research biosample repository
RDQ	Readiness for Discharge Questionnaire
RNA	Ribonucleic acid
ROW	Rest of the world
RR	RR interval
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SoA	Schedule of activities
SOP	Standard operating procedure
SUMD	Scale to Assess Unawareness of Mental Disorder
SUSAR	Suspected unexpected serious adverse reactions
TAAR	Trace amine-associated receptor
TAAR1	Trace amine-associated receptor 1
ULN	Upper limit of normal
US	United States
WASI-II	Wechsler Abbreviated Scale of Intelligence – Second Edition
WRAT-4	Wide Range Achievement Test
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of non-childbearing potential

1. PROTOCOL SUMMARY

1.1 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:	5
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 *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 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 *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 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 week 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 ≤ 10 years.
5. Have a *current* 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.
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. *In exceptional situations (e.g., delay due to the administrative procedures), hospitalization up to a maximum of 10 days prior to screening is permitted (prior* discussion with the Medical Monitor *is recommended).*
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. Screening and baseline PANSS *with scores* 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:

    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 *contraception*.

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. *Successful* 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 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.

E. No history of confirmed or suspected vasculitis and/or no clinically significant abnormality in laboratory assessments taken for evaluation of the possible presence of vasculitis (i.e., C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], anti-neutrophil cytoplasmic antibodies [ANCA], anti-nuclear antibodies [ANA], anti-double-stranded DNA [anti-dsDNA] antibodies, and anti-phospholipid antibodies).

Exclusion Criteria

General exclusions

1. Has been inpatient for > 1 week *(or in exceptional situations [e.g., delay due to the administrative procedures] > 10 days)* or *had* 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.
2. Disease duration longer than 10 years.
3. Is currently an inpatient on an involuntary basis.
4. *The C-SSRS* "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) *answered* "Yes" or any *"Yes" answers to "*Suicidal Behavior*"* within one month from Screening or between Screening and Baseline (i.e., since last visit). *In addition, any Investigator judgment of* significant risk of suicide or harming *themselves* or others.
5. Lifetime history of homicidal behavior.
6. Moderate to severe substance use disorder within six months (excluding nicotine) as defined by DSM-5.
7. Other current DSM-5 diagnosis (e.g., bipolar disorder, major depressive disorder).

Medical conditions

8. 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).
9. Positive result at screening for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), or human immunodeficiency virus (HIV)-1 or -2. Participants *with positive anti-hepatitis C antibody* who have been successfully treated and test negative for HCV RNA *are* eligible for study entry.
10. Tardive dyskinesia that is moderate to severe or requires treatment.
11. History of neuroleptic malignant syndrome.
12. Clinically significant abnormalities in laboratory safety test results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis), including:
    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.
    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, not clinically significant.

13. 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

14. 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®.
15. Participant treated with a long-acting injectable antipsychotic (LAI) or other antipsychotics that cannot be washed-out *within* the *allotted* screening period *(*see list of specific medications in Section 6.5*)*.
16. History of electroconvulsive therapy (ECT) *for any reason*.
17. Participant treated with clozapine *at any dose in the* 12 months *preceding the* screening visit or participants treated with clozapine at > 200 mg/day at any time. *Note:* low dose (< 200mg/day) use for insomnia or dyskinesia *longer than* 12 months prior to screening visit *is* permitted.
18. Participant currently receiving a psychotropic or other medication used as a psychotropic, which cannot be discontinued during the screening period.
19. 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 *only in case of a* sporadic use of cannabis. *Regular consumption meeting the criteria for cannabis use disorder (mild, moderate, or severe) is not permitted*.
20. 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

21. Participant has previously received RO6889450.
22. 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*, depending on the anti-psychotic 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 72 hours prior to the first dose of study medication *and* 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 72 hours prior to the first dose of study medication and 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 deaconate. 2 months • haloperidol deacanoate. 2 months • olanzapine LAI. 2 months	Permitted as prior medication if *it* had been stopped before the indicated *time* period*s* prior to *the first dose of study medication. Prohibited during Study Periods 2 and 3 and the 36-Week Safety Extension Phase (blinded treatment).* Note: Single doses (before reaching steady state) of aripiprazole, brexpiprazole*, or* blonanserin administered to control current exacerbation *may be used (upon discussion with the Medical Monitor) but not within 72 hours prior to the first dose of study medication* upon 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 *time* periods prior to *the first dose of study medication*. Participants excluded if there is a history of lack of response or intolerance to risperidone or paliperidone. *Prohibited during Study Periods 2 and 3 and the 36-Week Safety Extension Phase (blinded treatment).*
• clozapine	Excluded any use in previous 12 months before screening, *or* 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 hallucinogens	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. Clinically relevant substrates of P-gp, including quinidine and loperamide	From enrollment until the end of the treatment period. From enrollment until the end of the treatment period.

Restricted Therapy

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

Restricted Therapies

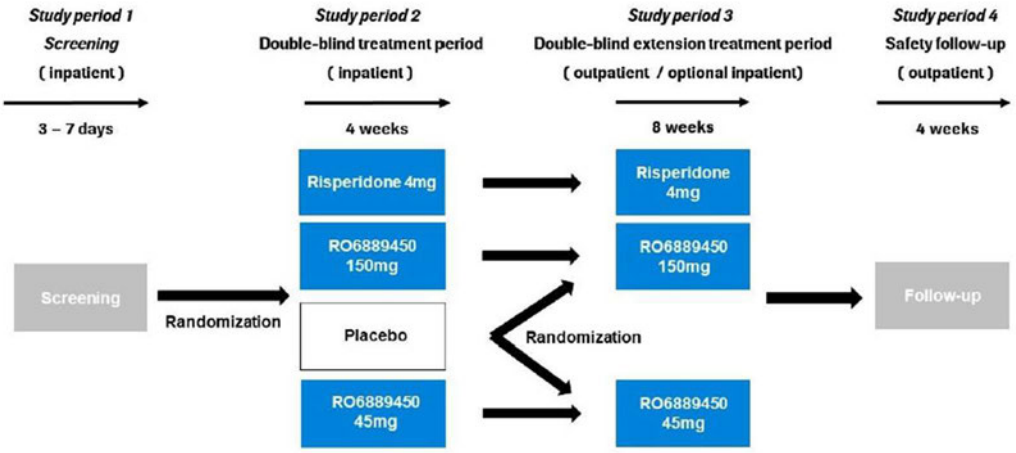
Type of medication	Timelines and instructions
Medication for extrapyramidal symptoms (EPS) • benztropine: up to 4 mg/day (up to 2 mg single dose), • or biperiden up to 6 mg/day (up to 2 mg single dose), • or trihexyphenidyl up to 6 mg/day (up to 3 mg single dose) • *propranolol* (up to 60 mg/day)	Initiation 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.
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.

1.2 SCHEMATIC OF STUDY DESIGN

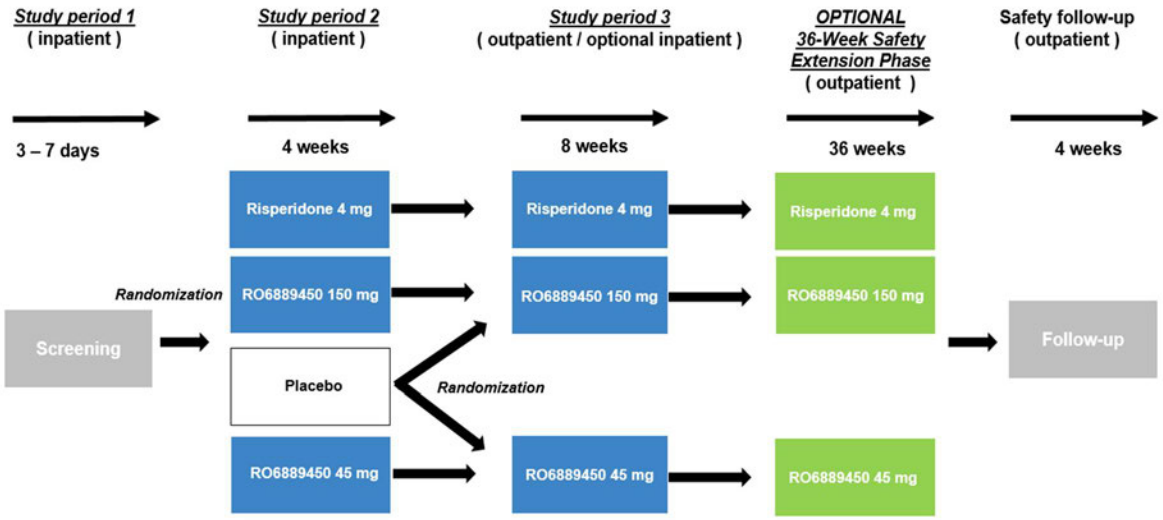
An overview of the study design is provided in Figure 1.

Figure 1 Overview of Study Design

A. Without 36-Week Safety Extension Phase



B. With Optional 36-Week Safety Extension Phase



1.3 SCHEDULE OF ACTIVITIES

The schedule of the activities *(SoA)* is provided in Table 1 *(without the 36-week safety extension phase)* and *Table 2 (for the 36-week safety extension phase)*.

Table 1 Schedule of Activities without 36-Week *Safety* Extension 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 *Checklist* 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

	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
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
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

	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
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	
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

Table 2 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 Test[g bb]		X	X	X	
PK samples[h,bb]		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**
Plasma[i,bb]		X	X	X	
Safety Samples (plasma and serum)[bb,ff]	X	X	X	X	
Samples for vasculitis monitoring [bb,gg]	*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
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, gg]		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 *discussion with the* Medical Monitor 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 7.1 and 8.10.3).

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, COVID-19 test (when not performed centrally), *and erythrocyte sedimentation rate (ESR)*, will be performed by a central laboratory. Microscopic urinalysis if deemed necessary to be performed centrally (see Appendix 4).

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*, 24, 36, and 48* 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 8.6.1). 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 4.1.1).

l Done by centralized raters.

m IMP dispensing (see Section 6).

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 8.10.4).

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 *or Study Period 3 and 36-Week Safety Extension Phase*, 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 *subsequent to the Period 2 EOT visit* are not *possible (*due to, e.g., local COVID-19 restrictions *or emergency situations*), this assessment can be performed remotely if *approved* by the Sponsor. The scope of the assessment remains the same. Source documentation should detail if the assessment has been performed remotely.

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

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

x In exceptional situations (i.e., *local* COVID-19 *restrictions or emergency situations*), 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 *possible (*due to, e.g., local COVID-19 restrictions *or emergency situations)* 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 participant's source file.

bb If the post Period 2 EOT visit study assessments and procedures cannot be administered because the visit cannot take place (due to, e.g., *local* COVID-19 *restrictions or emergency situations*), the Home HealthCare System can be used *if approved by Sponsor. The Home HealthCare System will not be used in Japan.* 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.

gg Samples for vasculitis monitoring (i.e., C-reactive protein [CRP] (Note: CRP is analyzed as part of the chemistry panel), erythrocyte sedimentation rate [ESR], anti-neutrophil cytoplasmic antibodies [ANCA], anti-nuclear antibodies [ANA], anti-double-stranded DNA [anti-dsDNA] antibodies, anti-phospholipid antibodies) will be taken as indicated and in case of an AE or physical examination finding that is assessed as suspected vasculitis (see Section 8.2.1).

2. INTRODUCTION

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.

2.1 STUDY RATIONALE

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 (Koblan et al 2020). 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 (Correll et al 2020).

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.

The rationale for the study design is provided in Section 4.2.

2.2 BACKGROUND

2.2.1 Background on Schizophrenia

Schizophrenia is a major chronic psychiatric disorder with a lifetime prevalence of 1% in the general population. It starts in late adolescence and early adulthood and typically progresses throughout the life of the patient with a course of exacerbations and remissions. Usually, there is functional deterioration after each psychotic exacerbation leading to a poor outcome in up to 70% of patients consisting of unemployment, homelessness, and poverty and a consequent disintegration of their social network. Besides chronic deterioration in their social functioning, patients with schizophrenia have several co-morbidities, including severe medical conditions; metabolic syndrome, attributable at least partly to side-effects of currently available antipsychotic medications; increased suicidal risk; and significant rates of substance abuse (Sadock and Sadock 2007, Meyer and Stahl 2009, Wobrock and Soyka 2009). Symptoms and signs of schizophrenia are clustered into three major domains: positive symptoms (e.g., psychotic symptoms like delusions or hallucinations), negative symptoms (e.g., blunted affect, amotivation/apathy), and cognitive deficits (e.g., executive dysfunction, poor verbal memory), with frequent occurrences of co-morbid depressive symptoms.

Antipsychotic treatment of schizophrenia mainly targets the symptoms found during acute exacerbations, including acute positive symptoms. These drugs act as antagonists at the dopaminergic D_2 receptor, as well as acting on other receptors such as the serotonergic (e.g., 5-HT_{2A}), cholinergic (e.g., muscarinic M_1), and histaminergic (e.g., H_1) receptors (Kim et al 2009). These include first-generation drugs such as phenothiazines and butyrophenones, which, despite having great potency as antipsychotics, are associated with frequent and severe extrapyramidal symptoms (EPS), such as Parkinsonism, acute dystonia and akathisia. Second- generation (atypical) antipsychotics (SGAs) are currently the mainstay of therapy and include drugs such olanzapine, quetiapine, risperidone, and aripiprazole, and in case of treatment resistance, clozapine. These latter compounds are associated with less severe EPS, but are associated with metabolic syndrome (dyslipidemia, insulin resistance, weight gain, elevations in blood pressure [BP]), which can unfavorably alter the benefit-risk ratio (Meyer and Stahl 2009; Kim et al 2009; Gründer et al 2009; Thomas et al 2009). Metabolic syndrome and obesity are estimated to occur in 33% of patients with particular SGAs, such as olanzapine, clozapine, risperidone, and quetiapine. There is an obvious need for new therapies that may effectively treat psychotic symptoms with improved safety and tolerability profiles compared to current medicines.

Current atypical antipsychotics are efficacious in the treatment of positive symptoms, but have minimal effects on the negative and cognitive symptoms. Thus, there is also a need for treatments of these symptom domains in schizophrenia (Sanger 2004; Stip et al 2005).

Schizophrenia is believed to be caused by a combination of genetic and environmental factors that impact early neurodevelopmental processes, and include abnormalities of neuronal structure and function in targeted sub-cortical and cortical circuits. Underlying the symptomatic phenomena are disturbances in monoaminergic and glutamatergic neurotransmission (e.g., dopamine, serotonin, noradrenaline, and glutamate). These pathways are widely present in the central nervous system (CNS) and are potentially capable of influencing many areas involved in emotional processing, cognition, and behavior (Belmaker and Agam 2008; Racagni and Popoli 2008; Sen and Sanacora 2008). Until recently, the excess dopamine hypothesis was the major pathophysiological theory of psychosis, based largely on the effectiveness of D_2 antagonists. Currently, dysfunctions in other neurotransmitters, such as glutamate, are known to exist and are being explored as new therapeutic targets (Moghaddam and Javitt 2012).

2.2.2 Background on RO6889450

Trace amines (phenylethylamine, p- and m-tyramine, p- and m-octopamine, and tryptamine) are present throughout the CNS in close proximity to monoaminergic pathways although they are expressed at much lower endogenous levels than monoaminergic neurotransmitters (Berry 2004; Burchett and Hicks 2006). Trace amines act as neuromodulators at physiological levels. In this capacity, their main role appears to be the modulation of serotonergic, dopaminergic, and glutamatergic synaptic transmission. Recently, a family of GPCRs has been identified and named trace amine-associated receptor (TAAR), with TAAR1 being the best characterized of these receptors and the main target for endogenous trace amines (Burchett and Hicks 2006; Lindemann and Hoener, 2005; Zucchi et al 2006). Abnormalities in trace amine physiology have long been associated with schizophrenia. Furthermore, the TAAR genes map closely to one of the major genetic susceptibility loci for schizophrenia, SCZD5 (Burchett and Hicks 2006; Berry 2007). Hence, specific drugs targeting this novel neuromodulatory system may have clinical applications in the treatment of schizophrenia (Berry 2007; Branchek et al 2003).

RO6889450 is a selective partial agonist for TAAR1 being developed for the treatment of schizophrenia. RO6889450 has been extensively tested in nonclinical models predictive of antipsychotic, stress-response modulating, anti-addictive, and glucose-regulating activities, indicating therapeutic potential.

RO6889450 is not an inhibitor or an inducer of the major human cytochrome (CYP) enzymes, but is a substrate for human CYP3A4, CYP2C19, and flavin-containing monooxygenase. RO6889450 is directly sulfo-conjugated by sulfotransferases. The potential for interaction with other drugs that inhibit or induce these metabolizing enzymes is unlikely due to mixed elimination and metabolic pathways. The relative contribution of CYP3A4 and CYP2C19 is estimated to be 10% each based on recent in vitro work (Report 1095250). Results from an ongoing Phase I study (JP40960) showed no relevant difference in exposure between different genotypes of CYP2C19.

A Phase 1 single ascending dose (SAD) and multiple-ascending dose (MAD) study (BP30134) was conducted in 82 healthy volunteers to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of single doses of RO6889450 at 5, 15, 50, 100, 200, 300, or 450 mg (or placebo) and multiple doses of RO6889450 at 15, 50, 150, 300, or 450 mg once daily for 2 weeks.

Pharmacokinetics of RO6889450 were well characterized after single and multiple doses and support once daily (QD) dosing in the subsequent studies. Steady-state plasma concentration was achieved after 5 to 6 days of dosing.

No clinically significant or relevant abnormalities, including dose-related trends were observed in electrocardiograms (ECGs), ambulatory BP measurements, and laboratory safety parameters (blood chemistry, hematology, urinalysis) for either single or multiple dose administrations. Two Dose-Limiting Events (DLE) occurred in the 450 mg multiple dose cohort: one event of generalized exanthema resulting in treatment discontinuation and one patient experiencing several episodes of postural orthostatic tachycardia (POT; increased pulse rate $\geq$ 30 bpm without hypotension). Both subjects had received active treatment. There were no serious adverse events (SAEs) or severe adverse events (AEs) reported. The most common AE observed was headache. POT was observed in most subjects including those receiving placebo; however, there was a trend towards higher pulse rates at the highest dose levels (450 mg single dose and multiple doses) and this POT was never associated with orthostatic hypotension.

Given its positive metabolic profile, RO6889450 may provide benefits for the general medical condition of patients with schizophrenia having metabolic syndrome co-morbidities. A detailed description of the chemistry, pharmacology, and safety of RO6889450 is provided in the RO6889450 Investigator's Brochure (IB).

2.3 BENEFIT/RISK ASSESSMENT

RO6889450 has the potential to improve both positive and negative symptoms of schizophrenia. In healthy volunteers, RO6889450 was well tolerated when administered as a multiple dose up to 300 mg for 14 days. No clinically significant or relevant abnormalities, including dose-related trends, were observed in ECGs, ambulatory BP measurements, or laboratory safety parameters in either single or multiple dose administrations up to the maximum tolerated dose (MTD) of 300 mg. In this study, the doses tested will be 150 mg QD, i.e., half of the MTD defined in the MAD study (BP30134) and 45 mg QD.

The unmet medical need for effective treatment of both positive and negative symptoms in patients with schizophrenia with an improved safety profile is immense. Given the potential of RO6889450 to significantly improve symptoms in schizophrenia, the observed safety/tolerability profile in healthy volunteers and the measures implemented

to ensure the patient's safety, the overall benefit/risk assessment for clinical trial participation is considered favorable.

An assessment was conducted to determine whether there is any impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit/risk assessment of this study protocol including, but not limited to, the patient population under study and study treatment being evaluated. On the basis of that assessment, no impact is anticipated and the existing safety monitoring and management guidelines, and risk mitigation measures provided in the study protocol are considered adequate.

At the time of writing, there was no evidence to suggest any interaction between RO6889450 and SARS-CoV-2 vaccines. When required, SARS-CoV-2 vaccines may be administered at any time during the study. SARS-CoV-2 vaccines should be given in accordance with the approved vaccine label. Any vaccine should be documented in the electronic case report form (eCRF) as a concomitant medication.

More detailed information about the known and expected benefits in the context of potential risks and reasonably expected AEs of RO6889450 is provided in the RO6889450 Investigator's Brochure.

3. OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints are provided in Table 3.

Table 3 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.
• 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).

Table 3 Objectives and Endpoints (cont.)

Objectives	Endpoints
• 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.
• 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]).

Table 3 Objectives and Endpoints (cont.)

Objectives	Endpoints
• 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)
• 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

4. STUDY DESIGN

4.1 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. An overview of the study design is provided in Section 1.2.

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 week if required according to the clinical judgment of the Investigator. If the participant must remain in the hospital beyond the first week 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).

4.1.1 Length of the 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 (If the participant must remain in the hospital beyond the first week of Study Period 3 according to the clinical judgment of the Investigator, the Investigator will need to obtain approval from the Sponsor. For Asia region, Sponsor approval is not required).
- 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 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.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study rationale is provided in Section 2.1.

4.2.1 Rationale for Study Population and Study Duration

The primary objective of the study is to test the efficacy of RO6889450 for the treatment of acute exacerbation of schizophrenia or schizoaffective disorder; therefore participants in this study will be patients diagnosed with schizophrenia or schizoaffective disorder who are experiencing an acute exacerbation as determined by their clinical history, current clinical assessment, and confirmed by a minimum severity of symptoms measured through the PANSS total score, specific positive symptom items of the PANSS and the CGI-S scale.

In a recent large meta-analysis of 167 placebo-controlled clinical trials conducted in schizophrenia (Leucht et al 2019), mean patient age was negatively correlated with placebo-drug differences in the primary endpoint, suggesting that trials in an older population with schizophrenia and more chronic may have a lower potential for signal detection. For that reason, this Phase II trial will include participants between 18 to 45 years of age.

Clinical investigations of the treatment of acute exacerbations of schizophrenia have occurred in studies of durations varying from 4 to 8 weeks (Beasley et al 1997; Marder et al 1994; Citrome 2010). Older literature, suggested a delayed onset of response to antipsychotic treatment resulting in a need for prolonged exposure of a subset of patients to placebo. However several meta-analyses have demonstrated that the biggest improvement in controlled trials occurs within the first 2 weeks (Agid et al 2003;Leucht et al 2005) In a re-analysis of data from placebo-controlled registry trials of olanzapine and risperidone, most of the reduction in symptoms occurred by the fourth week in the study (McMahon et al 2008). In addition, drop-out rates in the placebo groups reached up to 60% in 6-week studies making statistical inferences less reliable. In the recent large meta-analysis, study duration was not associated with drug-placebo differences. As this is the first study of RO6889450 in patients with an acute exacerbation of schizophrenia, a duration of 4 weeks was selected for the assessment of the primary efficacy endpoint, while reducing patient burden and addressing ethical concerns of prolonged placebo treatment as well as potential bias due to high dropout rates in longer clinical trials.

Patients who complete the Study Period 2 will have the option to continue into a double-blind 8-week extension period (Study Period 3), in treatment with RO6889450 150 mg or 45 mg, or with risperidone 4 mg. This period is intended to further assess the

safety and efficacy of RO6889450 over a longer period. Participants who complete Study Period 3 will have the option to enter a 36-Week Safety Extension Phase, continuing with their allocated treatment. This 36-Week Safety Extension Phase is intended to further assess long-term safety and drug effect of RO6889450.

4.2.2 Rationale for Placebo Control Group

Currently, superiority over placebo is considered the gold standard method to demonstrate safety and efficacy of new medications, including antipsychotic agents (Kemmler et al 2005). Despite advances in clinical trial methodology, alternative trial designs offer more challenges to interpretation of results. Without a placebo comparator within the same study, it is difficult to estimate whether improvements in symptoms correspond to nonspecific treatment effects or the natural course of the disease. Additionally, in non-placebo-controlled designs, it is difficult to assess whether the apparent non-significant difference is related to the investigational agent being equally effective or ineffective to the active comparator or study deficiencies (Streiner et al 2008). Thus for methodological reasons, this study will employ four treatment groups: RO6889450 (150 mg or 45 mg), risperidone 4 mg, or placebo.

While placebo-controlled trials may be necessary, it is imperative to minimize the duration of exposure to ineffective treatment and provide required safety measures to protect the well-being of study patients. For this reason, patients are required to remain in an inpatient setting for the entire duration of the 4-week double-blind period and will be allowed certain concomitant medications (see Section 6.5).

4.2.3 Rationale for Selection of Risperidone as Active Control

Antipsychotic treatment has become the mainstay in the management of patients with acute exacerbations of schizophrenia. In a recent meta-analysis of 32 oral antipsychotics risperidone was confirmed as one of the most widely studied antipsychotic medications and also confirmed to be one of the most efficacious treatments for the treatment of acute exacerbation of schizophrenia, particularly for positive symptoms (Huhn et al 2019). Given observations that placebo responses have increased in recent years (Agid et al 2013) the risk of a falsely negative study is addressed by including a risperidone treatment group for assay sensitivity. The 4 mg/day dose of risperidone has been selected based on the recommendations of approved labeling for the treatment of adults with schizophrenia. Risperidone at a dose of 4 mg/day has been used frequently in recent years as an active control arm in placebo-controlled trials to evaluate other new treatments for schizophrenia (Durgama et al 2014, Downing et al 2014).

4.2.4 Rationale for Biomarker Assessments

Increased understanding of interactions between the immune system and the brain in several chronic neurological and psychiatric disorders stimulated recent interest in the investigation of immune system alterations in schizophrenia. Advances in genetics have led to the identification of associations between genes involved in the regulation of the

immune system and increased risk of schizophrenia. A considerable body of evidence supports the immune hypothesis of schizophrenia, i.e., the notion that patients with schizophrenia have immunological alterations in the blood. The particular evidence includes immune cell numbers, inflammatory markers, oxidative stress, and antibody titers. Further, potential predictive values of baseline blood levels of these markers to therapeutic agents have been studied and confirmed by several independent studies (Miller and Goldsmith 2017). A dedicated exploratory biomarker assessment (see Section 8.6) will be performed in order to investigate the role of the immune system in the study population and assess the potential predictive value of these markers to the RO6889450 response.

Furthermore, more than 100 loci in the human genome contain single nucleotide polymorphism haplotypes that associate with risk of schizophrenia. The strongest evidence thus far is schizophrenia's association with genetic markers across the major histocompatibility complex locus also best known for its role in immunity (Sekar et al 2016; Ripke et al 2014). This study will therefore also collect blood for genotyping analyses to explore the potential of genetic markers for stratification, i.e., to identify a subset of patients with a specific genetic profile that may be more likely to respond to RO6889450.

4.2.5 Rationale for Digital Biomarker Assessments

Ecological Momentary Assessment (EMA) involves participants being prompted by notifications several times a day to complete a series of questions via a mobile device such as a smartphone (Shiffman et al 2008). Data collected reflects an individual's momentary experiences at a given time point in the context of their daily life, improving ecological validity of assessment data and overcoming memory deficits and recall and potential expectation biases of both participant and examiner (Shiffman et al 2008). Studies have demonstrated the feasibility and validity of digital EMA methods in schizophrenia (Granholm et al 2008; Granholm et al 2013; Granholm et al 2020) and the ability of EMAs to capture information on symptoms and functioning in schizophrenia such as autonomic regulation and auditory hallucinations (Kimhy et al 2017), self-stigma (Ben-Zeev 2012), suicidal ideation (Depp et al 2018), paranoia and positive symptoms (Ben-Zeev et al 2012, So et al 2014) and motivational negative symptoms (Moran et al 2017).

The digital biomarker approach EMA will therefore be implemented in the study as an exploratory and optional tool to help understand a potential therapeutic effect of RO6889450, regarding participant's functioning and behavior and to refine such outcome measures for future studies (see Section 8.9.4 for more details).

4.3 JUSTIFICATION FOR DOSE

Doses of 45 mg QD and 150 mg QD have been selected based on both preclinical and clinical observations with RO6889450. Improvements were observed in reward-related behavioral tasks in Study BP30134. In the reinforcement learning working memory task, the ability to learn appropriate stimulus-response mappings through trial-and-error feedback was assessed. Greater gains in reinforcement learning from baseline were observed under both 50 mg and 150 mg of RO6889450 when compared to placebo. The effort-choice benefit task assesses the participant's willingness to expend effort to obtain a reward of variable magnitude under low versus high probability of reward receipt. Treatment with 150 mg of RO6889450 increased the proportion of effortful choices under conditions of guaranteed reward (i.e., 100% reward probability) relative to placebo after controlling for proportion effortful choices at baseline. For these reasons, a dose of 150 mg QD of RO6889450 is considered adequate to demonstrate potential effects on key deficits in schizophrenia. The dose of 45 mg QD of RO6889450 is expected to have a pharmacological effect based on pre-clinical and clinical observations and will provide a clear blood exposure difference with 150 mg.

Further details are provided in the RO6889450 Investigator's Brochure.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed all phases of the study including the last study visit.

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

5. STUDY POPULATION

The study population rationale is provided in Section 4.2.1.

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 and none of the exclusion criteria.

Prospective approval of protocol deviations from recruitment and enrollment criteria (e.g., protocol waivers or exemptions) is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

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 *current* 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.

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. *In exceptional situations (e.g., delay due to the administrative procedures), hospitalization up to a maximum of 10 days prior to screening is permitted (prior* discussion with the Medical Monitor *is recommended).*

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 $\geq$ 4 (moderate or worse).

10. Screening and baseline PANSS total score $\geq$ 80.

11. Screening and baseline PANSS $with\ scores$ 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:

    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 $contraception$.

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. $Successful$ 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 Section 5.1, Inclusion Criterion 13.

D. No signs or symptoms of worsening 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.

E. No history of confirmed or suspected vasculitis and/or no clinically significant abnormality in laboratory assessments taken for evaluation of the possible presence of vasculitis (i.e., C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], anti-neutrophil cytoplasmic antibodies [ANCA], anti-nuclear antibodies [ANA], anti-double-stranded DNA [anti-dsDNA] antibodies, and anti-phospholipid antibodies).

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

General Exclusions

1. Has been inpatient for *> 1* week *(or in exceptional situations [e.g., delay due to the administrative procedures] > 10 days)* or *had* 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.

2. Disease duration longer than 10 years.

3. Is currently an inpatient on an involuntary basis.

4. *The C-SSRS* "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) *answered* "Yes" or any *"Yes" answers to "*Suicidal Behavior*"* within one month from Screening or between Screening and Baseline (i.e., since last visit). *In addition, any Investigator judgment of* significant risk of suicide or harming *themselves* or others.

5. Lifetime history of homicidal behavior.

6. Moderate to severe substance use disorder within six months (excluding nicotine) as defined by DSM-5.

7. Other current DSM-5 diagnosis (e.g., bipolar disorder, major depressive disorder).

Medical Conditions

8. 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).

9. Positive result at screening for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), or human immunodeficiency virus (HIV-1 or -2). Participants *with positive anti-hepatitis C antibody* who have been successfully treated and test negative for HCV RNA *are* eligible for study entry.

10. Tardive dyskinesia that is moderate to severe or requires treatment.

11. History of neuroleptic malignant syndrome.

12. Clinically significant abnormalities in laboratory safety test results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis), including:

    a) Aspartate aminotransferase (AST), or alanine aminotransferase (ALT) $2 \times$ upper limit of normal (ULN), or total bilirubin > $1.5 \times$ ULN with the exception of known Gilbert syndrome.

    b) Serum creatinine $>1.5 \times$ 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 not clinically significant.

13. 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

14. Participant 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®.

15. Participant treated with a long-acting injectable antipsychotic (LAI) or other antipsychotics that cannot be washed-out *within* the *allotted* screening period (see list of specific medications in Section 6.5).

16. History of electroconvulsive therapy (ECT) *for any reason*.

17. Participant treated with clozapine *at any dose in the* 12 months *preceding the* screening visit or participants treated with clozapine at ≥ 200 mg/day at any time. *Note:* low dose (< 200mg/day) use for insomnia or dyskinesia *longer than* 12 months prior to screening visit *is* permitted (*Appendix 6*).

18. Participants currently receiving a psychotropic or other medication used as a psychotropic, which cannot be discontinued during the screening period.

19. Positive urine drug screen for amphetamines, methamphetamines, opiates, buprenorphine, methadone, cocaine, and barbiturates (see Section 8.2.4). In case of positive urine drug screen for cannabinoids (including cannabidiol), the participant may be allowed to enter the study *only in case of a* sporadic use of cannabis. *Regular consumption meeting the criteria for cannabis use disorder (mild, moderate, or severe) is not permitted.*

20. 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

21. Participant has previously received RO6889450.
22. 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).

5.3 CONFIRMATION OF ELIGIBILITY AT BASELINE

1. Participant will be excluded if unable to taper off an antipsychotic at least 72 hours prior to baseline (see Appendix 6).
2. Female participants who are of childbearing potential (see Appendix 5) must have a negative pregnancy test result at baseline.

5.4 LIFESTYLE CONSIDERATIONS

5.4.1 Alcohol Consumption

Consumption of alcohol is not recommended while participating in the study.

5.5 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized to study treatment. Screen failures may be tracked separately.

The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure.

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened only once after discussion between the Investigator and the Medical Monitor or delegate. Individuals who screen fail due to clinical signs of COVID-19 or a positive COVID-19 PCR test, or other diagnostic tests when available, may be rescreened only once after *discussion with Medical Monitor or delegate.* Re-screening of participants who were screen failures for safety reasons is not allowed.

Individuals for whom screening was stopped due to Sponsor's decision to temporarily halt recruitment (e.g., due to an outbreak of COVID-19) can be re-screened after *discussion with* Sponsor*/Medical Monitor.* Re-screened participants should be assigned a new participant number.

In order to re-screen such a participant, all inclusion and exclusion criteria should be re-evaluated and all applicable screening assessments repeated.

5.6 RECRUITMENT PROCEDURES

This is a global competitive study without a target number of participants to be enrolled at any site outside Japan. Participants will be identified for potential recruitment per site-specific recruitment plans prior to consenting to participate in the study. Any patient-facing recruitment materials will receive Institutional Review Board (IRB) approval prior to use.

6. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

For Study BP41743, there are four formulations that are being administered:

- active RO6889450 film-coated tablets (45 mg and 150 mg)
- placebo film-coated tablets (to match 45 mg and 150 mg active RO6889450)
- active comparator (risperidone) over-encapsulated tablets in hard gelatin capsules (2 mg)
- placebo hard gelatin capsules (to match 2 mg comparator).

For the RO6889450 film-coated tablets, the active tablet core consists of RO6889450 drug substance and the inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, sodium stearyl fumarate, and colloidal silicon dioxide. The film-coat is composed of the following ingredient: Opadry II white 32F280008. All the ingredients used in the film-coated tablet formulation are of compendial grade (USP/NF and/or Ph. Eur). For clinical studies, film-coated tablets are available containing 45 mg and 150 mg of RO6889450 (amounts given as RO6889450 free base).

A placebo matching the RO6889450 film-coated tablets, in terms of size, shape and color, has also been developed for clinical usage. Placebo film-coated tablets have been manufactured containing: Isomalt, microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, sodium stearyl fumarate, and colloidal silicon dioxide and no active substance. The film-coat is composed of the following ingredient: Opadry II white 32F280008. All the ingredients used in the film-coated tablet formulation are of compendial grade (USP/NF and/or Ph. Eur).

For the blinded active risperidone comparator, the risperidone tablet 2 mg is over-encapsulated with the following ingredients: lactose agglomerated and magnesium stearate. The capsule shell is composed of the following ingredients: gelatin, red iron oxide, yellow iron oxide, and titanium dioxide. All the ingredients used in the capsule shell formulation are of compendial grade (USP/NF and/or Ph. Eur).

For the blinded placebo for 2 mg risperidone comparator, the capsule fill only contains microcrystalline cellulose and no active substance. The capsule shell is composed of the following ingredients: gelatin, red iron oxide, yellow iron oxide, and titanium dioxide. All the ingredients used in the capsule shell formulation are of compendial grade (USP/NF and/or Ph. Eur).

All investigational medicinal products (IMPs) required for completion of this study (RO6889450 and matching placebo and risperidone and matching placebo) will be provided by the Sponsor.

The first dose of medication will be administered in the hospital or study center on Study Day 1, once all Baseline/Day 1 pre-dose assessments have been conducted, including the confirmation of eligibility at baseline. During Study Period 2, all study drug administration will be at the study center under supervision of site staff. During Study Period 3, study drug will be dispensed to patients as detailed in SoA (Section 1.3).

Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated AEs, should be reported as described in Appendix 2, Section 5.2.

6.1 TREATMENTS ADMINISTERED

Study drug should be taken at bedtime, without food, and swallowed whole with fluid. Ideally, no food should be consumed for at least 2.5 hours before and after dosing. If the interval between the meals cannot be respected, an interval as long as possible should be reached and documented.

Table 4 summarizes the treatments administered.

Table 4 Summary of Treatments Administered

Study Treatment Name:	RO6889450	RO6889450 Placebo	Risperidone	Risperidone-Placebo
IMP and NIMP	IMP	IMP	IMP	IMP
Dose Formulation:	Film-coated tablets	Film-coated tablets	Hard capsules	Hard capsules
Unit Dose Strength(s)/Dosage Level(s):	150 mg 45 mg	Matching active film-coated tablet, one per strength	2 mg	Matching active hard capsule
Dose:	150 mg 45 mg	NA	4 mg	NA
Route of Administration:	Oral	Oral	Oral	Oral
Sourcing:	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling:	Study treatment will be provided in HDPE bottles. Each HDPE bottle will be labeled as required per country requirement.	Study treatment will be provided in HDPE bottles. Each HDPE bottle will be labeled as required per country requirement.	Study treatment will be provided in HDPE bottles. Each HDPE bottle will be labeled as required per country requirement.	Study treatment will be provided in HDPE bottles. Each HDPE bottle will be labeled as required per country requirement.

Each participant will receive bottles with three study treatments:

- one HDPE bottle (Bottle A) with 45 mg dose of RO6889450 or corresponding placebo,
- one HDPE bottle (Bottle B) with 150 mg dose of RO6889450 or corresponding placebo,
- one HDPE bottle (Bottle C) with risperidone or risperidone placebo.

Each participant will take the study treatments from all three bottles daily as detailed below:

- one 45 mg tablet of RO6889450 or corresponding placebo tablet from Bottle A,
- one 150 mg tablet of RO6889450 or corresponding placebo tablet from Bottle B,
- two risperidone 2 mg or corresponding placebo capsules from Bottle C (except for Day 1, when only one risperidone 2 mg or corresponding placebo capsule should be taken).

Guidelines for treatment interruption or discontinuation are provided in Section 7.

Please see the IB(s) for more details.

For risperidone, see the local prescribing information for more details.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Study drug packaging will be overseen by the Roche clinical trial supplies department.

The packaging and labeling of the study medication will be in accordance with Roche standards and local regulations.

The investigational site will acknowledge receipt of IMPs and confirm the shipment condition and content. Any damaged shipments will be replaced. Upon arrival of the IMPs at the site, site personnel will complete the following:

- Check the IMPs for damage.
- Verify proper identity, quantity, integrity of seals and temperature conditions.
- Report any deviations or product complaints to the Study Monitor upon discovery.

Each double-blind bottle will be labeled with a unique medication number (MEDNO). The qualified individual responsible for dispensing the study drug will dispense the correct containers of IMP to the participant at each dispensing visit by matching the MEDNOs allocated by the Interactive response technology (IRT) for that visit with the MEDNOs printed on the IMP labels. If the IMP dispensing visit cannot take place in the clinic (e.g., due to travel restrictions due to an outbreak of COVID-19) and alternative methods of delivery are not feasible, the IMP dispensing may be done with direct site to patient shipment (with prior approval from relevant health authority if applicable).

The Investigator or delegate must confirm that appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment. Please refer to IMP Label for storage conditions.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation and final disposition records).

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure (SOP) or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. Local or institutional regulations may require immediate destruction of used IMP for safety reasons. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.3.1 Method of Treatment Assignment

Approximately 280 participants will be randomized outside Japan (US and ROW) in the study. In addition to these 280 participants, approximately 28 participants will be recruited in Japan. After being screened, those participants who meet all eligibility criteria will be randomly assigned in equal proportions to one of the four treatment groups: RO6889450 150 mg QD; RO6889450 45 mg QD; risperidone 4 mg QD; or placebo. 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 completing Study Period 2 will be eligible to enter the Study Period 3. Participants treated with risperidone, with 150 mg QD of RO6889450 or with 45 mg QD of RO6889450 during Study Period 2 will continue with their respective blinded treatments. Participants assigned to placebo will be randomized to either 150 mg QD or 45 mg QD of RO6889450, in a ratio of 1:1 using their baseline values for stratification. Participants who enter the 36-Week Safety Extension Phase will continue with their respective blinded treatments.

A participant randomization list will be created for the initial randomization and the randomization of the placebo participants into the Study Period 3.

All participants will be centrally assigned to randomized study treatment using an IRT. Before the study is initiated, the log in information and directions for the IRT will be provided to each site.

Study treatment will be dispensed at the study visits summarized in SoA.

Returned study treatment should not be re-dispensed to the participants.

6.3.2 Blinding

This is a double-blind study, i.e., the study participants, the Investigators, and all individuals in direct contact with the study participants at the investigational site and the Sponsor Study Management Team (SMT) will be blinded to the study treatment (randomized and actually given).

Treatment codes should not be broken except in an emergency. If unblinding is necessary for participant management (e.g., in case the knowledge is needed for treatment of an SAE), the Investigator will be able to break the treatment code using IRT. The Sponsor must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the participant's condition. In this case, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF, as applicable. If the Investigator wishes to know the identity of the study drug for any other reason, he or she should contact the Medical Monitor directly.

As per Health Authority reporting requirements, the Sponsor will break the treatment code for all unexpected SAE (see Section 8.3.4 and Appendix 2) that are considered by the Investigator to be related to study drug.

The randomization list will be made available to the individuals responsible for PK sample bioanalysis and to statisticians or statistical programmers at Roche. Unblinding of any Roche individual will be according to the relevant Roche SOPs.

PK data can be received and cleaned on an ongoing basis. The data will be handled and cleaned in a secure area that is not accessible by any blinded SMT member.

The primary analysis of the study will be performed and interpreted when Week 4 data are available for all randomized patients. The Sponsor will be unblinded for analysis and interpretation, while patients and Investigators will remain blinded for the extension phase of the study.

The Sponsor may choose to conduct up to two interim efficacy analyses for internal decision making. The interim analysis will be performed and interpreted by members of the Sponsor's study team 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.

6.4 TREATMENT COMPLIANCE

During the Study Period 2, qualified site personnel will dispense the correct dose according to the randomization schedule. This individual will write the date dispensed and participant number on the study treatment bottle labels and the Drug Accountability Record. This individual will also record in the participant's records the medication numbers that are printed on the bottles each participant receives during the study.

During Study Period 3 (extension phase), qualified site personnel will dispense the correct dose according to the randomization schedule, will write the date dispensed and participant number on the study treatment bottle labels and will also record in the participant's records the medication numbers that are printed on the bottles each participant receives. If the IMP dispensing visit cannot take place in the clinic (e.g., due to travel restrictions due to an outbreak of COVID-19) and alternative methods of delivery are not feasible, the IMP dispensing may be done with the direct site to patient shipment *upon Sponsor/Medical Monitor approval* (with prior approval from relevant health authority if applicable).

During Study Period 3 (extension phase) only, treatment compliance verification will be done using the medication adherence platform via a smartphone app (see Section 6.4.1). At each visit day, participant should bring the study treatment containers and drug accountability will be checked by the site. The use of the medication adherence platform via a smartphone app in Japan may not be required.

During the 36-Week Safety Extension Phase, treatment compliance will be verified through phone calls once a month with the participant or participant's caregiver who will be asked to keep a weekly account of the participant's compliance. At each visit, the participant should bring the study treatment containers, and drug accountability will also be checked by the site. The medication compliance platform via a smartphone app will not be used during the 36-Week Safety Extension Phase.

If the compliance of participant is insufficient ($<$80%) *on a weekly basis*, it has to be discussed with the Sponsor.

6.4.1 Medication Adherence Platform

This trial will employ a medication adherence monitoring platform via a smartphone AiCure app ("Platform") during Study Period 3 in all countries except Japan, where the use of medication adherence platform may not be required. The Platform may either be provided to a participant preloaded on a smartphone, or the participant may download the Platform onto their own smartphone. Platform workflow is as follows: participants will receive a medication reminder at a time within a pre-defined window to take their medication. Participants will follow a series of prescribed steps in front of the front-facing

webcam of the smartphone to confirm participant identity and medication to be taken. In addition, built-in reminders and a communication system allow real-time intervention in case of non-compliance. Use of this Platform will in no way supersede or replace the physician and/or prescribed medication protocol. Because the Platform does not change the medication protocol, but rather encourages adherence, use of this Platform presents minimal risk to the participants.

After local determination by the Platform of proper medication administration, video recordings and data indicating whether the participant has properly taken the medication will be encrypted and transmitted to a secure centralized location for further analysis, including testing for duplicate enrollment. The captured video and data is reviewable through a roles- and rules-restricted Health Insurance Portability and Accountability Act (HIPAA)-compliant system ensuring privacy of the information and only accessible to authorized personnel through two-way authentication.

Phone numbers of the participants will be collected and stored in an encrypted manner, allowing for direct communication to each participant from the system in an automated manner, or by study staff or other study monitoring personnel. Individuals who are not part of the study staff will not know the identity of study participants and will have no access to any medical or health records of the participants.

Participants who do not take their medication regularly will be contacted by study staff for retraining and motivational interventions.

6.5 CONCOMITANT THERAPY

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 eCRF.

All medication administered to manage adverse events should be recorded on the Adverse Event eCRF.

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

6.5.1 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*, depending on the anti-psychotic medication*. Washout periods for a specific anti-psychotic medication are provided in Appendix 6, Table 1.

6.5.1.1 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. The reasons for use of rescue medication should be documented in detail.

Investigators should make a reasonable effort to complete a final assessment including efficacy endpoints before starting antipsychotic medication (see Section 1.3, Section 7.1 and Appendix 6, Table 1). Patients should be followed up as specified in Sections 7, 8.10.3 and 8.10.4.

6.5.2 Non anti-psychotic concomitant medication

6.5.2.1 Permitted Therapy

Non-psychoactive medications, including OTC medications, that are required to treat pre-existing conditions or 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, 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.

6.5.2.2 Prohibited Therapy

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

As a general rule, no new concomitant medication or therapies including non-pharmacological interventions (e.g., individual psychotherapy, cognitive behavioral therapy, smoking cessation therapy, and rehabilitative therapy) 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 Appendix 6, Table 2.

6.5.2.3 Restricted Therapy

The list of restricted therapies is provided in Appendix 6, Table 3.

6.6 TREATMENT AFTER THE END OF THE STUDY

The Sponsor does not intend to provide RO6889450 or other study interventions to participants after conclusion of the study or any early participant withdrawal.

Participants should consult with their physician on available treatment options, such as antipsychotics, to begin after the last dose of study drug. Participants should be followed up as specified in Sections 7, 8.10.3 and 8.10.4.

7. DISCONTINUATION OF STUDY, STUDY TREATMENT, AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

An excessive rate of withdrawals (either participants discontinuing study treatment or withdrawing from the study) can render the study non-interpretable. Therefore, unnecessary withdrawal of participants should be avoided and efforts should be taken to motivate participants to comply with all the study-specific procedures as outlined in this protocol. Temporary study drug interruption is an acceptable method to manage adverse events if deemed appropriate by the Investigator.

Details on study and site closures are provided in Appendix 1 Regulatory, Ethical, and Study Oversight Considerations.

7.1 DISCONTINUATION OF STUDY TREATMENT

Participants must discontinue study drug if they have withdrawn consent or experience any of the following:

- Pregnancy
- Participant is unable to continue to comply with study requirements
- Any medical condition that the Investigator or Sponsor determines may jeopardize the participant's safety if he or she continues in the study. The Sponsor should be informed by the Investigator, preferably prior to or immediately after withdrawal of the participant, as feasible, considering the safety of the participant is first priority.
- Investigator or Sponsor determines it is in the best interest of the participant.

- Participant must be discontinued from the study treatment in the case of suicidal behavior or active suicidal ideation with specific plan and intent, or violent or aggressive behavior resulting in any type of injury or property damage.
- If the participant has worsening of psychotic symptoms that require treatment with anti-psychotic medication in addition to the study treatment, in the opinion of the Investigator, the participant should be discontinued from the study treatment and appropriate anti-psychotic medication should be initiated.
- After the participant is discharged after the mandatory hospitalization, but the participant has worsening of psychotic symptoms that requires new hospitalization, the participant should be discontinued from the study treatment.
- Symptomatic patients with moderate or severe COVID-19 infection (as per WHO guidelines) with signs of pneumonia or hypoxia must be withdrawn from the study treatment.
- *Participants entering the 36-Week Safety Extension Phase: if the participant has confirmed vasculitis. In addition, the participant may be discontinued if vasculitis is suspected on the basis of (1) any clinically significant abnormality on the laboratory assessments for vasculitis monitoring or (2) a relevant AE (i.e., rash, myalgia, arthritis, and fever) or (3) a clinically significant physical examination finding that indicates the possible presence of vasculitis. Cases of suspected vasculitis are to be discussed with the Medical Monitor, and action taken with study treatment will be determined accordingly.*

See the SoA (Section 1.3) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

Every effort should be made to obtain information on participants who withdraw from the study treatment but have not withdrawn consent. Participants who discontinue study treatment prematurely will be asked to return to the clinic for a study completion/early termination visit (ETV; see Section 8.10.3) and should be asked to return for follow-up assessments (see Section 8.10.4), unless the participant withdrew consent.

If a participant voluntarily withdraws from the study or is withdrawn by the Investigator during Study Period 2, the participant will be asked to complete Study Period 2 end of treatment (EOT) visit as soon as possible after the last dose of study drug. 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 early termination visit (ETV) to complete assessments of the primary and secondary efficacy outcomes (PANSS, CGI-S, CGI-S MTS, CGI-I and CGI-I MTS), regardless of their adherence to treatment. Participants will also be asked to return for the follow-up visit (4 weeks after the last dose). If a participant voluntarily withdraws from the study or is withdrawn by the Investigator during Study Period 3, the participant should return to complete Study Period 3 EOT visit as soon as possible after the last dose of study drug. Participant will be asked to return for the follow-up visit assessments (4 weeks after the last dose). If a participant voluntarily withdraws from the study or is withdrawn by the Investigator during the 36-Week Safety

Extension Phase, the participant should return to complete the 36-Week Safety Extension Phase EOT visit as soon as possible after the last dose of study drug. The participant will be asked to return for the follow-up visit assessments (4 weeks after the last dose). For the participants who discontinue study treatment prematurely, if the EOT visit for Study Periods 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 8.10.3). The primary reason for premature study treatment discontinuation should be documented on the appropriate eCRF. Participants who discontinue study treatment prematurely will not be replaced.

Discontinuation of study intervention for abnormal liver function should be considered by the Investigator when a participant meets one of the conditions outlined in Appendix 3 or if the Investigator believes it is in the best interest of the participant.

If a clinically significant finding is identified (including, but not limited to QT interval corrected using QTcF exceeding 500 msec [if confirmed in control ECG to be recorded within 60 minutes] or a change from screening QTcF by more than 60 msec [if confirmed in control ECG to be recorded within 60 minutes]) after enrollment, the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants have the right to voluntarily withdraw from the study at any time for any reason.

In addition, the Investigator has the right to withdraw a participant from the study for medical conditions that the Investigator or Sponsor determines may jeopardize the participant’s safety if he/she continues in the study.

Every effort should be made to obtain information on participants who withdraw from the study. Information on reason for withdrawal from the study should be obtained. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Participants will not be followed for any reason after consent has been withdrawn.

When a participant voluntarily withdraws from the study, or is withdrawn by the Investigator, samples collected until the date of withdrawal will be analyzed unless the participant specifically requests for these to be discarded or local laws require their immediate destruction. However, if samples have been tested prior to withdrawal, results from those tests will be used as part of the overall research data. A participant's withdrawal from this study does not, by itself, constitute withdrawal of samples donated to the Research Biosample Repository (RBR).

Participants who withdraw from the study will not be replaced.

See SoA (Section 1.3) for data to be collected at the time of study discontinuation and at safety and follow-up visits, and for any further evaluations that need to be completed.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of sites or of study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their time-points are summarized in the Schedules of Activities (SoA; Section 1.3). Protocol waivers or exemptions are not allowed. If the post Study Period 2 EOT visit study assessments and procedures cannot be administered because the visit cannot take place (due to, e.g., *local* COVID-19 *restrictions or emergency situations*), the Home HealthCare System can be used (e.g., ECG, Labs, PK sampling, physical *examinations* etc.) *if approved by the Sponsor. The Home HealthCare System will not be used in Japan.*

Post Period 2 EOT visit safety and efficacy assessments can be performed remotely due to local restrictions (due to, e.g., *local* COVID-19 restrictions *or emergency situations*), *if approved by the Sponsor* as detailed in Section 1.3.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Training, guidance on rater qualifications and procedures are described separately in the Ratings Manual.

Scales to be administered in the study are listed in Table 5. The order in the table does not indicate the order in which the scales should be performed (see Section 8.10.2).

Table 5 Scale Administration

No.	Scale	Patient-reported	Qualified Site Rater / Trained Psychometrician	Centralized Rater
1	PANSS			X
2	PANSS-IC		X	X[1]
3	MINI		X	
4	CGI-I		X	
5	CGI-I MTS		X	
6	CGI-S		X	
7	CGI-S MTS		X	
8	PGI-C	X		
9	CDSS		X	
10	ReQoL-20	X		
11	RDQ		X	
12	WRAT-4		X	
13	WASI-II		X	
14	Assessment of Sleep, Mood, Well-being and Cognitive Functioning and Treatment Expectancy	X		
15	SUMD-9		X	
16	BCIS	X		
17	VAGUS-SR	X		
18	VAGUS-CR		X	
19	C-SSRS		X	
20	ESRS-A		X	
21	FTND	X		
22	EMA	X		
23	Feedback questions		X	
24	PAS		X	

[1] During the outpatient period of the study, if participants do not have a designated caregiver, the independent raters may, as an exception, rate the PANSS based on information collected from an Informant, i.e., study personnel.

8.1 EFFICACY ASSESSMENTS

Scale administration will be performed according to Table 5.

8.1.1 Clinical Outcome Assessments

8.1.1.1 Positive and Negative Syndrome Scale (PANSS) and PANSS-Informant Checklist (PANSS-IC)

The PANSS is a 30-item rating scale that evaluates positive, negative, and other symptoms in patients with schizophrenia (Kay et al 1987). The Positive sub-scale assesses the features exhibited in schizophrenia that are not present in those with a normal mental state. The Negative sub-scale (7 items) 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. Each item is rated on a 7-point scale (1 = absent, 7 = extreme). A total score as well as subscale and factor scores will be derived. It takes approximately 40 minutes to administer. The PANSS assessment will be performed by an approved remote centralized rater. 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.

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.

During the outpatient period of the study, if participants do not have a designated caregiver, the independent raters may, as an exception, rate the PANSS based on information collected from an Informant, i.e., study personnel.

8.1.1.2 Clinical Global Impression-Improvement (CGI-I) and Severity (CGI-S) Scales

The CGI (Guy 1976) is one of the most commonly used outcome measures in psychopharmacology clinical trials. The CGI is the general name for two scales: the CGI- Severity scale (CGI-S) that measures global severity of illness at a given point in time and the CGI-improvement scale (CGI-I) that measures change from the baseline state at following visits. The CGI rating scale permits a global evaluation by the clinician of the subject's improvement over time. The CGI-S is a 7-point scale ranging from 1 (no symptoms) to 7 (very severe). The CGI-I is a 7-point scale, ranging from 1 (very much improved) to 7 (very much worse).

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). 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.

Duration of the scales will be approximately 15 to 20 minutes to complete all CGI-I and CGI-S scales.

8.1.1.3 Patient Global Impression of Change (PGI-C) Scale

The generic Global Impression is a measure commonly used in clinical trials to provide concise information on overall health state (Guy 1976). The change component is intended as a measure of change in health state and can be adapted for participant self-assessment (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

8.1.1.4 Calgary Depression Scale for Schizophrenia (CDSS)

The CDSS (Addington et al 1990) 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). The duration of the CDSS assessment will be approximately 15 to 20 minutes to complete.

8.1.1.5 Fagerström Test for Nicotine Dependence (FTND)

The FTND (Heatherton et al 1991) will be used to assess nicotine consumption during the course of the study. The FTND is a standard instrument for assessing the intensity of physical addiction to nicotine. The test was designed to provide 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 choice items are scored from 0 to 3. The items are summed to yield a total score of 0-10. The higher the total Fagerström score, the more intense is the participant's physical dependence on nicotine. The scale takes approximately five minutes to complete. The FTND excludes cigar, snuff, oral, and vaping (e-cigarette) users.

8.1.1.6 Recovering Quality of Life (ReQoL-20)

Recovering Quality of Life (ReQoL; Keetharuth et al 2018) is a new instrument that measures mental health service users' own perspectives of 'recovery' and quality of life. It was developed from the outcomes that service users identified as being central to them, as well as from the literature (Connell et al 2014; Connell et al 2018; Keethaurt et al 2018). The stages of measurement development include the identification of themes and items (Stage 1), the face and content validity with service users (Stage 2), and the psychometric testing by collecting data on the draft questionnaires (Stage 3) before finalizing the measures. The scoring options of the items are: None of the time, Only occasionally, Sometimes, Often, and Most or all of the time. The measure is suitable for self-completion and for use across a wide spectrum of mental health conditions (both psychotic and non-psychotic) and for different levels of severity, for individuals aged 16 or over. The duration of the scale will take approximately 5 minutes to complete.

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.

8.1.1.7 Readiness for Discharge Questionnaire (RDQ)

The RDQ is a tool used to assess inpatients with schizophrenia on their readiness for discharge, independent of socio-economic factors (Potkin et al 2005). 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. The duration of the scale will take approximately 5 minutes to complete.

8.1.1.8 Assessment of Sleep, Mood, Well-being and Cognitive Functioning and Treatment Expectancy

Three Likert scales assessing sleep quality, mood / well-being, and cognitive functioning and treatment expectancy is optional but strongly recommended. The scales will be administered via the smartphone or the Medavante Virgil Platform (Appendix 7). Participant will be instructed to fill in the Likert scales (made of six "smiley" icons) at defined time points during the trial. In addition, participants will be asked to answer the following question at the end of the Study Period 2: "Do you think you were taking

placebo or drug?" The scales will be completed up to 28 times by the participant at pre-defined time points appearing random to patients.

8.1.1.9 Scale to Assess Unawareness of Mental Disorder (Short Version) (SUMD-9)

The Scale to Assess Unawareness of Mental Disorder (SUMD) short form (Amador et al, 1994) is a 9-item clinician-reported outcome designed to measure current awareness of mental illness. The instrument is a shortening of the 74-item Scale to Assess Unawareness of Mental Disorder (Amador et al 1994), consists of three general items and six symptom items. Each item is scored on a 3-point Likert scale, with following response options (Michel et al 2013): "not applicable" (0), "aware" (1), "somewhat/unaware" (2) and "severely unaware" (3), hence higher scores indicating poorer awareness. Each item is examined separately without calculation of subscale scores. The assessment is likely to take 5 to 10 minutes to complete.

8.1.1.10 Beck Cognitive Insight Scale

The Beck Cognitive Insight Scale (BCIS) (Beck et al 2004) 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 was calculated by subtracting the score for the self-certainty scale from that of the self-reflectiveness scale. The duration of this assessment is likely to take less than 15 minutes to complete.

8.1.1.11 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. If validated translations become available, they may be used. Equivalent scales may be used, if available.

8.1.1.11.1 VAGUS Self-report.

The VAGUS self-reported (VAGUS-SR) (Gerretsen et al 2014) is a 10-item patient-reported outcome measure designed to measure clinical insight into psychosis. 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. The assessment will take less than 5 minutes to complete.

8.1.1.11.2 VAGUS Clinician-reported

The VAGUS clinician-reported (VAGUS-CR) (Gerretsen et al 2014) is a 5-item clinician-reported outcome measure designed to measure clinical insight into psychosis. 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. The assessment is expected to take less than 5 minutes to complete.

8.2 SAFETY ASSESSMENTS

Planned time-points for all safety assessments are provided in the SoA (Section 1.3).

Safety assessments will consist of monitoring and recording AE, including SAEs and non-serious AEs of special interest; 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.

Scales administration will be performed according to Table 5.

8.2.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, dermatological and neurological, musculoskeletal in addition to head, eyes, ears, nose, throat, neck, and lymph nodes systems.

Height will also be measured and recorded at screening only.

Body mass index (BMI) will be calculated with the measure of weight and height according to SoA (Section 1.3).

Further examination of other body systems may be performed in case of evocative symptoms at the Investigator’s discretion.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Investigators should pay special attention to clinical signs of rash, myalgia, arthritis, and fever, and report these as AEs. These AEs should be evaluated for the possible presence of vasculitis and discussed with the Medical Monitor.

The physical examination will NOT include genital, pelvic, rectal, or breast examinations.

Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in participant's notes. New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event eCRF.

8.2.2 Vital Signs

Vital signs will include participant's temperature, systolic and diastolic BP and pulse. They will be taken before blood collection and will be measured in a supine position after the participant has been lying for at least five minutes. Additionally, BP and pulse measurements will be taken again after two minutes in a standing position (standing vital signs) at the time point specified in Section 1.3.

BP and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. When possible, the same arm should be used for all BP measurements.

8.2.3 Electrocardiograms

Sites will be provided with ECG equipment by the central ECG analysis vendor. Twelve-lead ECG will be obtained as outlined in the SoA (see Section 1.3) with the following parameters: heart rate, PQ (PR), QRS, QT, RR, and QTcF intervals, along with information on T- and U-waves. 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 will be collected. Any clinically significant ECG abnormalities will be captured on the eCRF.

ECGs should be performed 2 hours or longer after the last meal (with mealtime recorded) and before any scheduled vital sign measurements and blood draws. To minimize variability, it is important that participants be in a resting position for at least 10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. Whenever possible, the same brand/model of a standard high-quality, high-fidelity electrocardiograph machine equipped with computer-based interval measurements should be used for each participant. The conditions should be as close as possible to screening visit conditions; this includes but is not limited to food intake, activity level, stressors, and room temperature. In case of an absolute QTc of > 500 msec and/or an increase from screening visit QTc > 60 msec, another ECG triplicate must be recorded within the next 5 minutes. It may be appropriate to repeat abnormal ECGs to rule out improper lead placement potentially contributing to

the ECG abnormality. Refer to Section 7.1 for QTc withdrawal criteria and additional QTc readings that may be necessary.

For safety monitoring purposes, the Investigator or designee must review, sign, and date all ECG tracings. Paper or electronic copies will be kept as part of the participant's permanent study file at the site. Any clinically relevant changes occurring during the study will be recorded in the AE section of the eCRF. The recordings will be electronically transferred to a central ECG analysis vendor.

The following parameters will be obtained from the digital recordings: heart rate and rhythm, QRS duration, PQ (PR), RR, and QT intervals (QTcF).

Changes in T-wave and U-wave morphology and overall ECG interpretation will be documented. T-wave information will be captured as normal or abnormal, U-wave information will be captured in two categories: absent/normal or abnormal.

8.2.4 Clinical Safety Laboratory Assessments

A central laboratory designated by the Sponsor will be used for all laboratory testing required during the study with the exception of dipstick urinalysis, urine dipstick alcohol test, drugs of abuse, urine pregnancy test, COVID-19 test (when not performed centrally), *and ESR* (see Appendix 4). The central laboratory should be used for all laboratory testing whenever possible (including unscheduled and follow-up laboratory testing, if needed).

Normal ranges for the study laboratory parameters must be supplied to the Sponsor before the study starts. A list of clinical laboratory tests to be performed is provided in Appendix 4 and these assessments must be conducted in accordance with the separate laboratory manual and the SoA (Section 1.3).

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

- In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found.
- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.

Results of clinical laboratory testing will be recorded on the eCRF or be received as electronically produced laboratory reports submitted directly from the local or central laboratory.

Additional blood or urine samples may be taken at the discretion of the Investigator if the results of any test fall outside the reference ranges, or clinical symptoms necessitate additional testing to monitor participant safety.

Where the clinical significance of abnormal lab results at screening is considered uncertain, screening lab tests may be repeated before randomization to confirm eligibility.

If there is an alternative explanation for a positive urine or blood test for drugs of abuse, e.g., previous occasional intake of a medication or food containing for example, codeine, benzodiazepines or opiates, the test could be repeated to confirm wash out.

Based on continuous analysis of the data in this study and other studies, any sample type not considered critical for safety may be stopped at any time if the data from the samples collected does not produce useful information.

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

RO6889450 is a CNS-active study treatment. There has been concern that some CNS-active study treatments may be associated with an increased risk of suicidal ideation or behavior. Although this study treatment or other similar drugs in this class have not been shown to be associated with an increased risk of suicidal thinking or behavior when given to healthy volunteers OR people with schizophrenia, the Sponsor considers it important to monitor for such events before or during this clinical study.

Participants will be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Consideration should be given to discontinuing treatment in participants who experience signs of suicidal ideation or behavior.

Families and informants of participants should be instructed to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the study Investigator.

Baseline assessment of suicidal ideation and behavior or treatment-emergent suicidal ideation and behavior will be monitored during the study using the Columbia-Suicide Severity Rating Scale (C-SSRS).

The C-SSRS is a tool used to assess the lifetime suicidality of a patient (C-SSRS baseline) as well as any new instances of suicidality (C-SSRS since last visit). The

C-SSRS incorporates a structured interview to prompt recollection of suicidal ideation, including the intensity of the ideation, behavior, and attempts at actual/potential lethality (Posner et al 2011). The “baseline” version will be completed at the screening visit and a “since last visit” version will be completed at subsequent visits. This assessment takes approximately 5 to 10 minutes to complete.

8.2.6 Extrapyramidal Symptom Rating Scale- Abbreviated Version

The presence and severity of extrapyramidal symptoms will be evaluated using the ESRS-A as specified in the SoA (Section 1.3) (Alphs 2010). The reliability and validity of the ESRS has been demonstrated in antipsychotic-induced movement disorders (Chouinard et al 1980, Chouinard et al 2005). Additionally, the ESRS-A has been found specifically to measure movement disorders independent of changes in psychiatric symptoms as measured by the PANSS. 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 of these symptoms. All are evaluated on a scale of 0 (absent) to 5 (extreme). The ESRS-A typically takes 10 minutes to complete.

8.2.7 Psychiatric/Medical History and Demographic Data

Medical history includes clinically significant diseases, smoking history, use of alcohol and drugs of abuse and all medications (e.g., prescription drugs, OTC drugs, herbal or homeopathic remedies, nutritional supplements) and any non-pharmacological interventions (e.g., individual psychotherapy, cognitive behavioral therapy, smoking cessation therapy, and rehabilitative therapy) used by the participant within 28 days prior to the screening visit.

A detailed psychiatric history will be taken during the screening period (including Mini International Neuropsychiatric Interview [MINI]). This will include information regarding specific symptoms, number of hospitalizations, and treatment history (including treatment response, detailed description of current episode, type / reason for exacerbation, e.g., compliance problem or breakthrough relapse). Sources for this information may include reliable caregivers or treating psychiatrists or medical records. In particular, information necessary to evaluate eligibility criteria will be noted.

Demographic data will include age, sex, and self‑reported race/ethnicity. This includes collection of details on the relationship between the caregiver and participant.

During screening, the Eligibility Checklist Form (ECF) will be completed. This will include the information mentioned above along with other pertinent information as specified on the ECF. The completed ECF will be forwarded as soon as all requested information is available during screening to the Clinical Team Manager (CTM) or local Site Monitor via the Clinical Research Organization (CRO) electronic Protocol Inquiry Platform (ePIP) for documentation and monitoring purposes. The *Investigator* will act as final decision maker regarding exclusion or inclusion of participants in the study.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The definitions of an AE or SAE can be found in Appendix 2. The non-serious AEs of special interest and disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs are discussed in Section 8.3.6.

The Investigator and any qualified designees are responsible for ensuring that all adverse events (including assessment of seriousness, severity and causality; see Appendix 2) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Appendix 2.

Procedures used for recording AEs are provided in Appendix 3:

- Diagnosis versus signs and symptoms:
- Other AEs
- AEs occurring secondary to other events
- Persistent or recurrent AEs
- Abnormal laboratory values
- Abnormal vital sign values
- Abnormal liver function tests
- Deaths
- Preexisting medical conditions
- Lack of efficacy or worsening of the condition being studied
- Hospitalization or prolonged hospitalization
- Patient-reported outcome data

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

Investigators will seek information on adverse events at each participant's contact. All adverse events, whether reported by the participant or noted by study personnel, will be recorded in the participant's medical record and the Adverse Event eCRF as follows:

After informed consent has been obtained **but prior to initiation of study treatment**, only serious adverse events caused by a protocol-mandated intervention should be reported (e.g., serious adverse events related to invasive procedures such as biopsies). Any other adverse event should not be reported.

After initiation of study treatment, all adverse events, regardless of relationship to study treatment, will be reported until 28 days after the final dose of study treatment.

Post-study adverse events and serious adverse events: The Investigator is not required to actively monitor participants for adverse events after the end of the adverse event reporting period of 28 days.

However, if the Investigator learns of any SAE (including a death) or other adverse events of concern that the Investigator considers the event to be related to study treatment or study participation at any time after a participant has been discharged from the study, the Investigator must promptly notify the Sponsor. For the procedure of reporting, see Appendix 2.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all participant evaluation time−points.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

8.3.3.1 Investigator Follow-Up

The Investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the event is otherwise explained, the participant is lost to follow-up (Section 7.3), or the participant withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome and reported according to the instructions provided in Appendix 5.

8.3.3.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then, file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

For immediate and expedited reporting requirements from Investigator to Sponsor and from Sponsor to Health Authority, Investigators, IRB, and EC, see Appendix 2.

8.3.4.1 Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical Monitor is available 24 hours a day 7 days a week.

The Medical Monitor's contact details will be available on a separate list generated by the study management team.

8.3.5 Pregnancy

Female participants of childbearing potential will be instructed to immediately inform the Investigator if they become pregnant during the study or within 28 days after the final dose of study treatment.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the pregnancy reporting process as detailed in Appendix 5.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs (Appendix 5).

8.3.6 Non-Serious Adverse Events of Special Interest

Non-serious adverse events of special interest are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Appendix 2 for reporting instructions).

Non-serious adverse events of special interest for this study include the following:

- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Appendix 3.
- Suspected transmission of an infectious agent by the study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.

8.4 TREATMENT OF OVERDOSE

The MTD of RO6889450 has been defined as 300 mg QD (based on tolerability demonstrated when administered as a single dose up to 450 mg [Phase I SAD study] and the occurrence of two dose-limiting events [DLEs] in the 450 mg cohort in a 14- day Phase I MAD study in healthy volunteers). For this study, treatment overdose is considered as the accidental or intentional use of a drug in a quantity that is two times higher in a day than the assigned dose at any group within a 24-hour time period.

An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects (see Appendix 2 for further details).

For RO6889450, specific information regarding treatment of overdose is currently not available. In the event of any AE or overdose, appropriate supportive treatment should be initiated according to the participant's clinical signs and symptoms.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant. In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until resolved.
3. Obtain a blood sample for PK analysis within 1 day from the date of the final dose of study treatment, if requested by the Medical Monitor (determined on a case-by-case basis).

4. Document the quantity of the excess dose, as well as the duration of the overdose, in the eCRF.

8.5 PHARMACOKINETICS

Mandatory blood samples will be collected from all participants, independent of study group assignment at the time points specified in Section 1.3. Additional PK samples will be taken at the time of treatment discontinuation. The exact time of dose administration on the day of PK collection at Week 4, and the exact time of last dose administration preceding the PK collection at Week 1 and 2 or treatment discontinuation should also be recorded in the eCRF. Plasma concentrations of RO6889450 and derived metabolite(s), as applicable, will be measured by a specific and validated LC-MS/MS method. 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. PK/PD or dose exposure response analyses may be conducted as appropriate. The results of the analysis will be reported separately from the clinical study report (CSR). Any volume of blood samples remaining after the specified analyses may also be used for additional assay development/validation experiments and for metabolite investigations. The blood samples will be destroyed no later than two years after the date of the final CSR. Details on sampling procedures, sample storage, and shipment are given in the Sample Handling Manual. Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.6 PHARMACODYNAMICS AND BIOMARKERS ANALYSES

Blood samples for the analysis of exploratory biomarkers will be collected according to the SoA (Section 1.3). The analysis may include but is not limited to biomarkers measured in plasma samples related to the immune/inflammation hypothesis of schizophrenia or associated pathways: e.g., cytokines (IL-1β, IL-6, TGF- β, IL-12, IFN-γ, TNF-α, sIL-2 R, sCD25).

The specimens may also be used for research purposes to identify biomarkers useful for predicting and monitoring response to RO6889450, identifying biomarkers useful for predicting and monitoring RO6889450 safety, assessing pharmacodynamic effects of RO6889450, and investigating mechanism of therapy resistance. Additional markers may be measured in the case that a strong scientific rationale develops.

For eligible participants entering the 36-Week Safety Extension Phase of the study, additional samples will be collected according to the SoA (Section 1.3, Table 2) for further investigation of any clinical safety signal that may emerge during the study.

Details on samples are specified in Section 8.7.

8.6.1 Clinical Genotyping

A mandatory whole blood sample will be taken for DNA extraction from every participant. If the sample is missed on baseline, it can be collected at any other scheduled visit. The DNA may be used for, but analysis is not limited to:

- Genetic variants of cytochrome P450s (e.g., CYP3A4, CYP3A5, CYP2C19), transporters (e.g., multidrug resistance protein 1 [MDR1]), transferases, or other proteins that might affect the metabolism, pharmacokinetics, pharmacodynamics, or safety of RO6889450.
- Genetic variants of the TAAR1 gene.
- Genetic variants of pathways related to schizophrenia and schizoaffective disorder, including but not limited to, genes related to disease and safety of RO6889450.
- Genes coding for human leukocyte antigens (i.e., human leukocyte antigen [HLA] gene family).

Data arising from all biosamples including samples for analyses of inherited DNA will be subject to the confidentiality standards described in Section 1.4 of Appendix 1. For participants who consent to research biosample repository (RBR), leftover samples will be transferred to RBR (see Section 8.8) otherwise, specimens will be destroyed after successful analysis.

Blood samples will be destroyed within five years after the date of the final CSR. Details on processes for collection and shipment of these samples can be found in the Sample Handling Manual.

8.7 PHARMACODYNAMICS AND BIOMARKER SAMPLES

Mandatory plasma samples will be collected for the analysis of exploratory biomarkers related to the immune/inflammation hypothesis of schizophrenia or associated pathways as described in Section 8.6.

Additional mandatory serum and plasma samples will be collected during the 36-Week Safety Extension Phase that will be analyzed in the event of any clinical safety signal that may emerge during the study. *Mandatory blood samples will also be taken for the assessment of possible vasculitis, i.e., CRP (collected in the blood chemistry panel), ESR, ANCA, ANA, anti-dsDNA antibodies, and anti-phospholipid antibodies.*

Mandatory whole-blood samples will be collected to isolate DNA for clinical genotyping and may also be used for RNA isolation for gene expression analyses as described in Section 8.6. Samples should be collected as specified in the SoA. Based on continuous analysis of the data in this study and other studies, any sample type and/or analysis not considered critical for safety may be stopped at any time if the data from the samples collected does not produce useful information.

Unless otherwise specified below, samples will be destroyed no later than 5 years after the date of final CSR. For participants who consent to RBR, leftover samples will be transferred to RBR (see Section 8.8).

Any remaining samples after the specified analyses may also be used for additional (assay) validation experiments. Samples may be used for research to develop methods, assays, prognostics, and/or companion diagnostics related to pathways associated with schizophrenia, and/or mechanism of action of RO6889450.

Details on processes for collection and shipment of these samples can be found in separate sample documentation.

8.8 SAMPLES FOR RESEARCH BIOSAMPLE REPOSITORY

8.8.1 Overview of the Research Biosample Repository

The Roche Research Biosample Repository (RBR) is a centrally administered group of facilities for the long-term storage of human biologic samples, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of the RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests that may allow for individualized drug therapy for patients in the future.

For the RBR, leftover blood samples from participants who give specific consent to participate in this RBR will be stored. RBR samples will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, AEs, or progressive disease.
- To increase knowledge and understanding of disease biology.
- To study treatment response, including drug effects and the processes of drug absorption and disposition.
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays.

8.8.2 Sample Collection

Leftover blood samples will be stored in the RBR and for additional (assay) validation requirements or for other research purposes, including, but not limited to, research on biomarkers related to RO6889450 or schizophrenia.

For all samples, dates of consent and specimen collection should be recorded on the associated RBR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the separate Laboratory Manual.

RBR specimens will be stored and used until ten years after the provision of the CSR. The RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form (ICF) and applicable laws (e.g., Health Authority requirements).

The repository specimens will be subject to the confidentiality standards (as described under Confidentiality and Appendix 1).

8.9 OTHER ASSESSMENTS

8.9.1 Mini International Neuropsychiatric Interview

The MINI (Sheehan et al 1998) is a brief, semi-structured diagnostic interview used to assess DSM-5 disorders and will be used to confirm the diagnosis of schizophrenia for inclusion into this study. The MINI has been validated against the Structured Clinical Interview for DSM diagnoses. The interview with the participant will be conducted by a trained clinician or mental health professional. Administration time is approximately 20 minutes at screening visit only.

8.9.2 Wide Range Achievement Test 4

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.

8.9.3 Wechsler Abbreviated Scale of Intelligence – Second Edition

The Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II) is an intelligence test designed to estimate IQ in individuals aged 6 to 90 years (Wechsler 2011). The WASI-II (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 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 WASI-II four-subtest form should take approximately 30 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. 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.

8.9.4 Ecological Momentary Assessment (EMA)

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.

In the present study, 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.

Data are encrypted and uploaded to secure servers whenever the phone is connected to Wi-Fi or if cellular data is available. If no Wi-Fi network is available and cellular data is unavailable, the sensor data will be transferred during site visits.

The assessment is optional but strongly recommended. The decision not to install the EMA app will not affect the participant's eligibility for the study. Participants can decide at any time point to remove the EMA app from their smartphone.

EMA assessment will not be performed in Japan.

8.9.5 Feedback Questions

Patients will be asked two sets of questions 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. If validated translations become available, they may be used. Equivalent scales may be used, if available.

8.9.6 Premorbid Adjustment Scale

Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al 1982, Rabinowitz et al 2007) 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 across five domains: sociability/ withdrawal, peer relationships, scholastic performance, adaptation to school and socio-sexual functioning (socio-sexual

functioning is not assessed during childhood), 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. PAS is administered by raters on the basis of all available sources of information, including interviews with patients and their family members, mainly parents (a close relationship with the patient during his childhood and adolescence is necessary) as well as medical and school records. PAS 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 should take approximately 30 minutes to administer.

8.10 TIMING OF STUDY ASSESSMENTS

8.10.1 Screening and Pre-treatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms (ICFs) for enrolled participants and for participants who are not subsequently enrolled will be maintained at the study site.

All screening and all pre-treatment assessments (related to entry criteria) must be completed and reviewed to confirm that participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure.

Screening and pre-treatment assessments will be performed within 7 days prior to Day 1, unless otherwise specified. The screening period may be extended after discussion with the Sponsor (Medical Monitor/designee).

During screening, the ECF will be completed. This will include all pertinent information as specified on the ECF. The completed ECF will be forwarded as soon as all requested information is available during screening to the CTM or local Site Monitor via the CRO ePIP system for documentation and monitoring purposes. The Investigator will act as final decision maker regarding exclusion or inclusion of participants in the study.

8.10.2 Assessments during Treatment

Under no circumstances will participants who enroll in this study and who have completed treatment as specified, be permitted to be allocated a new randomization number and re-enroll in the study.

All assessments *should* be performed according to the SoA (see Section 1.3). All assessments must be performed on the day of the specified visit, unless a time window is specified in the SoA (see Section 1.3). Assessments scheduled on the day of study treatment administration *must* be performed prior to administration of study treatment,

unless otherwise noted in the schedule of assessments. Patient-reported outcome (PRO) and clinical outcome assessments (COA) performed by an Investigator/rater *should* be performed prior to the completion of any other study assessments (see Section 1.3 and Table 5). *If the latter cannot be followed, every effort should be made to conduct ECG and vital signs assessments prior to the blood draws (see Section 8.2.2 and Section 8.2.3), and blood draws should be conducted at least 2 hours prior to PRO and COA. In exceptional situations, visits may be split over two consecutive days (as per SoA, see Section 1.3). In case the Baseline visit is split over two consecutive days, study treatment administration must be performed after all assessments have been performed.*

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 Study Period 3 if deemed necessary by the Investigator. Mandatory phone calls, at a minimum once weekly during Study Period 3 and once monthly during the 36-Week Safety Extension Phase will be made by a case manager to follow up with the participants (AE, concomitant treatment and treatment compliance will be assessed).

8.10.3 Assessments at Study Completion/Early Termination Visit

If a participant voluntarily withdraws from the study or is withdrawn by the Investigator during Study Period 2, the participant will be asked to complete Study Period 2 EOT visit as soon as possible after the last dose of study drug. 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 (PANSS, CGI-S, CGI-S MTS, CGI-I and CGI-I MTS), regardless of their adherence to treatment. Participants will also be asked to return for the follow-up visit (4 weeks after the last dose). If a participant voluntarily withdraws from the study or is withdrawn by the Investigator during Study Period 3 or the 36-Week Safety Extension Phase, the participant should return to complete Study Period 3 EOT visit or 36-Week Safety Extension EOT visit, respectively, as soon as possible after the last dose of study drug. Participant will be asked to return for the follow-up visit assessments (4 weeks after the last dose). 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. The primary reason for premature study treatment discontinuation should be documented on the appropriate eCRF. Participants who discontinue study treatment prematurely will not be replaced.

8.10.4 Follow-Up Assessments

Follow-up phone calls will be made approximately 7, 14 and 21 days after the last dose of study drug or after early termination. An on-site follow-up visit will be performed 4 weeks after the last dose of study drug or after early termination.

After the study completion/ETV, adverse events should be followed as outlined in Sections 8.3.1 and 8.3.3.

8.10.5 Assessments at Unscheduled Visits

Assessments at unscheduled visits are based on the medical need of the patient. Assessments that are conducted at regular scheduled visits can be conducted at unscheduled visits at the discretion of the Investigator.

9. STATISTICAL CONSIDERATIONS

9.1 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 and placebo to assess efficacy of each RO6889450 dose.

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

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

The risperidone comparison against placebo is mainly to assess validity of the study (assay sensitivity).

9.2 SAMPLE SIZE DETERMINATION

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. *In case of an unexpectedly high proportion of participants not completing the initial 4 weeks of treatment (i.e., more than 25%), the number of randomized participants may be increased to achieve 200 participants completing the initial 4 weeks of treatment.*

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.

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined in Table 6.

Table 6 Analysis Populations

Population	Description
Efficacy (modified intent-to-treat [ITT])	All randomized participants who received at least one dose of randomized study medication and have the primary efficacy assessments at both baseline and at least one post-baseline. Participants who received study medication different from that to which they were randomized will be included in the group to which they were randomized. The efficacy analysis population will be the primary analysis population for all efficacy data analyses.
Per protocol (PP)	The per-protocol (PP) analysis population will be defined as a subset of the ITT population, 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 ITT patients.
Safety	The safety analysis population will consist of all participants who have received at least one dose of study medication, regardless of whether they withdrew prematurely or not. All safety parameters will be summarized by the initial study medication actually taken for the safety population.
Pharmacokinetic	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.

9.4 STATISTICAL ANALYSES

9.4.1 Demographics and Baseline Characteristics

Demographic information and baseline characteristics will be summarized for all participants randomized. These summaries will be provided for the Safety Population. Summaries will be shown by randomized treatment arm.

9.4.2 Efficacy Analyses

The primary analysis of the study will be performed and interpreted when all randomized patients have completed Period 2 or withdrawn from the study earlier and Period 2 data from all patients have been verified and locked. The primary and secondary efficacy analyses will be based on the Efficacy population defined in Table 7.

The efficacy parameters of continuous variables 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. The model will include independent variables of fixed categorical effects of treatment (4 levels: 45 mg dose of RO6889450, 150 mg dose of RO6889450, risperidone, placebo), assessment weeks (Week 1, Week 2, Week 3, Week 4) and treatment-by-time interaction and a covariate of the baseline value. Factors used for stratification at the time of randomization will be added to the model.

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.

As a supportive analysis, the primary efficacy variable will also be analyzed for the Week 4 assessments by analysis of covariance (ANCOVA) adjusting for baseline values. The model will include the baseline measure and stratification factors as covariate and treatment as the main effect.

Table 7 Efficacy Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Primary:	
Change from baseline in PANSS *total score* at Week 4	Repeated Measures Model as described in Section 9.4.2.
Secondary:	
– Change from baseline in PANSS factor scores – CGI-I and CGI-I MTS – CGI-S and CGI-S MTS	Similar models as described in Section 9.4.2 will be used for change from baseline endpoints of approximately continuous variables
– Proportion of participants with at least 20% or 50% improvement from baseline on PANSS total *and factor* score*s*	Binary data will be evaluated by generalized estimating equation (GEE) method accounting for correlation among repeated measures from the same participant. The GEE model will include terms of treatment, time, and treatment-by-time interaction.
– Time from first randomized treatment intake to readiness for discharge as assessed by RDQ	The time-to-readiness for discharge will be analyzed using an unstratified log rank test. In addition, a stratified log rank test of treatment difference will be performed if the cell sizes are reasonable.
– PANSS total score up to Week 12 – PANSS factor scores up to Week 12 – CGI-S and CGI-S MTS up to Week 12 – CGI-I and CGI-I MTS up to Week 12	Efficacy assessments performed during the Study Period 3 will be analyzed descriptively only.
Exploratory: – SUMD – VAGUS – BCIS – CDSS – Assessment of Sleep, Mood, Well-being and Cognitive Functioning and Treatment Expectancy – WRAT-4 – WASI-II – PGI-C – ReQoL – FTND – EMA – Feedback questions – PAS – PANSS total score up to Week 48 – PANSS factor scores up to Week 48 – CGI-S up to Week 48 – CGI-I up to Week 48	Analysis of exploratory endpoints will be descriptive only.

Adjustment for Multiple Testing
The primary objective of the study is to demonstrate that at least one RO6889450 dose is significantly (overall type I error rate of 0.1, 2-sided) different from placebo. Difference between risperidone and placebo will be tested independently to check internal validity of the study.

To maintain overall type I error rate for multiple testing of the RO6889450 groups, the following two hypotheses will be tested applying the Hochberg's method for adjustment of multiple testing.

a. The larger p-value will be tested at the 0.05 (one-sided) level. When the larger p-value is ≤ 0.05, both null hypotheses are rejected.

b. When the larger p-value is > 0.05 (one-sided), the smaller p-value will be tested at the 0.025 level (one-sided). When it is ≤ 0.025 the null hypothesis is rejected.

Missing Data Handling
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*, if not specified otherwise in the user manuals*.

The main analysis of the primary and secondary continuous efficacy variables will be done using a mixed effects model for repeated measures; no imputation for missing data will be applied.

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

- Timing of discontinuations by treatment group
- Reasons for discontinuation by treatment group and time
- Mean of the primary efficacy variable of those who dropped out vs. those who remained at each scheduled assessment week

9.4.3 Safety Analyses

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

Table 8 Safety Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Adverse events	The original terms recorded on the eCRF by the Investigator for adverse events will be coded by the Sponsor. Adverse events will be summarized by mapped term and appropriate thesaurus level.
Columbia-Suicide Severity Rating Scale (C-SSRS)	The items of the C-SSRS will be summarized and presented by individual listings. The number and percentage of participants will be summarized for each suicidality ideation or behavior (i.e., those marked “yes”) by study treatment and scheduled assessment week. All ratings will be presented by individual listings.
Extrapyramidal symptom rating scale, abbreviated (ESRS-A)	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 CGI-S score by treatment group using descriptive statistics at each scheduled assessment visit. Change from baseline to week 4 score will be summarized using descriptive statistics including the safety population. In addition, participants (n, %) with clinically relevant severity in each of the four symptoms will be summarized All ratings will be presented by individual listings.
Clinical laboratory tests	All clinical laboratory data will be stored on the database in the units in which they were reported. Laboratory test values will be presented in International System of Units (SI units; Système International d’Unités) by individual listings with flagging of abnormal results. *In addition, tabular summaries will be used*
Vital signs	Vital signs data will be presented by individual listings with flagging of values outside the normal ranges and flagging of abnormalities. In addition, tabular summaries will be used.
ECG data analysis	ECG data will be presented by individual listings. In addition, tabular descriptive summaries for the change from baseline in ECG intervals: HR, PQ (PR), QRS, QT, RR, QTcF, T- and U-waves will be displayed.
Concomitant medications	The original terms recorded on the participants’ eCRF by the Investigator for concomitant medications will be standardized by the Sponsor by utilizing a mapped term and appropriate drug dictionary level. Concomitant medications will be presented in summary tables and listings.

9.4.4 Pharmacokinetic Analyses

Population PK analyses using nonlinear mixed effects modelling will be performed as described in Section 8.5. The results of the analysis will be reported separately from the CSR**.** Additional PK, PK-PD, or dose/exposure-response analyses will be conducted as appropriate.

9.4.5 Pharmacodynamic Analyses

All pharmacodynamic (PD) parameters will be presented by listings and descriptive summary statistics separately by group or cohorts. The PD analysis will be presented separately from the main CSR.

9.4.6 Other Analyses

Biomarker exploratory analyses will be specified before database lock.

For ReQoL, all ratings will be presented by individual listings. In addition, tabular summaries will be used.

9.5 INTERIM ANALYSES

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct up to two interim efficacy analyses for internal decision making. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. Any interim analysis 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.

9.6 SUMMARIES OF CONDUCT OF STUDY

The number of participants screened and the total number of participants randomized will be reported. The number of participants prematurely withdrawn from study treatment and the study will be reported.

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

The following section includes standard appendices such as Appendix 1 (For regulatory, ethical and study oversight considerations), Appendix 2 (For AE definitions, reporting) and Appendix 3 (Procedures of recording), Appendix 4 (Clinical laboratory tests), Appendix 5 (Contraceptive guidance and collection of pregnancy information), Appendix 6 (List of Anti-psychotic, Prohibited, and Restricted Medications), and Appendix 7 Assessment of Sleep, Mood, Well-being and Cognitive Functioning and Treatment Expectancy.

Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

1. REGULATORY AND ETHICAL CONSIDERATIONS

1.1. COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws. Studies conducted in the EU/European Economic Area will comply with the EU Clinical Trial Directive (2001/20/EC).

1.2. INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the ICFs, any information to be given to the participant (e.g., advertisements, diaries etc.), and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any participant recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (Section 2.3.1 of this Appendix).

The Investigator should follow the requirements for reporting all adverse events to the Sponsor. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with Health Authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

1.3. INFORMED CONSENT

The Sponsor's Master Informed Consent Form, including the consent form for the 36-Week Safety Extension Phase (and ancillary sample ICFs such as a Child's Assent or Caregiver's Informed Consent Form, if applicable), will be provided to each site. If applicable, it will be provided in a certified translation of the local language. Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that

meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample ICFs or any alternate consent forms proposed by the site (collectively, the “Consent Forms”) before IRB/EC submission. The final IRB/EC‑approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes according to local requirements. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study. A copy of the ICF(s) signed by all parties must be provided to the participant or the participant’s legally authorized representative.

The Consent Forms must be signed and dated by the participant or the participant’s legally authorized representative before his or her participation in the study. The case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the participant to take part. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes if required as per local regulations.

If the Consent Forms are revised (through an amendment or an addendum) while a participant is participating in the study, the participant or a legally authorized representative may be re-consented by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study. The study team will provide guidance for which patients need to re-consent in the event of an update to the Consent form.

A copy of each signed Consent Form must be provided to the participant or the participant’s legally authorized representative. All signed and dated Consent Forms must remain in each participant’s study file or in the site file and must be available for verification by study monitors at any time.

Participants who are re-screened may be required to sign a new ICF.

Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The Investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will

be told that they are free to refuse to participate and may withdraw their samples at any time and for any reason during the storage period. A separate, specific signature will be required to document a participant's agreement to provide RBR samples. Participants who decline to participate will not provide a separate signature.

The Investigator should document whether or not the participant has given consent to participate by completing the RBR Sample Informed Consent eCRF.

In the event of death or loss of competence of a subject who is participating in the Research, the participant's samples and data will continue to be used as part of the RBR.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol will not be applicable at that site

Withdrawal from the Research Biosample Repository

Participants who give consent to provide samples for the RBR have the right to withdraw their samples at any time for any reason. If a participant wishes to withdraw consent to the testing of his or her samples, the Investigator must inform the Medical Monitor and Site Monitor in writing of the participant's wishes using the RBR Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Withdrawal of Informed Consent eCRF. The participant will be provided with instructions on how to withdraw consent after the trial is closed. A participant's withdrawal from Study BP41743 does not, by itself, constitute withdrawal of samples from the RBR. Likewise, a participant's withdrawal from the RBR does not constitute withdrawal from Study BP41743. Data already generated before time of withdrawal of consent to RBR will still be used.

1.4. CONFIDENTIALITY

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant

names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

Medical information may be given to a participant's personal physician or other appropriate medical personnel responsible for the participant's welfare, for treatment purposes.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted clinical study reports and other summary reports will be provided upon request.

Confidentiality for Research Biosample Repository

Data generated from RBR samples must be available for inspection upon request by representatives of national and local Health Authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Participant medical information associated with RBR samples is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Data derived from RBR sample analysis on individual participants will generally not be provided to study Investigators unless a request for research use is granted. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

Genetic research data and associated clinical data may be shared with researchers who are not participating in the study or submitted to government or other health research databases for broad sharing with other researchers. Participants will not be identified by name or any other personally identifying information. Given the complexity and

exploratory nature of these analyses, genetic data and analyses will not be shared with Investigators or participants unless required by law.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR sample data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

Monitoring and Oversight Research Biosample Repository

Samples collected for the RBR will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to participant participation in RBR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and Health Authority inspections by providing direct access to source data and documents related to the samples.

1.5. FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate Health Authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study (i.e., LPLV).

2. DATA HANDLING AND RECORD

2.1. DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

2.1.1. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

2.1.2. Clinical Outcome Assessment Data

The study will use both electronic and paper, clinical outcome assessment (COA) data.

2.1.2.1 Electronic Clinical Outcome Assessment Data

Participants, central raters and site clinicians will use an electronic device to complete electronic clinical outcome assessments (eCOAs). The data will be transmitted via electronically to a centralized database at the eCOA vendor. The data may be reviewed by site staff via secure access to a web. Entries should be reviewed for completeness by the site staff during the visit. Sites should only use paper forms if there are issues with the electronic device. A backup device will be provided to each site in the event of device issues. Once the study is complete, the eCOA data, audit trail, and trial and system documentation will be archived. The Investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality storage device (e.g., compact disc, USB drive) that must be kept with the study records as source data. Acknowledgement of receipt of the data is required. In addition, the Sponsor will receive all patient data in a machine-readable format.

eCOA data will be collected using an electronic device provided by an eCOA vendor. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR Part 11). System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

2.1.2.2. Paper Clinical Outcome Assessment Data

Participants will use paper booklets to capture COA data All item-level, score data will be entered into electronic data capture (EDC). All original forms on which participants records responses are source documentation as described in Section 2.1.3 of this Appendix. Entries on the paper forms should be reviewed for completeness by the site staff during the visit.

2.1.3. Source Data Records

Source documents (paper or electronic) are those in which participant data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, COAs (paper or eCOA), evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays,

patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data must be defined in the Trial Monitoring Plan.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described below.

To facilitate source data verification, the Investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable Health Authorities.

2.1.4. Use of Computerized Systems

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with Health Authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

2.2. RETENTION OF RECORDS

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for at least 15 years after study completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities.

2.3. STUDY RECORDS

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully reconstructed, including but not limited to the protocol, protocol amendments, ICFs, and documentation of IRB/EC and governmental approval.

Roche shall also submit an Annual Safety Report once a year to the IEC and CAs according to local regulatory requirements and timelines of each country participating in the study.

2.3.1. Protocol Amendments

Any substantial protocol amendments will be prepared by the Sponsor. Substantial protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or any non-substantial changes, as defined by regulatory requirements.

2.3.2. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor for approval prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating Investigator will be designated by mutual agreement.

Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate Sponsor personnel.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

2.3.3. Dissemination of Clinical Study Data

A clinical study report containing the results of this trial will be made available to anyone who requests a copy. A description of this clinical trial and a summary of its results will be available at http://www.ClinicalTrials.gov and https://eudract.ema.europa.eu.

2.3.4. Management of Study Quality

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

2.3.5. Site Inspections

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, participants' medical records, and eCRFs. The Investigator will permit national and local Health Authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

4. STUDY AND SITE CLOSURE

The Sponsor (or designee) has the right to close the study site or terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to participants.
- Participant enrollment is unsatisfactory.
- The Sponsor decides to discontinue the development program.

The Sponsor will notify the Investigator and Health Authorities if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study treatment development.

Appendix 2
Adverse Events: Definitions and Procedures for Evaluating, Follow-up and Reporting

1. DEFINITION OF ADVERSE EVENTS

According to the E2A ICH guideline for Good Clinical Practice, an **adverse event** is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event can therefore be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Events Meeting the AE Definition:

- Deterioration in a laboratory value (hematology, clinical chemistry, or urinalysis) or other clinical test (e.g., ECG, X−ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment (see Appendix 3, Section 4).
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

“Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE unless the progression is unexpectedly accelerated and not in line with the natural history of the disease. If the “Lack of efficacy” would not require safety reporting such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

2. DEFINITION OF SERIOUS ADVERSE EVENTS

If an event is not an AE per definition above, then it cannot be a serious adverse event (SAE) even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that at any dose:

- **Results in death.**
- **Is life-threatening.**

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization** (see Appendix 3).

  In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.

  Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- **Results in persistent or significant disability/incapacity**

  Disability means substantial disruption of the participant’s ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- **Is a congenital anomaly/birth defect**.
- **Other significant events**:

  Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

3. RECORDING OF ADVERSE EVENT AND/OR SERIOUS ADVERSE EVENT

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information in the CRF.

It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Medical Monitor in lieu of completion of the eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

3.1. ASSESSMENT OF SEVERITY

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe) the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event.

Table 1 Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see above).

3.2. ASSESSMENT OF CAUSALITY

Investigators should use their knowledge of the participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study treatment.
- Course of the event, considering especially the effects of dose-reduction, discontinuation of study treatment.
- Known association of the event with the study treatment or with similar treatments.
- Known association of the event with the disease under study.
- Presence of risk factors in the participant or use of concomitant medications known to increase the occurrence of the event.
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

For participant receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

4. FOLLOW-UP OF AES AND SAES

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.

New or updated information will be recorded in the originally completed eCRF.

The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

5. IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The Investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the Investigator learns of the event. The following is a list of events that the Investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study treatment:

- Serious adverse events
- Non-serious adverse events of special interest (NSAESI)
- Pregnancies (see Section 8.3.5)

The Investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis.
- Significant new diagnostic test results.
- Change in causality based on new information.
- Change in the event's outcome, including recovery.
- Additional narrative information on the clinical course of the event.

Investigators must also comply with local requirements for reporting serious adverse events to the local Health Authority and IRB/EC.

5.1 REPORTING REQUIREMENTS OF SERIOUS ADVERSE EVENTS, AND NON-SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST

Events that Occur prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to Investigators should be completed and submitted to the Serious Adverse Event Responsible immediately (i.e., no more than 24 hours after learning of the event).

Events that Occur after Study Treatment Initiation

For reports of serious adverse events and non-serious adverse events of special interest (Section 8.3.6) that occur after initiation of study treatment (Section 8.3.1), Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the appropriate Adverse Event of Special Interest/ Serious Adverse Event eCRF form and submit the report via the EDC system. A report will be generated and sent to the Sponsor's Safety Risk Management department.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to Investigators should be completed and submitted to the Serious Adverse Event Responsible immediately (i.e., no more than 24 hours after learning of the event).

Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Reporting of Post-Study Adverse Events and Serious Adverse Events

If the Investigator becomes aware of any other serious adverse event occurring after the end of the AE reporting period, if the event is believed to be related to prior study treatment the event should be reported directly to the Sponsor or its designee, either by faxing or by scanning and emailing the SAE Reporting Form using the fax number or email address provided to Investigators.

5.2 REPORTING REQUIREMENTS FOR CASES OF OVERDOSE, MEDICATION ERROR, DRUG ABUSE, OR DRUG MISUSE

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is two times higher in a day than the assigned dose at any arm.
- Intentional overdose: intentional administration of a drug in a quantity that is two times higher in a day than the assigned dose at any arm.
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse.

  In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). For RO6889450 or matching placebo or Risperidone, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with RO6889450 or matching placebo or Risperidone, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and should be recorded as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.

- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require the completion of two Adverse Event eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

6. EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and NSAESI against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators, IRBs, ECs, and applicable Health Authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed below:

Drug	Document
RO6889450	RO6889450 Investigator's Brochure
Risperidone	US Product Information (USPI)

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

Appendix 3
Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

1. DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

2. ADVERSE EVENTS OCCURRING SECONDARY TO OTHER EVENTS

In general, adverse events occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all 3 events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

3. PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation time-points. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent adverse event is one that resolves between participant evaluation time-points and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the Adverse Event eCRF.

4. ABNORMAL LABORATORY VALUES

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy.
- Clinically significant in the Investigator's judgment.

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase [ALP] and bilirubin 5 times the upper limit of normal [ULN] associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium", as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia".

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5. ABNORMAL VITAL SIGN VALUES

Not every vital sign abnormality qualifies as an adverse event. A vital sign result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention or a change in concomitant therapy.
- Clinically significant in the Investigator's judgment.

It is the Investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high BP), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

6. ABNORMAL LIVER FUNCTION TESTS

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, Investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN.
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice.

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 8.3) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 8.3).

7. DEATHS

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5 of Appendix 2), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor. This includes death attributed to progression of schizophrenia.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, “unexplained death” should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), “unexplained death” should be replaced by the established cause of death. The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

8. PREEXISTING MEDICAL CONDITIONS

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

9. LACK OF EFFICACY OR WORSENING OF SCHIZOPHRENIA

Medical occurrences or symptoms of deterioration that are anticipated as part of schizophrenia should be recorded as an adverse event if judged by the Investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of schizophrenia on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., “worsening of schizophrenia”).

10. HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Appendix 2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for wash out of previous medication, study treatment administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

  The participant has not suffered an adverse event.

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available.

11. PATIENT-REPORTED OUTCOME DATA (COA DATA REPORTED DIRECTLY BY PATIENT)

"Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the Investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF."

Appendix 4
Clinical Laboratory Tests

The tests detailed in Table 1, with the exception of urinalysis, urine dipstick alcohol test, drugs of abuse, urine pregnancy test, COVID-19 test (when not performed centrally), *and erythrocyte sedimentation rate (ESR)*, will be performed by the central laboratory. If the local laboratory results are used, the results must be captured in source documentation and entered into the eCRF.

Local laboratory results may be utilized in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, with the exception of urinalysis, drugs of abuse, and urine pregnancy test, it is important that the sample for central analysis be obtained at the same time.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and 5.2, respectively, of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 1 Protocol-Required Safety Laboratory Assessments

All study-required laboratory assessments, with the exception of urinalysis, urine dipstick alcohol test, drugs of abuse, urine pregnancy test, COVID-19 test (when not performed centrally), *and ESR*, will be performed by a central laboratory. In cases where an immediate result is required for a particular laboratory test, the sample can be divided and sent to both a local laboratory and the designated central laboratory.

Laboratory Assessments	Parameters
Hematology	• Leucocytes, erythrocytes, hemoglobin, hematocrit, platelets, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes.
Clinical Chemistry	• Sodium, potassium, chloride, bicarbonate, glucose fasting, glycated hemoglobin, urea, creatinine, protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST, urate, lactate dehydrogenase (LDH), C-reactive protein (CRP) • Prolactin (all patients), follicle stimulating hormone (FSH, post-menopausal females, as applicable).
Coagulation	• International normalized ratio (INR), activated partial thromboplastin time (aPTT), PT.
Viral Serology	• PCR COVID-19 testing, or other COVID-19 diagnostic tests when available. HIV (specific tests HIV-1 antibody, HIV-1/2 antibody, HIV-2 antibody), hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (HBcAb), hepatitis C virus (HCV) antibody. In cases where HCV was successfully treated, a positive HCV serology result can be followed by HCV RNA testing
Lipids	• Fasting: Cholesterol, low-density lipoproteins (LDL) cholesterol, high-density lipoproteins (HDL) cholesterol, triglycerides.
Pregnancy Test	• 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. • Serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential).
Urinalysis	• Specific gravity • Dipstick: pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase • If there is a clinically significant positive result, urine will be sent to the laboratory for microscopy and culture. If there is an explanation for the positive dipstick results (e.g., menses), it should be recorded and there is no need to perform microscopy and culture. • Microscopic examination if deemed necessary will include sediment, RBCs, white blood cells (WBCs), casts, crystals, epithelial cells, and bacteria.
Other Screening Tests	• Drugs of abuse will be measured in urine: cannabinoids (including cannabidiol), amphetamines, methamphetamines, opiates, buprenorphine, methadone, cocaine, benzodiazepines, and barbiturates. Alcohol levels will be tested using a urine dipstick test.

Laboratory Assessments	Parameters
Vasculitis Monitoring Tests	• *C-reactive protein (CRP) (part of the chemistry panel), erythrocyte sedimentation rate (ESR), anti-neutrophil cytoplasmic antibodies (ANCA), anti-nuclear antibodies (ANA), anti-double-stranded DNA (anti-dsDNA) antibodies, anti-phospholipid antibodies*

Investigators must document their review of each laboratory safety report.

Prolactin levels that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Additional Statistical Considerations for Clinical Laboratory Data

- Standard Reference Ranges and Transformation of Data

Potential analysis considerations for analyzing Laboratory data includes the use of Standard Reference Ranges and potential transformation of data for specific lab tests.

In this scenario, Roche standard reference ranges, rather than the reference ranges of the Investigator, can be used for specific parameters. For these parameters, the measured laboratory test result will be assessed directly using the Roche standard reference range. Certain laboratory parameters will be transformed to Roche's standard reference ranges.

A transformation will be performed on certain laboratory tests that lack sufficiently common procedures and have a wide range of Investigator ranges, e.g., enzyme tests that include AST, ALT, and ALP and total bilirubin. Since the standard reference ranges for these parameters have a lower limit of zero, only the upper limits of the ranges will be used in transforming the data.

- Definition of Laboratory Abnormalities

For all laboratory parameters included in this analysis, there exists a Roche predefined standard reference range. Laboratory values falling outside this standard reference range will be labeled "H" for high or "L" for low in participant listings of laboratory data.

In addition to the standard reference range, a marked reference range has been predefined by Roche for these laboratory parameters. The marked reference range is broader than the standard reference range. Values falling outside the marked reference range that also represent a defined change from baseline will be considered marked laboratory abnormalities (i.e., potentially clinically relevant). If a baseline value is not available for a participant, the midpoint of the standard reference range will be used as the participant's baseline value for the purposes of determining marked laboratory abnormalities. Marked laboratory abnormalities will be labeled in the participant listings as "HH" for very high or "LL" for very low.

Appendix 5
Contraceptive Guidance and Collection of Pregnancy Information

1. DEFINITIONS

- **Woman of Childbearing Potential (WOCBP)**

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

- **Women in the following categories are considered to be Woman of Non-Childbearing Potential (WONCBP)**

a) Pre-menarchal

b) Pre-menopausal female with one of the following:

- Documented hysterectomy.
- Documented bilateral salpingectomy.
- Documented bilateral oophorectomy.

  Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

c) Post-menopausal female

- A post-menopausal state is defined as no menses for ≥ 12 months without an alternative medical cause other than menopause. A high follicle-stimulating hormone (FSH) level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status before study enrollment.

2. CONTRACEPTION GUIDANCE

- **Female Participants**

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g.,

calendar, ovulation, symptothermal, or post ovulation methods) and withdrawal are not acceptable methods of contraception.

Female participants of childbearing potential are eligible to participate if they agree to use highly effective method of contraception consistently and correctly as described in Table 1 below.

Per ICH M3(R2), highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly as described in Table 1 below.

Table 1 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User-Dependent[a] (Failure rate of < 1% per year when used consistently and correctly)

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  ○ Oral
  ○ Intravaginal
  ○ Transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation:
  ○ Oral
  ○ Injectable

Highly Effective Methods That Are User-Independent (Failure rate of < 1% per year)
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[a] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Acceptable Birth Control Methods Which May Not Be Considered As Highly Effective (Failure rate of > 1% per year when used consistently and correctly)
• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the Primary mode of action • Male or female condom with or without spermicide [b] • Cap, diaphragm or sponge with spermicide [b]

a) Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

b) A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods. i.e., when the risk of teratogenicity and genotoxicity is unlikely.

3. PREGNANCY TESTING

For WOCBP enrolled in the study, blood sample and urine pregnancy tests will be performed according to Schedule of Activity tables (see Section 1.3). If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test.

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected and according to local practice.

4. COLLECTION OF PREGNANCY INFORMATION

- **Female participants who become pregnant**

The Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study (see Section 8.3.5 Pregnancy). Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, which will be forwarded to the Sponsor. Monitoring of the participant should continue until conclusion of the pregnancy. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is not considered to be an AE or SAE, and should not be recorded on the AE eCRF, any pregnancy complication will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study treatment by the Investigator, will be reported to the Sponsor as described in Appendix 2. While the Investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

5 ABORTIONS

Any spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5 of Appendix 2).

Any induced abortion due to maternal toxicity and/or embryo-fetal toxicity should also be classified as serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5 of Appendix 2).

Elective or therapeutic abortion not associated with an underlying maternal or embryo-fetal toxicity (e.g., induced abortion for personal reasons) does not require expedited reporting but should be reported as outcome of pregnancy on the Clinical Trial Pregnancy Reporting Form.

6 CONGENITAL ANOMALIES/BIRTH DEFECTS

Any congenital anomaly/birth defect in a child born to a female participant exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF (prior to database lock), and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5 of Appendix 2).

Appendix 6
List of Anti-psychotic/Rescue, Prohibited, and Restricted Medications

Table 1 Anti-psychotic/rescue medications

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 72 hours prior to the first dose of study medication *and* 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 72 hours prior to the first dose of study medication *and* 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 deaconate. 2 months • haloperidol decanoate. 2 months • olanzapine LAI. 2 months	Permitted as prior medication if *it* had been stopped before the indicated *time* period*s* prior to *the first dose of study medication. Prohibited during Study Periods 2 and 3 and the 36-Week Safety Extension Phase (blinded treatment).* Note: Single doses (before reaching steady state) of aripiprazole, brexpiprazole*, or* blonanserin administered to control current exacerbation *may be used (upon discussion with the Medical Monitor) but not within 72 hours prior to the first dose of study medication* upon 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 *time* periods prior to *the first dose of study medication*. Participants excluded if there is a history of lack of response or intolerance to risperidone or paliperidone. *Prohibited during Study Periods 2 and 3 and the 36-Week Safety Extension Phase (blinded treatment).*
• clozapine	Excluded any use in previous 12 months before screening, *or* any lifetime use at doses of 200 mg/day or greater.

Table 2 Prohibited Therapies

Type of medication	Timelines and instructions
Illegal substance use (including legal cannabis) : opiates, amphetamine, barbiturate, cocaine, cannabis, cannabidiol, or hallucinogens	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.

Table 3 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) • *propranolol* (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.
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 7
Assessment of Sleep, Mood, Well-being and Cognitive Functioning and Treatment Expectancy

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 28 ±1)

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

Placebo ☐

Study drug ☐