Official Title: Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Effects of RO6889450 (Ralmitaront) in Patients With Schizophrenia or Schizoaffective Disorder and Negative Symptoms

NCT Number: NCT03669640

Document Dates: Protocol Version 6: 27-September-2021

PROTOCOL

TITLE:	**PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFECTS OF RO6889450 (RALMITARONT) IN PATIENTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER AND NEGATIVE SYMPTOMS**
PROTOCOL NUMBER:	BP40283
VERSION:	6
IND NUMBER:	[redacted]
TEST PRODUCT:	RO6889450
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 27 June 2018
DATE AMENDED:	Version 2: 23 May 2019 Version 3: 12 March 2020 Version 4: 10 July 2020 Version 5: 15 Sep 2020 Version 6: See electronic date stamp below

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
27-Sep-2021 07:04:49	Company Signatory	[redacted]

PROTOCOL ACCEPTANCE FORM

TITLE:	**PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFECTS OF RO6889450 (RALMITARONT) IN PATIENTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER AND NEGATIVE SYMPTOMS**
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TEST PRODUCT:	RO6889450
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 Study Monitor.

PROTOCOL AMENDMENT, VERSION 6: RATIONALE

Version 6 was implemented to allow enrollment of participants without prior approval by the Medical Monitor. Additional changes have been made, as specified below.

- **Section 1.3, Table 2 Footnote 24 (new) and Appendix 4:** The requirements for blood sampling to assess antipsychotic drug blood levels are clarified.

- **Section 2.3 Benefit/Risk Assessment:** A statement has been added to clarify the impact of the Covid-19 pandemic on the benefit/risk assessment of this study protocol.

- **Section 4.1 Overall Study Design; Section 5.1 Inclusion Criteria (#4 and #5); Section 5.2 Exclusion Criteria (#13); Section 8.2.7 Medical History and Demographic Data; Section 8.11.1 Screening and Pretreatment Assessments; and Appendix 6:** Medical Monitor language was updated to reflect new guidelines on medical monitoring in accordance with ICH E6(R2) 4.3.1.

- **Section 5.1 Inclusion Criteria:**
  - Inclusion Criterion #4: Version 6 clarifies the stability requirements of antipsychotics.
  - Inclusion Criterion #5 Version 6 clarifies, that medication changes within the three months prior to screening are permitted, if not associated with medical stability.
  - Inclusion Criterion #10 Version 6 increases the upper limit of the body mass index from 35 to 40 kg/m^2 (inclusive) to adequately reflect the patient population in this study.

- **Section 5.2 Exclusion Criteria:**
  - Exclusion Criterion #4 Version 6 further clarifies the scoring requirements.
  - Exclusion Criterion #13 has been amended to clarify that laboratory tests of uncertain or questionable results may be accepted if they are, in the opinion of the Investigator, not clinically significant.
  - Exclusion Criterion #16. The history of clozapine treatment has been further clarified.

- **Section 6.5.2. Permitted Therapy:** This section has been updated to allow changes in D2/5HT2A antagonists or D2 partial agonist medication if the change is not associated with the participant's psychiatric stability. Treatment changes may be acceptable up to a minimum of three months prior to screening. Confirmation that SARS-CoV-2 vaccines were permitted during the study was also added.

- **Section 6.5.3. Prohibited Therapy:** Language has been updated to remove Sponsor acceptance for new concomitant medication.

- **Section 8.11.2. Assessments During Treatment:** Guidelines for the order of assessments have been revised.

- **Section 9.2 Sample Size Determination:** This section was updated to allow an increase in the sample size of Part B in case of an unexpectedly high number of participants not completing 12 weeks of treatment.

Minor corrections and clarifications have also been made. New text is shown in *Book Antiqua italics*.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
5HT2A	Serotonin 2A receptor
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BACS	Brief Assessment of Cognition in Schizophrenia
BMI	Body Mass Index
BNSS	Brief Negative Symptom Scale
CGI-I	Clinical Global Impression of Improvement
CGI-I NS	Clinical Global Impression of Improvement negative symptoms
CGI-S	Clinical Global Impression of Severity
CGI-S NS	Clinical Global Impression of Severity negative symptoms
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*
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTM	*Site Clinical Team Manager*
D2	dopamine 2 receptor
DLE	dose limiting events

Abbreviation	Definition
DNA	Deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders , Fifth Edition
DPAS	Defeatist Performance Attitude Scale
EC	Ethics Committee
ECF	Eligibility $Checklist$ Form
ECB	Effort-choice benefit
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eCOA	Electronic clinical outcome assessment
EMA	Ecological Momentary Assessment
EOT	End of treatment
EPS	Extrapyramidal symptoms
ESF	Eligibility screening form
ESRS-A	Extrapyramidal symptom rating scale, abbreviated
EU	European Union
FDA	Food and Drug Administration
FMO1	Flavin containing monooxygenase
FSH	Follicle-stimulating hormone
FSIQ	Full Scale Intelligence Quotient
FTND	Fagerström Test for Nicotine Dependence
HCV	Hepatitis C
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HLA	human leukocyte antigen
HR	heart rate
ICF	Informed Consent Form
ICH	International Council for Harmonisation
iDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
ITT	intent-to-treat
IMP	Investigational medicinal product
IND	Investigational New Drug (application)
IQ	Intelligence quotient

Abbreviation	Definition
IC-PANSS	Informant checklist Positive and Negative Syndrome Scale
IRB	Institutional Review Board
IxRS	Interactive (voice/web) response system
LDH	Lactate dehydrogenase
LPLO	Last participant, last observation
MAD	Multiple-ascending doses
MDR1	Multidrug resistance protein 1
MEDNO	Medication number
MINI	Mini International Neuropsychiatric Interview
MTD	Maximum tolerated dose
MTS	Most troubling symptom
NCI CTCAE	National Cancer Institute Common terminology criteria for adverse events
NMDA	N-methyl-D-aspartate
NSAESI	Non-serious adverse event of special interest
OTC	Over-the-counter

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFECTS OF RO6889450 (RALMITARONT) IN PATIENTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER AND NEGATIVE SYMPTOMS**
PROTOCOL NUMBER:	BP40283
VERSION:	6
TEST PRODUCT:	RO6889450
PHASE:	II

RATIONALE

The trace amine-associated receptor 1 (TAAR1) partial agonist RO6889450, a modulator of dopaminergic transmission, leads to a normalization of behaviors in rodent models of negative symptoms of schizophrenia. Results of a clinical study with RO6889450 in healthy volunteers suggest performance improvements in tasks that probe reward-based learning and motivated behavior, functions that are deficient in patients with negative symptoms (e.g., blunted affect, avolition/apathy). These results indicate a potential utility of RO6889450 in the treatment of negative symptoms associated with schizophrenia or schizoaffective disorder.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
Part A: To compare the efficacy of [redacted] once daily (QD) of RO6889450 as monotherapy with placebo on negative symptoms in patients with schizophrenia or schizoaffective disorder. Part B: To compare the efficacy of [redacted] QD of RO6889450 as add-on therapy with placebo on negative symptoms in patients with schizophrenia or schizoaffective disorder.	Part A & B: Change from baseline at Week 12 in the Brief Negative Symptoms Scale (BNSS) avolition/apathy subscore (sum of items "behavior" and "internal experience").

Objectives	Endpoints
• **Secondary**	
To compare the effect of RO6889450 with placebo on: • Clinical Global Impression Severity (CGI-S) and change (CGI-I) (overall and negative symptoms)	• Change from baseline in CGI-S and CGI-S negative symptoms scores • CGI-I, and CGI-I negative symptoms scores
To compare the effect of RO6889450 with placebo on: • Symptoms of schizophrenia or schizoaffective as assessed with the Positive and Negative Syndrome Scale (PANSS), BNSS, and Defeatist Performance Attitude Scale (DPAS)	• Change from baseline in PANSS total and symptom factor scores • Change from baseline in BNSS total and subscores • Change from baseline in DPAS scores
• To compare the safety and tolerability of 12 weeks of treatment with RO6889450 as monotherapy (Part A) or add-on therapy with placebo (Part B)	• 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 vital signs • 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, coagulation and urinalysis test results • Change from baseline in Columbia-Suicide Severity Rating Scale (C-SSRS) and Extrapyramidal symptom rating scale, abbreviated (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, of RO6889450-derived metabolite(s) • Cmax of RO6889450 and, if feasible, of RO6889450-derived metabolite(s) • Other PK parameters as appropriate

OVERALL DESIGN

This is a Phase 2, multicenter, randomized, double-blind, two-part, placebo-controlled, parallel-group, study in patients with schizophrenia or schizoaffective disorder.

Study Design

Part A (monotherapy):

Participants will be washed out (one week) from their antipsychotic therapy before being randomized to either [redacted] QD of RO6889450 or placebo for 12 weeks. Stratification will be based on baseline BNSS avolition/apathy subscore (BNSS ≤6 vs >6), age (18-35 years vs. 36-55 years), and sex. The participants will have the option of an inpatient stay or partial hospitalization during the washout period as well as the first week of study drug.

Part B (add-on therapy):

Participants will be randomized 1:1:1 to [redacted] QD of RO6889450, [redacted] QD of RO6889450, or placebo for 12 weeks. Stratification will be based on region (Ex-Japan; Japan). For non-

Japanese sites, stratification will additionally be based on baseline BNSS avolition/apathy subscore (sum of items "behavior" and "internal experience"; ≤6 vs. >6), age (18-35 years vs. 36-55 years), sex, and antipsychotic treatment (1:1 stratification ratio between dopamine 2 receptor [D2]/serotonin 2A [5HT2A] receptor antagonists and D2 partial agonist). For Japanese sites, stratification will additionally be based on antipsychotic treatment (1:1 stratification ratio between dopamine 2 receptor [D2]/serotonin 2A receptor [5HT2A] antagonists and D2 partial agonist). Approximately equal numbers of participants on D2/5HT2A antagonists or D2 partial agonists will be enrolled.

Participants who were screened for, but not enrolled in Part A can be screened for Part B *if meeting criteria for re-screening and* only after *discussion with* the Medical Monitor or delegate. The reason(s) for the decision must be documented.

Part B is planned to start after Part A. If the result of Part A is negative, the Sponsor may choose not to conduct Part B.

Interim analyses:

The Sponsor may choose to conduct an interim efficacy analysis in Part A. 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. The interim analysis will be performed and interpreted by members of the Sponsor 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.

The results of this analysis may support initiation of Part B enrollment during Part A if a positive results threshold is met as defined in the statistical analysis plan (SAP). In case of very slow recruitment, Part A may be stopped and/or Part B may be started without the interim analysis.

The Sponsor may choose to conduct up to two additional interim analyses of Part B to determine the chance of final success. The results of such an analysis may support an early termination of Part B. 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. The interim analysis will be performed and interpreted by members of the Sponsor 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.

Treatment Groups and Duration

The investigational medicinal product (IMP) is RO6889450 (and matching placebo) and will be given orally QD at a daily dose of [redacted] in Part A and at a daily dose of either [redacted] in Part B.

Length of Study

Part A: The total duration will be approximately 147 days (from screening through study completion) for each enrolled participant as follows:

- Screening: up to 35 days (including the placebo compliance and a 7-day washout period)
- Treatment period: 84 days (12 weeks)
- Follow up: 28 days

Part B: The total duration will be up to approximately 154 days (from screening through study completion) for each enrolled participant as follows:

- Screening: up to 42 days (including the placebo compliance period)
- Treatment period: 84 days (12 weeks)
- Follow up: 28 days

End of Study

The end of the study is defined as the date when the last participant last observation (LPLO) occurs. LPLO is expected to occur approximately 28 days after the last participant's last dose.

Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will regularly review unblinded safety and efficacy (as appropriate) data for Part A of the study. The iDMC will be composed of at least two psychiatrists external to the Sponsor and will be responsible for monitoring safety data to help assure that continuation of the study in its current design does not pose unacceptable safety risks to participants. Planned and ad hoc safety reviews will be performed as described within the iDMC charter.

PARTICIPANT POPULATION

The participants of this study will be male and female outpatients between 18 to 55 years of age with a Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnosis of schizophrenia or schizoaffective disorder with negative symptoms, who are stable. For Part B, participants also need to be stable on antipsychotic treatment. Participants who are in a residential inpatient setting are eligible for this study.

Inclusion/Exclusion Criteria

Unless otherwise stated, inclusion and exclusion criteria refer to evaluations or assessments at screening.

Inclusion Criteria:

Informed Consent

1. Able and willing to provide written informed consent according to International Council for Harmonisation (ICH) and local regulations as assessed using the Evaluation to Sign Consent. If the participant has a legal representative, the informed consent must be signed by this person.

Patient and Disease Characteristics

2. Male or female participants aged 18-55 years (inclusive).
3. Patients with a DSM-5 diagnosis of schizophrenia or schizoaffective disorder as confirmed by the Mini International Neuropsychiatric Interview (MINI).
4. **Part B only:** Stable treatment with a D2/5HT2A antagonists or pure D2 *antagonist(s)* or a D2 partial agonist for a minimum of six months and receiving no more than two antipsychotics (if no blood concentration of the prescribed antipsychotic medication [or active metabolites] is detected, the participant, should not be enrolled). Antipsychotic regimen: *participants* must be on a "primary" antipsychotic and may be on a secondary antipsychotic. *Note: compliance* of *blonanserin and perospirone will be monitored via informant report. The* secondary antipsychotic *dose* has to be equal to or less than the equivalent dose of the primary antipsychotic. *The* sum of the primary and secondary antipsychotics must be ≤ 6 mg of risperidone equivalents. Participants who have had a change of medication not associated with a change in the participant's psychiatric stability in the *Investigator's* opinion (e.g., insurance reasons*, adjustment of dose*) in the six months prior to screening may be considered for entry into the study*; however no change of antipsychotic medication regimen will be allowed within 3 months prior to screening*.
5. Medically stable during the prior three months. Medication changes (other than antipsychotics) in the three months prior to screening may be acceptable*, if, in the opinion of the Investigator, the change of medication does not affect the participant's medical stability throughout the duration of the study*
6. Participant is outpatient with no psychiatric hospitalizations within the prior six (6) months (hospitalization for social management within this time is acceptable).
7. PANSS-NSFS score of 18 or higher.
8. The following rating on items of the PANSS:
    (a) less than 5 on G8 (uncooperativeness), P1 (delusions), P3 (hallucinations), P4 (excitement/hyperactivity), and P6 (suspiciousness/persecution)
    (b) less than 4 on P7 (hostility) and G14 (poor impulse control)
9. Has an informant who is considered reliable by the Investigator to provide support to the participant and to help ensure compliance with study visits and protocol procedures; who

preferably is also able to provide input helpful for completing study rating scales and is in regular contact with the participant in order to be able to alert the Investigator of worsening signs and symptoms for the participant.

10. Body mass index (BMI) between 18 and 40 kg/m^2 inclusive.

Reproductive

11. A woman is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:
    (a) Not a woman of childbearing potential (WOCBP).
    (b) WOCBP, who

    - agrees 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, male sterilization, 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.

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.

Exclusion Criteria:

Medical Conditions

1. **Part A only:** Confirmed suicidal behavior based on Investigator judgment or violent behavior resulting in injury or property damage in the prior five years. A history prior to the last five years requires approval by the PRC on a case-by-case basis.
2. **Part A only:** Lifetime history of homicidal behavior.
3. Moderate to severe substance use disorder within six months (excluding nicotine) as defined by DSM-5.
4. Any ESRS-$A\ CGI\ subscore$ greater or equal to 3.
5. Other current DSM-5 diagnosis (e.g., bipolar disorder, major depressive disorder).
6. PANSS item G6 (depression) greater than or equal to 5.
7. Significant risk of suicide or harming him- or herself or others according to the Investigator's judgment.
8. A prior or current general medical condition that might be impairing cognition or other psychiatric functioning (e.g., migraine headaches requiring prophylactic treatment, head trauma, dementia, seizure disorder, stroke; or neurodegenerative, inflammatory, infectious, neoplastic, toxic, metabolic, endocrine conditions).
9. Positive result at screening for hepatitis B surface antigen (HBsAg), hepatitis C (hepatitis C antibody), or human immunodeficiency virus (HIV)-1 and -2. HCV antibody positive patients are eligible if HCV RNA is negative.
10. Tardive dyskinesia that is moderate to severe or requires treatment.
11. History of neuroleptic malignant syndrome.
12. 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.

13. Clinically significant abnormalities in laboratory safety test results (including hepatic and renal panels, complete blood count, chemistry panel, coagulation, and urinalysis), including:
    - Aspartate transaminase (AST), alanine transaminase (ALT) >2 × upper limit of normal (ULN)
    - Total bilirubin >1.5 ULN with the exception of Gilbert syndrome
    - Serum creatinine >1.5 ULN

    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.
14. Significant or unstable physical condition that in the Investigator's judgment might require a change in medication or hospitalization during the course of the study.

Prior/Concomitant Therapy

15. On more than one antidepressant (Trazodone used at a dose up to and including 50 mg at bedtime is considered a hypnotic agent), or if on one antidepressant, a change in dose within 28 days prior to screening.
16. *History of clozapine treatment: Clozapine treatment for schizophrenia within 5 years prior to screening is prohibited. Low dose (< 200 mg/day) use is permitted for insomnia or dyskinesia only, but not within 12 months prior to screening.*
17. History of treatment with electroconvulsive therapy (ECT)
18. Concomitant use of prohibited medications.
19. Positive urine drug screen for amphetamines, methamphetamines, opiates, buprenorphine, methadone, cannabinoids, cocaine and barbiturates. In case of uncertain or questionable results, the urine drug screen may be repeated once during the screening period to confirm eligibility.

Other Exclusions

20. Receipt of an investigational drug within 28 days or five times the half-life of the investigational drug (whichever is longer) before the first study drug administration.
21. Donation of blood over 400 mL within three months prior to screening.
22. 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.

Confirmation of Eligibility at Baseline

1. **Part A only:** Patient will be excluded if unable to taper off an antipsychotic in the one week prior to baseline (e.g., in the case of symptom exacerbation or antipsychotics with a longer half-life).
2. Female participants who are of childbearing potential must have a negative pregnancy test result at baseline.

NUMBER OF PARTICIPANTS

In Part A, approximately 125 participants were planned to be randomized to one of two treatment arms to ensure that approximately 100 participants complete the treatment phase as described in this protocol, with the primary endpoint assessed at Week 12. [redacted]

In Part B, approximately 200 participants will be randomized to one of three treatment arms to ensure that approximately 150 participants complete the treatment phase as described in this protocol with the primary endpoint assessed at Week 12. *In case of an unexpectedly high proportion of participants not completing 12 weeks of treatment (i.e., > 25%), the number of randomized participants may be increased to achieve 150 participants completing 12 weeks of treatment.* These 200 participants will be recruited outside Japan. In addition to these 200 participants, approximately 20 participants will be recruited in Japan.

CONCOMITANT MEDICATIONS

Rescue Medicine During Part A

If early signs of relapse requiring treatment are noticed/recorded by the Investigator, an antipsychotic should be prescribed and the participant will be immediately withdrawn from the study drug.

Permitted Therapy

The use of stable, scheduled doses of benzodiazepines is permitted. The use of stable, scheduled doses of non-benzodiazepine hypnotics is permitted.

If deemed necessary by the Investigator to treat occasional anxiety, agitation or sleep problems, lorazepam, alprazolam, or oxazepam are allowed as needed ([PRN], up to a maximum daily dose of lorazepam 6 mg, alprazolam 3 mg, or oxazepam 90 mg). If PRN treatment of more than five consecutive days is necessary, this should be discussed with the Medical Monitor. PRN doses of benzodiazepines should not be administered within 12 hours of a clinic visit.

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, provided that they have been stable for 28 days prior to screening and are intended to remain stable throughout the study up to the follow-up visits.

Patients in Part B of the study have to be on stable treatment (i.e., no medication changes or significant dose adjustments) with D2/5HT2A antagonists or D2 partial agonist for a minimum of six months prior to screening*. In cases, where change in medication is not associated with the participant's psychiatric stability, treatment changes can be accepted up to three months prior to screening.* Co-administration of RO6889450 and weak P-gp substrates, such as risperidone, amisulpride, aripiprazole, and paliperidone, though permitted may result in slight elevations of the P-gp substrate so continued monitoring is suggested.

SARS-CoV-2 vaccines were permitted during the study.

Prohibited Therapy

Use of the following therapies (non-topical formulation where applicable) is prohibited during the study unless otherwise specified:

- Clinically relevant substrates of P-gp, including quinidine and loperamide.
- Cannabidiol (may affect schizophrenia symptoms [McGuire 2018])

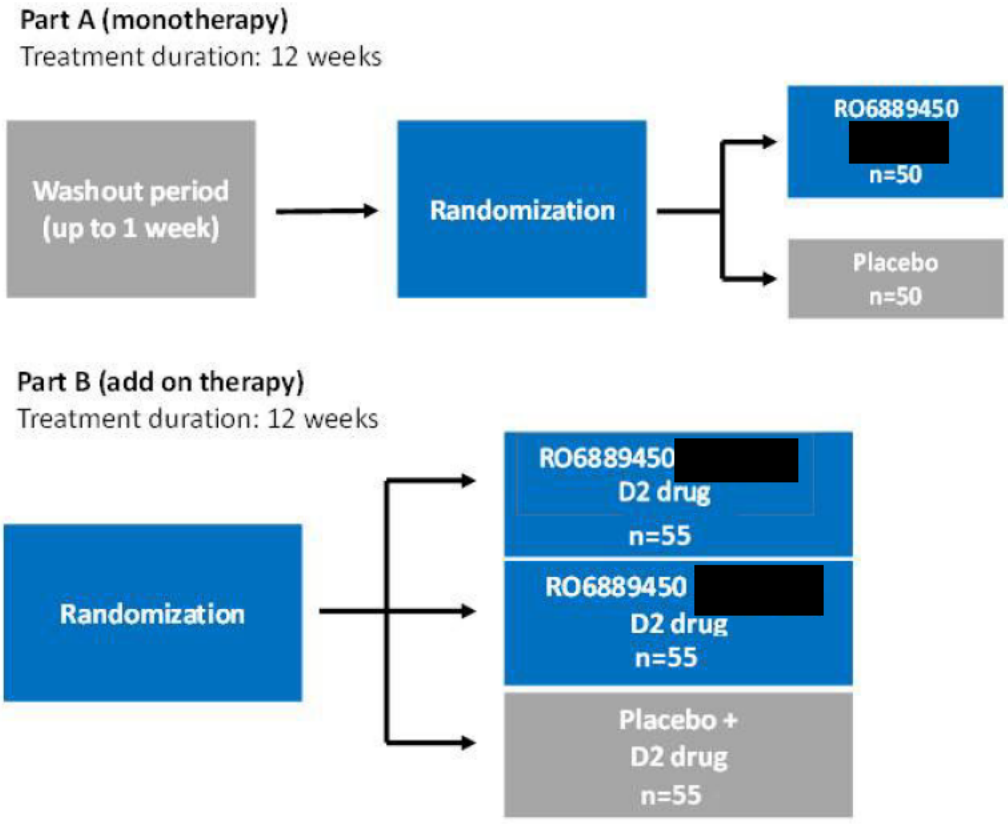
In Part A, all antipsychotic treatment as well as medications used to treat extrapyramidal symptoms (EPS) (e.g., anticholinergics) will be discontinued before randomization. Antipsychotic medications that require longer washout periods (i.e., more than two weeks), such as cariprazine, brexpiprazole, and long-acting injectable antipsychotics (e.g., aripiprazole lauroxil, olanzapine pamoate, and haloperidol decanoate) are exclusionary.

Patients receiving treatment for tardive dyskinesia (e.g., valbenazine or deutetrabenazine) are excluded. As a general rule, no new concomitant medications will be permitted, with the exception of medications to treat AEs, unless the rationale for exception is discussed with the Sponsor or designee and clearly documented between the Investigator and the Sponsor.

1.2 SCHEMATIC OF STUDY DESIGN

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

Figure 1 Overview of Study Design



D2 = D2/5HT2A antagonists or D2 partial agonist; n = number of completers

1.3 SCHEDULE OF ACTIVITIES

The schedule of the activities is provided in Table 1 and Table 2.

Table 1 Schedule of Activities for Part A of the Study

Period	Screening			Treatment Period													Follow-Up Visits		
		Placebo Compliance																	
Week	Week -4	Week -2	Week -1	1		2	3	4	5	6	7	8	9	10	11	12	13	14	16
Day	Day -35 to Day -19	Day -14	Day -7	Baseline[1]/ Day 1	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42[1]	Day 49	Day 56	Day 63	Day 70	Day 77	Day 84/ EOT[1, 2]	Day 91	Day 98	Day 112[1]
Visit window (days)		±1	±1	-1	±1	±1	±1	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±4
On-site visit	X	X		X	X	X		X		X		X		X		X			X
Inpatient/partial hospitalization (optional)			←		→														
Phone call[3]			X				X		X		X		X		X		X	X	
Informed consent	X																		
Inclusion/exclusion criteria	X			X[4]															
Eligibility *Checklist* Form submission	X																		
Latest start of Antipsychotic washout[8]			X																
Randomization				X															
Demography	X																		
Medical history	X																		
Physical examination [5]	X			X								X				X			X
ECG-12 lead[6]	X			X		X						X				X			X
Meal-time	X			X		X						X				X			X

Period	Screening			Treatment Period													Follow-Up Visits		
		Placebo Compliance																	
Week	Week -4	Week -2	Week -1	1		2	3	4	5	6	7	8	9	10	11	12	13	14	16
Day	Day -35 to Day -19	Day -14	Day -7	Baseline[1]/ Day 1	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42[1]	Day 49	Day 56	Day 63	Day 70	Day 77	Day 84/ EOT[1, 2]	Day 91	Day 98	Day 112[1]
Visit window (days)		±1	±1	-1	±1	±1	±1	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±4
Orthostatic vital signs	X			X		X		X				X				X			X
Viral serology	X																		
Prolactin sample	X															X			
Alcohol levels	X			X		X		X				X				X			X
Drugs of abuse	X			X		X		X				X				X			X
Urinalysis	X			X		X		X				X				X			X
Pregnancy test [7]	X			X												X			
Blood chemistry and lipids	X			X		X				X						X			X
Hematology	X			X		X				X						X			X
Antipsychotic blood levels	X				X					X						X			
PK sample					X[9]	X[9,10]				X[9,10]						X[9,10]			
Genotyping				X[11]															
RBR DNA (optional)				X[11]															
MINI	X																		
WASI-II	X																		
WRAT-4[17]	X																		

Period	Screening			Treatment Period													Follow-Up Visits		
		Placebo Compliance																	
Week	Week -4	Week -2	Week -1	1		2	3	4	5	6	7	8	9	10	11	12	13	14	16
Day	Day -35 to Day -19	Day -14	Day -7	Baseline[1]/ Day 1	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42[1]	Day 49	Day 56	Day 63	Day 70	Day 77	Day 84/ EOT[1, 2]	Day 91	Day 98	Day 112[1]
Visit window (days)		±1	±1	-1	±1	±1	±1	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±4
PANSS and IC-PANSS	X			X		X		X		X		X		X		X			X
BNSS[17]	X			X		X		X		X		X		X		X			X
DPAS				X						X						X			
CGI-S and CGI-S Negative Symptoms				X		X		X		X		X		X		X			X
CGI-I and CGI-I Negative Symptoms						X		X		X		X		X		X			X
CGI-S MTS	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
CGI-I MTS					X	X	X	X	X	X	X	X	X	X	X	X			X
FTND				X						X						X			X
BACS[17]				X						X						X			
VRFCAT[17]				X						X						X			
Reward learning tasks: RLWM and ECB				X		X				X						X			
Study Phone Usage Tracker (optional)[12]		←														→			
ESRS-A	X			X		X		X								X			X
C-SSRS	X		X	X	X	X		X		X		X		X		X			X

Period	Screening			Treatment Period													Follow-Up Visits		
		Placebo Compliance																	
Week	Week -4	Week -2	Week -1	1		2	3	4	5	6	7	8	9	10	11	12	13	14	16
Day	Day -35 to Day -19	Day -14	Day -7	Baseline[1]/ Day 1	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42[1]	Day 49	Day 56	Day 63	Day 70	Day 77	Day 84/ EOT[1, 2]	Day 91	Day 98	Day 112[1]
Visit window (days)		±1	±1	-1	±1	±1	±1	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±4
Adverse events[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Previous and concomitant treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administration of open label placebo[14]		←	→																
Administration of study drug[15]				←												→			
AiCure Adherence App		←														→			
AiCure App Questions[16]		←														→			
Study drug dispensing				X		X		X		X		X		X					

Abbreviations: BACS = Brief Assessment of Cognition in Schizophrenia, BNSS = Brief Negative Symptom Scale, CGI-I = Clinical Global Impression of Improvement, CGI-S = Clinical Global Impression of Severity, C-SSRS = Columbia-Suicide Severity Rating Scale, DNA = deoxyribonucleic acid, DPAS = Defeatist Performance Attitude Scale, ECB = Effort-choice benefit 18, ECG = Electrocardiogram, EOT = End of treatment, ESRS-A = Extrapyramidal symptom rating scale, abbreviated, FTND = Fagerström Test for Nicotine Dependence, IC-PANSS = informant checklist Positive and Negative Syndrome Scale, MINI = Mini International Neuropsychiatric Interview, MTS = most troubling symptom, PANSS = Positive and Negative Syndrome Scale, PK = pharmacokinetic, RBR = Research Biosample Repository, RLWM = Reinforcement learning working memory, SAE = serious adverse event, VRFCAT = Virtual Reality Functional Capacity Assessment Tool, WASI-II = Wechsler Abbreviated Scale of Intelligence – Second Edition, WRAT-4 = Wide Range Achievement Test

Table 1 Schedule of Activities for Part A of the Study (cont.)

1 To decrease patient burden, some assessments may be split within the visit window days. Baseline assessments should be done pre-dose on Day 1 or within 24 hours prior to the first double-blind dose (i.e., on Day -1).

2 If treatment is discontinued early, the Week 12 visit assessments as well as the follow-up visit assessments (four weeks after last dose) should be performed.

3 Phone calls listed are for scheduled visits. Informal calls by a case manager up to three times per week to follow up with patients, especially during the washout period, are encouraged.

4 Eligibility will be confirmed at baseline (see Section 5.3).

5 Complete physical exam includes height and weight at screening. Limited physical exams (symptom driven) and weight will be done at subsequent visits including the follow-up visit (see Section 8.2.1).

6 Triplicate ECGs will be performed at screening and a single ECG at subsequent visits ECGs should be performed prior to meals or any scheduled vital sign measurements and blood draws.

7 Pregnancy testing will be using a blood sample at screening and urine sample at subsequent visits. If urine test is positive, pregnancy must be confirmed by blood test.

8 Washout may start earlier for antipsychotics with long half-life (2 week washout for aripiprazole, olanzapine, see Appendix 6).

9 Sample should be taken prior to the morning dose (pre-dose/trough).

10 One additional sample should be taken two hours (± 0.5) post-dose.

11 Samples can be taken at any time between baseline and follow-up.

12 The Study Phone Usage Tracker will be used only with screened patients who have suitable smartphones and agree to the assessment.

13 After informed consent, but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention will be collected. After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until 28 days after the last dose of study drug.

14 The placebo compliance period will start with a visit reviewing instructions with the patient.

15 Study drug is three capsules administered once daily, preferably in the morning. The last dose is given at the Day 84/EOT visit.

16 Sleep, mood, cognition and treatment expectation questions will be presented on the AiCure app at select time points that will appear as random to the participant.

17 The exploratory endpoints Brief Assessment of Cognition in Schizophrenia (BACS) (digital version), Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-II), Wide Range Achievement Test (WRAT-4) and Virtual Reality Functional Capacity Assessment Tool (VRFCAT) are not available as validated Spanish translation. Therefore, sites will not be required to administer these tests to Spanish only speaking patients. If validated versions become available, they may be used.

Table 2 Schedule of Activities for Part B of the Study

Period	Screening		Treatment												Follow Up Visits		
		Placebo Compliance[4]															
Week	Week -5 to -2	Week -1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Day	Day -35 to Day -8	Day -7	Baseline[1]/ Day 1	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42[1]	Day 49	Day 56	Day 63	Day 70	Day 77	Day 84/ EOT[1, 2]	Day 91	Day 98	Day 112[2]
Visit Window (days)[20]		±1	-1	±1	±1	±1	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±4
On-site visit	X	X	X	X	X		X		X		X				X			X
Phone Call						X		X		X		X	X	X		X	X	
Informed Consent	X																	
Inclusion/exclusion criteria	X		X[3]															
Eligibility *Checklist* Form Submission	←	→																
Randomization			X															
Demography	X																	
Medical History	X																	
Physical Examination[4 16]	X[23]	X	X[23]	X	X		X		X		X[23]				X[23]			X[23]
ECG-12 lead[5 16]	X		X	X	X		X		X		X				X			X
Meal time[16]	X		X		X						X				X			X
Vital Signs[16]	X		X	X	X		X		X		X				X			X
Weight and waist circumference[16 22]	X		X								X				X			X
Viral Serology[16]	X																	
Prolactin Sample[16]	X														X			
Alcohol Test 16 21	X		X		X		X				X				X			X
Urine Drug Screen[16]	X		X		X		X				X				X			X
Urinalysis[16]	X		X		X		X				X				X			X
Pregnancy Test[6 16]	X		X												X			
Blood Chemstry & lipids[16]	X		X		X				X						X			X
Hematology[16]	X		X		X				X						X			X
Covid-19 test[16 19]	X																	
Coagulation parameters[16]	X		X		X				X						X			X
Antipsychotics blood levels[16,24]	X			X					X						X			
PK Sample[16]				X[7]	X[7, 8]		X[7, 8]		X[7, 8]		X[7, 8]				X[7, 8]			X
Genotyping			X[9]															
RBR DNA (optional)			X[9]															

Table 3 Schedule of Activities for Part B of the Study (cont.)

Period	Screening		Treatment													Follow Up Visits		
		Placebo Compliance[3,4]																
Week	Week -5 to -2	Week -1	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15
Day	Day -35 to Day -8	Day -7	Baseline[1]/ Day 1	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42[1]	Day 49	Day 56	Day 63	Day 70	Day 77	Day 84/ EOT[1, 2]	Day 91	Day 98	Day 112[2]
Visit Window (days) [20]		±1	-1	±1	±1	±1	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±4
On-site visit	X	X	X	X	X		X		X		X				X			X
Phone Call						X		X		X		X	X	X		X	X	
MINI	X																	
WASI 15 [16]	X																	
WRAT-4 [15 16]	X																	
PANSS and IC PANSS [16]	X		X		X		X		X		X				X			X
BNSS [16]			X		X		X		X		X				X			X
DPAS			X						X						X			
CGI-Sand CGI-S Negative Symptoms [16]			X		X		X		X		X				X			X
CGI-I and CGI-I Negative Symptoms [16]					X		X		X		X				X			X
FTND [16]			X						X						X			X
BACS [15 16]			X						X						X			
VRFCAT [15]			X						X						X			
Reward learning tasks: RLWM and ECB15 [18]		X	X		X				X						X			
AiCure Adherence App		←	←	←	←	←	←	←	←	←	←	←	←	←	←			
AiCure App Questions[13]		←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←
Study Phone Usage Tracker [10]		←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←
Ecological Momentary Assessment (EMA) [15]		←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←
AICure Digital Biomarkers		←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←
ESRS-A [16]	X		X		X		X								X			X
C-SSRS [16]	X		X		X		X		X		X				X			X
Adverse Events[12 16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Previous and Concomitant Treatments [16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administration of Open Label Placebo		← →																
Administration of Study Drug[12]			←	←	←	←	←	←	←	←	←	←	←	←	←			
Study Drug Dispensing [17]			X		X		X		X		X							

Table 2 Schedule of Activities for Part B of the Study (cont.)

Abbreviations: BACS = Brief Assessment of Cognition in Schizophrenia, BNSS = Brief Negative Symptom Scale, CGI-I = Clinical Global Impression of Improvement, CGI-S = Clinical Global Impression of Severity, C-SSRS = Columbia-Suicide Severity Rating Scale, DNA = deoxyribonucleic acid, DPAS = Defeatist Performance Attitude Scale, ECB = Effort-choice benefit, ECG = Electrocardiogram, EMA = Ecological Momentary Assessment, EOT = End of treatment, ESRS-A = Extrapyramidal symptom rating scale, abbreviated, FTND = Fagerström Test for Nicotine Dependence, IC- PANSS = informant checklist Positive and Negative Syndrome Scale, MINI = Mini International Neuropsychiatric Interview, PANSS = Positive and Negative Syndrome Scale, PK = pharmacokinetic, RBR = Research Biosample Repository, RLWM = Reinforcement learning working memory, SAE = serious adverse event, VRFCAT = Virtual Reality Functional Capacity Assessment Tool, WASI-II = Wechsler Abbreviated Scale of Intelligence – Second Edition, WRAT-4 = Wide Range Achievement Test

1	To decrease patient burden, some assessments may be split within the visit window days. Baseline assessments should be done pre-dose on Day 1 or within 24 hours prior to the first double-blind dose (i.e. Day -1).
2	If treatment is discontinued early, the week 12 visit assessments as well as the follow-up visit assessments (4 weeks after last dose) should be performed.
3	Eligibility will be confirmed at baseline (see Section 5.3)
4	Limited physical examination will be done for all visits except for those denoted with footnote 23 (see below), for which a complete physical examination is required.
5	Triplicate ECGs will be performed at screening and a single ECG at subsequent visits. To minimize variability, it is important that patients be in a resting position for at least 10 minutes prior to each ECG evaluation. ECGs should be performed 2 hours or longer after the last meal (with meal-time recorded) and before any scheduled vital sign measurements and blood draws.
6	Pregnancy testing will be using a blood sample at screening and urine sample at subsequent visits. If urine test is positive, it must be confirmed by blood test.
7	Sample should be taken prior to the morning dose (pre-dose/trough)
8	One sample should be taken three hours (+/- 0.5) post-dose
9	Samples can be taken at any time between BL and FU
10	The Study Phone Usage Tracker will be used only with screened patients who have suitable smartphones and agreed to the assessment.
11	Study medication is 6 capsules administered once daily, preferably in the morning. The last dose is given at the Day 84/EOT visit.
12	After informed consent, but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention will be collected. After initiation of study treatment, all adverse events, regardless of relationship to study treatment, will be reported until 28 days after the last dose of study treatment.
13	Sleep, mood, cognition and treatment expectation questions will be presented on the AiCure app at select time points that will appear as random to the participant.
14	The placebo compliance period for Part B will be at least 1 week and may be extended by one week *(e.g.* if the compliance is insufficient (<80% or >120%*), participant requires further training).*

Table 2 Schedule of Activities for Part B of the Study (cont.)

15 The exploratory endpoints Brief Assessment of Cognition in Schizophrenia (BACS) (digital version), ECB = Effort-choice benefit, RLWM = Reinforcement learning working memory, Ecological Momentary Assessment (EMA), AiCure Digital Biomarkers, Phone usage monitoring, Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-II), Wide Range Achievement Test (WRAT-4) and Virtual Reality Functional Capacity Assessment Tool (VRFCAT) are not available as validated translations in several languages. These measures will not be performed for patients who are not proficient in the available language. If validated translations become available, they may be used. For the assessment of current and pre-morbid IQ, equivalent scales may be used, if available.

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

17 If onsite visits are not permitted due to local restrictions, (e.g. due to travel restrictions for COVID-19) study drug can be shipped from sites directly to a patient, for visits subsequent to the Baseline visit if approved by sponsor and relevant health authorities, if applicable. This must be confirmed and documented in the patient's source file.

18 If an onsite visit is not possible these tests might not be performed, the protocol deviation should be documented in patient's source file and should be clearly designated as “COVID 19 RELATED.

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

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

21 Alcohol test will be performed using a urine dipstick test

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

23 Complete physical examination includes height at screening (see Section 8.2.1)

24 *Testing of blonanserin and perospirone cannot be performed by the central laboratory. Therefore, no blood samples to assess antipsychotic drug levels will be drawn for participants being currently treated with blonanserin and/ or perospirone. Participants currently treated with other antipsychotics in addition to blonanserin or perospirone will have blood samples taken to assess antipsychotic blood levels. Antipsychotic medication compliance of participants taking blonanserin or perospirone will be monitored via informant report and recorded in the eCRF.*

2. INTRODUCTION

RO6889450 is a novel compound and a potent partial agonist of Trace Amine-Associated Receptor 1 (TAAR1) for the treatment of schizophrenia. RO6889450 is currently in Phase 2 clinical development.

2.1 STUDY RATIONALE

The TAAR1 partial agonist RO6889450, a modulator of dopaminergic transmission, leads to a normalization of behaviors in rodent models of negative symptoms. Results in healthy volunteers suggest performance improvements in tasks that probe reward-based learning and motivated behavior, functions that are deficient in patients with negative symptoms (e.g., blunted affect, amotivation/apathy). These results indicate a potential utility of RO6889450 in the treatment of negative symptoms associated with schizophrenia.

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

2.2 BACKGROUND

2.2.1 Background on Disease

Schizophrenia, a severe mental illness affecting approximately 1% of the adult population, is characteristically described by a heterogeneity of symptoms (Perälä et al 2007; Tandon et al 2008). Based upon the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), core symptoms in the diagnosis of schizophrenia include positive symptoms (e.g., delusions, hallucinations, or disorganized speech), negative symptoms (e.g., blunted affect, amotivation/apathy), grossly disorganized or catatonic behavior, and cognitive deficits. The onset is typically in late adolescence or early adulthood, then progresses with a course of exacerbations and remissions throughout the life of the patient (Rund et al 2016). Compared to the general population, there is a higher incidence of depression, suicide, homelessness, substance use disorders, medical comorbidities, and social isolation in patients with schizophrenia (Lehman et al 2010).

Treatment with antipsychotics only partially addresses the key symptoms in schizophrenia, i.e., positive symptoms, with many patients experiencing a persistence of negative, cognitive, and non-acute positive symptoms (Stahl and Buckley 2007). Many patients continue experiencing primary and persistent negative symptoms after their positive symptoms have been controlled. To address the residual symptoms, clinicians often use multiple medications to treat patients with chronic schizophrenia, including combinations of antipsychotics and anticonvulsants (Correll et al 2009 Tseng et al 2016; Zheng et al 2017), despite little evidence supporting the benefit of this approach (Stahl and Grady 2004; Chakos et al 2006). Therefore, there is an urgent need for the development of more effective treatments for negative symptoms of schizophrenia for use in patients treated with antipsychotic drugs.

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 subcortical and cortical circuits. Underlying the symptomatic phenomena are disturbances in monoaminergic and glutamatergic neurotransmission (e.g., dopamine, serotonin, norepinephrine, and glutamate). These pathways are widely present in the central nervous system (CNS) and are involved in emotional processing, cognition, and behavior (Belmaker and Agam 2008; Racagni and Popoli 2008; Sen and Sanacora 2008). The original dopamine hypothesis attributed the pathophysiology of schizophrenia to excess levels of dopamine. This theory was later expanded to indicate a scarcity of dopamine in the prefrontal cortex and an excess dopamine in the subcortical region of the brain (Howes and Kapur 2009).

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 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, noradrenergic, and dopaminergic neurotransmission. Recently, a family of G-protein coupled receptors has been identified and named Trace Amine-Associated Receptor, 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). Therefore, 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, showing antipsychotic, stress-reducing, anti-addictive, and glucose-regulating activities. In mechanistic assays mimicking non-competitive N-methyl-D-aspartate (NMDA) hypofunction and dopamine hyperfunction as seen in schizophrenic patients, RO6889450 inhibited hyperactivity in mice. In rats, RO6889450 dose-dependently normalized the social impairment induced by isolation rearing, and modulation of ventral tegmental area (VTA) activity was observed. RO6889450 was well absorbed in rats and monkeys following oral administration and has low plasma protein binding across species, including humans. Brain/cerebrospinal fluid exposure has been demonstrated in rodents.

RO6889450 is cleared in animals through a combination of mechanisms (metabolism and renal). RO6889450 is not an inhibitor or an inducer of the major human cytochrome

P450 enzymes, but is a substrate for human CYP3A4, CYP2C19, and flavin-containing monooxygenase (FMO1). 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 (RO6889450 Investigator's Brochure). Results from an ongoing Phase I study (JP40960) showed [redacted]

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 (PK), and pharmacodynamics of [redacted]

Pharmacokinetics of RO6889450 were well characterized after single and multiple doses. Following multiple oral administration of RO6889450 $C_{max,ss}$ was reached at a median t_{max} of 1.07 to 2.50 hours across dose groups. Subsequently, RO6889450 plasma concentration declined with an apparent terminal half-life ranging from 25.8 to 34.5 hours across dose groups supporting a once daily (QD) dosing in the subsequent studies. Steady-state plasma concentration was achieved after five to six days of dosing.

No clinically significant or relevant abnormalities, including dose-related trends were observed in electrocardiograms (ECGs), ambulatory blood pressure measurements, and laboratory safety parameters (blood chemistry, hematology, urinalysis) for either single or multiple-dose administrations. Peripheral blood lymphocytes were collected during the MAD phase and examined by electron microscopy for signs of phospholipidosis (increased lamellar bodies); no signs of phospholipidosis were found in samples taken from any dose level. Two dose-limiting events (DLE) occurred [redacted]: one event of generalized erythema resulting in treatment discontinuation,

and one participant had several episodes of Postural Orthostatic Tachycardia (POT= pulse rate increased by ≥30 bpm without hypotension). Both participants had received active treatment. There were no serious adverse events (SAEs) or severe adverse events (AEs) reported. The most common AE observed was headache. A slight trend towards higher elevated pulse rates with the higher doses was observed. There were also multiple measures that showed evidence of POT however, the incidence was as common with the placebo group as with the treatment groups and some subjects appeared to have a decrease in POT after more than seven days of dosing.

By targeting brain circuits implicated in psychotic and negative symptoms, as well as central and peripheral circuits that regulate energy homeostasis, RO6889450 represents a potential novel therapy for the treatment of schizophrenia. A detailed description of the chemistry, pharmacology, and safety of RO6889450 is provided in the RO6889450 Investigator's Brochure.

2.3 BENEFIT/RISK ASSESSMENT

RO6889450 has the potential to improve negative symptoms and ameliorate psychotic symptoms of schizophrenia. In healthy volunteers, RO6889450 was well tolerated when administered [redacted]. No clinically significant or relevant abnormalities, including dose-related trends, were observed in ECGs, ambulatory blood pressure measurements, or laboratory safety parameters in either single- or multiple-dose administrations up to the maximum tolerated dose (MTD) [redacted]

- During both Part A and Part B of this study, standard monitoring of blood chemistry, hematology, and urinalysis will be performed. In addition, some dedicated safety measures will be implemented to address mechanistic and pre-clinical safety considerations as well as known co-morbidities of schizophrenia. Observations from the completed SAD and MAD study (BP30134) showed POT in the placebo and treatment groups, with a slight trend towards higher pulse rates only at the [redacted] of RO6889450. As such, detailed cardiovascular assessments will be performed at multiple pre-defined time points, including ECG monitoring and orthostatic heart rate.

- Phospholipidosis was noted in rat and cynomolgus monkeys studies, though not in the healthy volunteer MAD part of the Phase 1 study.

- In an effort to consistently collect data in clinical trials, as well as to improve safety monitoring, certain regulatory agencies have requested inclusion of a prospective assessment for suicidality for CNS active compounds. Therefore, Columbia-Suicide Severity Rating Scale (C-SSRS) is part of the safety monitoring in this study. Additionally, in Part A, patients who had suicidal behavior in the prior five years as confirmed by chart data and/or caregiver will be excluded from study participation. For patients with a history of suicidal behavior that occurred prior to the last five years, additional review and approval will be sought through the Patient Review Committee (PRC) on a case by case basis. In Part B, patients with suicidal behavior or active suicidal ideation with specific plan and intent will be discontinued from study medication (see Section 7.1.2*)*. Of note, no evidence of suicidality has emerged from the previous clinical trial with RO6889450.

In Part A of this study, participants who are on antipsychotics will be taken off their antipsychotic medication for a maximum of 13 weeks, inclusive of the washout and treatment periods. There is an increased risk of relapse during this period while participants are not receiving antipsychotic treatment. For this reason, only participants who have a reliable support system to alert the Investigator of any early signs of relapse will be enrolled. Participants have the option to be inpatient for two weeks (i.e. the washout period as well as the first week of treatment period) if deemed necessary by the Investigator or as requested by the patient/caregiver to ensure patient safety. Throughout Part A of the study, participants will be seen in clinic or called by site staff every week. Informal calls by a case manager up to three times per week to follow up with patients are encouraged, especially during the washout period. In addition, some dedicated safety measures will be implemented to address the ongoing relapse risk, including the use of clinical scales at each visit (see Section 8.1.1.3) and the review of unblinded safety and efficacy (as appropriate) data for Part A of the study by an iDMC at scheduled time points (see Section 4.1.2). In case early signs of relapse requiring treatment are noticed/recorded by the Investigator in Part A, an antipsychotic should be provided and the participant will be immediately withdrawn from the study drug.

In Part B, participants will be allowed to continue their usual antipsychotic treatment in addition to the randomized study drug, provided the antipsychotic treatment has been stable and is expected to stay stable during the study.

The unmet medical need for effective treatment of negative symptoms in patients with schizophrenia is immense. Given the potential of RO6889450 to significantly improve negative symptoms in schizophrenia, the favorable safety profile [redacted] in healthy volunteers along with the measures implemented to ensure the patient's safety, the overall benefit/risk assessment for clinical trial participation is deemed positive. It should also be noted that analyses of pharmacokinetic data from Part A of this study and from Study BP39833 demonstrated lower than expected exposures in

patients, which will - if anything - lower the risk to patients. Please refer to Section 4 for details on study procedures, doses, and study design justifications.

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 this 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 this time, there is 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 eCRF as a concomitant medication.

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

3. OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints are provided in Table 4.

Table 4 Objectives and Endpoints

Objectives	Endpoints
Primary	
Part A: To compare the efficacy of [redacted] QD of RO6889450 as monotherapy with placebo on negative symptoms in patients with schizophrenia or schizoaffective disorder. Part B: To compare the efficacy of [redacted] QD of RO6889450 as add-on therapy with placebo on negative symptoms in patients with schizophrenia or schizoaffective disorder.	Part A & B: Change from baseline at Week 12 in the Brief Negative Symptoms Scale (BNSS) avolition/apathy subscore (sum of items "behavior" and "internal experience").
Secondary	
To compare the effect of RO6889450 with placebo on: • Clinical Global Impression Severity (CGI-S) and change (CGI-I) (overall and negative symptoms)	• Change from baseline in CGI-S and CGI-S negative symptoms scores • CGI-I and CGI-I negative symptoms scores

Objectives	Endpoints
To compare the effect of RO6889450 with placebo on: • Symptoms of schizophrenia or schizoaffective disorder as assessed with the Positive and Negative Syndrome Scale (PANSS), BNSS, and Defeatist Performance Attitude Scale (DPAS)	• Change from baseline in PANSS total and symptom factor scores • Change from baseline in BNSS total and subscores • Change from baseline in DPAS scores
• To compare the safety and tolerability of 12 weeks of treatment with RO6889450 as monotherapy (Part A) or add-on therapy with placebo (Part B).	• 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 vital signs • 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, coagulation and urinalysis test results • Change from baseline in C-SSRS and extrapyramidal symptom rating scale, abbreviated (ESRS-A)
• To evaluate the PK of RO6889450 and RO6889450-derived metabolite(s).	• Concentration per time point • AUC_{ss} of RO6889450 and, if feasible, of RO6889450-derived metabolite(s) • C_{max} of RO6889450 and, if feasible, of RO6889450-derived metabolite(s) • Other PK parameters as appropriate
Tertiary/Exploratory	
To explore the effects of RO6889450 on: • Reward learning tasks (Effort-choice benefit [ECB] task; Reinforcement learning working memory [RLWM] task)	• ECB: Percentage of high-effort choices under deterministic reward conditions for high-reward magnitudes • RLWM Learning Phase: Proportion of correct choices in late trials and for large blocks of stimuli. • RLWM Testing Phase: Interaction 'value difference modulated by value mean' (assessing the 'choose A avoid B' paradigm).
To explore the effects of RO6889450 on: • Overall functioning/cognition	• Change from baseline in Brief Assessment of Cognition in Schizophrenia (BACS) • Change from baseline in adjusted total time as measured by the Virtual Reality Functional Capacity Assessment Tool (VRFCAT)
To explore the effects of RO6889450 on: • Changes in smoking dependence	• Change from baseline in Fagerström Test for Nicotine Dependence (FTND) total score
To explore the effects of RO6889450 on: • Levels and patterns of social and general activity • Exploratory measures of negative symptoms	• Phone usage behavior data • EMA • AiCure digital biomarker app

Objectives	Endpoints
Part A & B: • To assess CYP2C19 status on PK parameters	• Genotyping of CYP2C19 (Section 8.8.1)

4. STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 2, multicenter, randomized, double-blind, two-part, placebo-controlled, parallel-group, study in patients with schizophrenia or schizoaffective disorder. An overview of the study design is provided in Section 1.2.

In Part A, approximately 125 participants were planned to be randomized to one of two treatment arms to ensure that approximately 100 participants complete the treatment period as described in this protocol, with the primary endpoint assessed at Week 12. [redacted]

In Part B, approximately 200 participants will be randomized to one of three treatment arms to ensure that approximately 150 participants complete the treatment period as described in this protocol, with the primary endpoint assessed at Week 12. These 200 participants will be recruited outside-Japan. In addition to these 200 participants, approximately 20 participants will be recruited in Japan.

Part B is planned to be started after Part A. If the results of Part A are negative, the Sponsor may choose not to conduct Part B.

Part A (monotherapy):

Participants who meet eligibility criteria for Part A of the study will take open-label placebo for two weeks before randomization (Day -14 to baseline/Day 1). Intake will be recorded/tracked using a web-based platform/app provided on a smartphone (see Section 6.4.1). The purpose of this open-label placebo phase is to help familiarize the participant with use of this platform and identify potential issues with compliance. One week before randomization (Day -7 to baseline/Day 1), participants will be washed-out from their antipsychotic therapy. At baseline/Day 1, participants will be randomized 1:1 to either [redacted] QD of RO6889450 or placebo for 12 weeks. Stratification will be based on baseline BNSS avolition/apathy subscore (sum of items "behavior" and "internal experience"; ≤6 vs. >6 [Marder and Galderisi, 2017]), age at screening (18-35 years vs. 36-55 years), and sex. The participants will have the option of an inpatient stay or partial hospitalization during the wash out period as well as the first week of the treatment period.

Part B (add-on therapy):

Participants who are enrolled in Part A cannot be screened for Part B. Participants who meet eligibility criteria for Part B of the study will take placebo for one or two weeks (depending on compliance) before randomization. Intake will be recorded/tracked using a web-based platform/app provided on a smartphone (see Section 6.4.1). The purpose of this open-label placebo phase is to help familiarize the participant with use of this platform and identify potential issues with compliance. At baseline/Day 1, participants will be randomized 1:1:1 to [redacted] QD of RO6889450, [redacted] QD of RO6889450, or placebo for 12 weeks. Stratification will be based on region (i.e., Ex-Japan; Japan). For non-Japanese sites, stratification will additionally be based on baseline BNSS avolition/apathy subscore (sum of items "behavior" and "internal experience"; ≤6 vs. >6), age at screening (18-35 years vs. 36-55 years), sex, and antipsychotic treatment (1:1 stratification ratio between dopamine 2 receptor [D2]/serotonin 2A receptor [5HT2A] antagonists and D2 partial agonist). For Japanese sites, stratification will additionally be based on antipsychotic treatment (1:1 stratification ratio between dopamine 2 receptor [D2]/serotonin 2A receptor [5HT2A] antagonists and D2 partial agonist). Approximately equal numbers of participants on D2/5HT2A antagonists or D2 partial agonists will be enrolled.

Participants who were screened for, but not enrolled in Part A can be screened for Part B *if meeting criteria as per Section 5.5 and* only after *discussion with* the Medical Monitor or delegate. The reason(s) for the decision must be documented.

Interim analyses:
The Sponsor may choose to conduct an interim efficacy analysis in Part A. 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. The interim

analysis will be performed and interpreted by members of the Sponsor 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.

The results of this analysis may support initiation of Part B enrollment during Part A if a positive results threshold is met as defined in the statistical analysis plan (SAP). In case of very slow recruitment, Part A may be stopped and/or Part B may be started without the interim analysis.

The Sponsor may choose to conduct up to two additional interim analyses of Part B to determine the chance of final success. The results of such an analysis may support an early termination of Part B (see Section 9.5).

4.1.1 Length of the Study

Part A: The total duration will be approximately 147 days (from screening through study completion) for each enrolled participant as follows:

- Screening: up to 35 days (including the placebo compliance and a 7-day washout periods)
- Treatment period: 84 days (12 weeks)
- Follow-up: 28 days

Part B: The total duration will be up to approximately 154 days (from screening through study completion) for each enrolled participant as follows:

- Screening: up to 42 days (including the placebo compliance period)
- Treatment period: 84 days (12 weeks)
- Follow-up: 28 days

4.1.2 Administrative Structure

4.1.2.1 Independent Data Monitoring Committee

An iDMC will regularly review unblinded safety and efficacy (as appropriate) data for Part A of the study. The iDMC will be composed of at least two psychiatrists external to the Sponsor, as well as a statistician external to the Sponsor, and will be responsible for monitoring safety data to help ensure that continuation of the trial in its current design does not pose unacceptable safety risks to participants. A restricted number of people from the Sponsor (including a statistician, a statistical programmer, a clinical data manager, and a data acquisition specialist) will be unblinded in order to prepare the outputs required for iDMC reviews. Representatives from other functions may join the iDMC open session (blinded) meetings as required. A separate iDMC charter will document the roles, responsibilities, membership as well as scope of activities, time of meetings, and communication plan.

The iDMC members will receive all Suspected Unexpected Serious Adverse Reactions (SUSARs) for RO6889450 within 72 hours of regulatory reporting and all other SAE reports on a scheduled basis. Planned and ad hoc safety reviews will be performed as described within the iDMC charter.

4.1.2.2 Patient Review Committee

The PRC will consist of at least two independent psychiatrists external to the Sponsor. The PRC in Part A will act as final decision maker regarding exclusion or inclusion of participants who have a history of suicidal or violent behavior extending beyond the past five years (see exclusion criterion 1 Part A).

The decisions of the PRC will be provided in writing to the medical monitor who will inform the study site and Sponsor. A separate PRC charter will document the roles, responsibilities, membership as well as scope of activities, time of meetings, and communication plan. No PRC will be implemented for Part B of the study.

4.1.2.3 General Administrative Structure

An interactive Voice/Web Response System (IxRS) will be used to register the screening/screening failures, enrollment, treatment allocation, withdrawal, discontinuation, and termination of participants.

A central laboratory will be used to provide laboratory kits to all sites and collect samples for the assessments listed in Appendix 4.

ECG recordings will be 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) as well as information on T-wave and U-wave.

A smartphone-based medication adherence monitoring platform will be used for investigational medicinal product (IMP) compliance verification.

Central vendors specialized in symptom assessments (Section 8.1.1.7 and Section 8.1.1.8) will provide equipment for the assessments and will collect such data electronically.

An external company(ies) and external consultants will provide training to all site raters on the various scales and will provide all sites with the relevant record forms, instruction manuals, and kits as appropriate. This company will also conduct centralized ratings for the primary and selected secondary endpoints (Section 8.1.1.1 and Section 8.1.1.2).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study rationale is provided in Section 2.1.

This study is a proof of concept study (Part A) followed by a dose-ranging study (Part B). A randomized, double-blind, 2-part, placebo-controlled, parallel-group, study design was chosen to first collect potential efficacy data, then collect safety and tolerability data in a patient population.

Due to concerns that background treatment with antipsychotics may curtail the ability of RO6889450 to ameliorate negative symptoms, the compound will also be evaluated in a monotherapy setting (Part A), i.e. the participants will withdraw from their antipsychotic treatment(s). Part B of the study is designed to evaluate potential efficacy of two dose levels of RO6889450 in combination with usual antipsychotic treatment(s).

4.2.1 Rationale for Study Population and Study Duration

Negative symptoms are a core feature of schizophrenia and schizoaffective disorder but the optimal patient population to evaluate in treatment trials remains a point of discussion among regulators as well as academia (Marder et al 2013). In order to demonstrate an improvement, a sufficiently high threshold of symptoms on the PANSS-Negative Symptom Factor Score (PANSS-NSFS) is required and is comparable to study entry thresholds in prior studies (Krause et al 2018). As negative symptoms generally persist from the first episode throughout the course of illness (Rapado-Castro et al 2010), it is essential that a clinical trial for establishing drug effectiveness be long-term rather than acute (Laughren and Levin 2006). Additionally, the study should be sufficiently long to assess the possibility of an increase or re-emergence of positive symptoms. The minimum duration considered likely to demonstrate efficacy with an effective treatment is three months, but may take as long as six months to demonstrate a functional improvement. For the purposes of this Phase 2 study, the duration of three months was the maximum covered by the current toxicology information. This is also in line with consensus recommendations and the possibility that, should efficacy be demonstrated earlier than three months, this longer duration will provide the opportunity to demonstrate sustained efficacy (Buchanan 2007; Marder et al 2013).

4.2.2 Rationale for Withdrawal of Antipsychotics in Part A

Preclinical data suggests that the use of an antipsychotic may reverse the cAMP effects of a TAAR1 agonist (Harmeier et al 2015) – one of the mechanisms by which TAAR1 is assumed to exert its potential clinical effects. Negative symptoms are only minimally improved by standard of care antipsychotic drugs. Both first- and second-generation antipsychotics may impair normal hedonic drive in patients through dopamine D2 receptor antagonism, contributing to poor adherence. D2 antagonists have also been shown to induce core negative symptoms (i.e. apathy/avolition) in healthy volunteers *(*Mas et al 2013; RO6889450 Investigator's Brochure*).*

These results suggest that clinical effects of TAAR1 might be reduced or even abolished by the concomitant treatment with antipsychotics.

4.2.3 Rationale for Inclusion of Antipsychotics in Part B

Currently antipsychotics are the mainstay of treatment in patients with schizophrenia, though data demonstrates efficacy only in the management of positive symptoms with no clinically relevant effects on negative symptoms. Therefore, in Part B of this study, antipsychotics are permitted in order to assess the impact of concomitant treatment with RO6889450. To further assess the potential impact of different classes of antipsychotics on the study outcome, patients will be randomized using the type of antipsychotics (D2/5HT2A antagonists and D2 partial agonist) as a stratification factor.

4.2.4 Rationale for Control Group

Using placebo as study comparator allows an unbiased evaluation of the magnitude of any treatment effects. Additionally, no active control is used, as there are no approved treatments for the negative symptoms of schizophrenia in the US, where most sites will be located.

In Part A, frequent and careful monitoring for early indicators of clinical worsening is in place with use of sensitive relapse criteria to declare an exacerbation of positive symptoms prior to the emergence of a full psychotic recurrence (Section 8.1.1.3). These dedicated safety measures will be implemented to address the ongoing relapse risk, including the use of clinical scales at each visit (see Section 8.1.1.3) and an iDMC (see Section 4.1.2). In case signs of relapse requiring treatment are noticed/recorded by the Investigator in Part A, the participant will be immediately withdrawn from the study drug (Section 6.5.1), and an antipsychotic should be prescribed. If possible, Investigators should perform the EOT assessment (including efficacy), before antipsychotic medication is started.

4.2.5 Rationale for Digital Biomarker Assessments

Studies have demonstrated the ability of phone usage behavior monitoring to capture information on symptoms and functioning in schizophrenia (Ben-Zeev et al 2017; Torous and Keshavan 2018). The assumed advantage of this method over traditional approaches to measure symptoms and functioning lies in its continuous real-time collection of information that is independent of the participant's recall and potential expectation bias of both participant and examiner. This digital biomarker approach, i.e., "Study Phone Usage Tracker", Ecological Momentary Assessment (EMA) and AiCure digital assessments 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 8.1.2 for more details).

4.2.6 Rationale for Clinical Genotyping

Dissection of the genetic architecture of a complex disorder such as schizophrenia is important to understand its biological basis, assess the individual predisposition of disease, and evaluate the capacity of therapeutic interventions.

4.3 DOSE JUSTIFICATION

In Part A, only the dose of [redacted] QD will be evaluated. The reasons for this approach are as follows:

- The goal is to keep the number of participants who will be recruited and hence are subject to the risk of a relapse as low as possible. Hence, only one dose will be explored.

- Secondly, based on the preclinical data collected so far, a high dose should maximize the probability to detect a positive effect.

- RO6889450 has been shown to be safe and well tolerated in the healthy volunteer study (see Section 2.2.2) up to the MTD dose of [redacted]. In addition, improvements were observed in reward-related behavioral tasks in Study BP30134. In the RLWM 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 [redacted] of RO6889450, as compared to placebo. The ECB 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 [redacted] 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 (RM-ANOVA $t(44) = 1.737$, $p = 0.09$). For these reasons, a dose of [redacted] QD of RO6889450 is considered adequate to demonstrate potential effects on key deficits driving negative symptoms.

In Part B, [redacted] QD will be tested. The dose of [redacted] was chosen for the following reasons:

- A comparison between the exposure of healthy volunteers dosed with [redacted] RO6889450 in fasted state in the Phase I Study BP30134 and the exposure of patients affected by schizophrenia dosed with [redacted] RO6889450 in the Phase Ib Study BP39833 and the Phase II study BP40283, Part A has shown a reduced RO6889450 exposure of up to approximately 50% in patients. The difference in exposure between the healthy subjects and patients can be explained both by food (difficult to control in outpatient settings) and body weight effect.

- It is critical at this stage of development to optimize the study to find an efficacy signal. As preclinical results demonstrated a linear increase of effects with higher exposure it is a reasonable hypothesis that higher exposures may be associated with stronger effects clinically. A daily dose of [redacted] was

determined as Maximum Tolerated Dose (MTD) in the healthy volunteer MAD study and is expected to be well tolerated in patients.

Based on these data, the initially planned doses of [redacted] for Part B have been replaced with [redacted]. Thus, both selected doses of [redacted] are predicted to provide plasma concentrations of RO6889450 that will remain above EC50 over the dosing interval with good separation in exposure between the two doses in patients, whilst not exceeding concentrations that were associated with MTD in healthy subjects.

4.4 END OF STUDY DEFINITION

The end of the study is defined as the date when the last participant last observation (LPLO) occurs. LPLO is expected to occur approximately 28 days after the last participant's last dose.

5. STUDY POPULATION

The study population rationale is provided in Section 4.2.1.

The participants of this study will be male and female outpatients between 18 to 55 years of age with a DSM-5 diagnosis of schizophrenia or schizoaffective disorder with negative symptoms, who are stable. For Part B, participants also need to be stable on antipsychotic treatment. Participants who reside in a group home setting are eligible for participation in this study.

Prospective approval of protocol deviations from recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Unless otherwise stated, inclusion and exclusion criteria refer to evaluations or assessments at screening.

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 according to International Council for Harmonisation (ICH) and local regulations as assessed using the Evaluation to Sign Consent (see Appendix 9). If the participant has a legal representative, the informed consent must be signed by this person.

Patient and Disease Characteristics

2. Male or female participants aged 18-55 years (inclusive).

3. Patients with a DSM-5 diagnosis of schizophrenia or schizoaffective disorder as confirmed by the Mini International Neuropsychiatric Interview (MINI).

4. **Part B only:** Stable treatment with a D2/5HT2A antagonists or pure D2 antagonist(s) (for a complete list, see Appendix 6*),* or a D2 partial agonist for a minimum of six months and receiving no more than two antipsychotics (if no blood concentration of the prescribed antipsychotic medication [or active metabolites] is detected, the participant should not be enrolled). *Note: compliance of blonanserin and perospirone will be monitored via informant report (see Appendix 4).* Antipsychotic regimen: participants must be on a "primary" antipsychotic and may be on a secondary antipsychotic. The secondary antipsychotic dose has to be equal to or less than the equivalent dose of the primary antipsychotic. The sum of the primary and secondary antipsychotics must be ≤ 6 mg of risperidone equivalents (see Appendix 7). Participants who have had a change of medication not associated with a change in the participant's psychiatric stability in the Investigator's opinion (e.g., insurance reasons*, adjustment of dose*) in the six months prior to screening may be considered for entry into the study*; however no change of antipsychotic medication regimen will be allowed within 3 months prior to screening. The reason for medication change must be documented.*

5. Medically stable during the prior three months. Medication changes (other than antipsychotics) in the three months prior to screening may be acceptable*, if, in the opinion of the Investigator, the change of medication does not affect the participant's medical stability throughout the duration of the study.*

6. Participant is outpatient with no psychiatric hospitalizations within the prior six months (hospitalization for social management within this time is acceptable).

7. PANSS-NSFS score of 18 or higher (see Section 8.1.1.2).

8. The following rating on items of the PANSS:

   (a) less than 5 on G8 (uncooperativeness), P1 (delusions), P3 (hallucinations), P4 (excitement/hyperactivity), and P6 (suspiciousness/persecution)

   (b) less than 4 on P7 (hostility)and G14 (poor impulse control)

9. Has an informant who is considered reliable by the Investigator to provide support to the participant and to help ensure compliance with study visits and protocol procedures; who preferably is also able to provide input helpful for completing study rating scales and is in regular contact with the participant in order to be able to alert the Investigator of worsening signs and symptoms for the participant.

10. Body mass index (BMI) between 18 and 40 kg/m^2 inclusive (Appendix 8)

Reproductive

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

    (a) Not a woman of childbearing potential (WOCBP, as defined in Section 1 of Appendix 5).
    (b) WOCBP, who:

    - agrees 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, male sterilization, 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. For further considerations regarding contraception guidance and abstinence 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.

5.2 EXCLUSION CRITERIA

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

Medical Conditions

1. **Part A only:** Confirmed suicidal behavior based on Investigator judgment or violent behavior resulting in injury or property damage in the prior five years. A history prior to the last five years requires approval by the PRC (Section 4.1.2.2) on a case-by-case basis.
2. **Part A only:** Lifetime history of homicidal behavior.
3. Moderate to severe substance use disorder within six months (excluding nicotine) as defined by DSM-5.
4. *Any* ESRS-*A CGI subscore* greater or equal to 3.
5. Other current DSM-5 diagnosis (e.g., bipolar disorder, major depressive disorder).
6. PANSS item G6 (depression) greater than or equal to 5.
7. Significant risk of suicide or harming him- or herself or others according to the Investigator's judgment.
8. A prior or current general medical condition that might be impairing cognition or other psychiatric functioning (e.g., migraine headaches requiring prophylactic treatment, head trauma, dementia, seizure disorder, stroke; or neurodegenerative, inflammatory, infectious, neoplastic, toxic, metabolic, endocrine conditions).
9. Positive result at screening for hepatitis B surface antigen (HBsAg), hepatitis C (hepatitis C antibody), or human immunodeficiency virus (HIV)-1 and -2. HCV antibody positive patients are eligible if HCV RNA is negative.
10. Tardive dyskinesia that is moderate to severe or requires treatment.
11. History of neuroleptic malignant syndrome.
12. 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.
13. Clinically significant abnormalities in laboratory safety test results (including hepatic and renal panels, complete blood count, chemistry panel, coagulation, and urinalysis), including:
    - Aspartate transaminase (AST), alanine transaminase (ALT) $>2 \times$ upper limit of normal (ULN)
    - Total bilirubin >1.5 ULN with the exception of Gilbert syndrome
    - Serum creatinine >1.5 ULN

    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.
14. Significant or unstable physical condition that in the Investigator's judgment might require a change in medication or hospitalization during the course of the study.

Prior/Concomitant Therapy

15. On more than one antidepressant (Trazodone used at a dose up to and including 50 mg at bedtime is considered a hypnotic agent), or if on one antidepressant, a change in dose within 28 days prior to screening.
16. *History of clozapine treatment: Clozapine treatment for schizophrenia within 5 years prior to screening is prohibited. Low dose (< 200 mg/day) usage is permitted for insomnia or dyskinesia only, but not within 12 months prior to screening.*
17. History of treatment with electroconvulsive therapy (ECT)
18. Concomitant use of prohibited medications (see Section 6.5.3).
19. Positive urine drug screen for amphetamines, methamphetamines, opiates, buprenorphine, methadone, cannabinoids, cocaine and barbiturates (see Section 8.2.4). In case of uncertain or questionable results, the urine drug screen may be repeated once during the screening period to confirm eligibility.

Other Exclusions

20. Receipt of an investigational drug within 28 days or five times the half-life of the investigational drug (whichever is longer) before the first study drug administration.
21. Donation of blood over 400 mL within three months prior to screening.
22. 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.

5.3 CONFIRMATION OF ELIGIBILITY AT BASELINE

1. **Part A only**: Participant will be excluded if unable to taper off an antipsychotic in the one week prior to baseline (e.g., in the case of symptom exacerbation or antipsychotics with a longer half-life, 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 taking RO6889450.

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 drug.

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

data will not be entered in the electronic case report form (eCRF) but will be shared with the monitor on a regular basis.

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 if screen failure was not for safety reasons. Individuals who fail *screening* 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 the Medical Monitor or delegate.* Re-screened participants should be assigned a new participant number. Participants who were not enrolled in Part A can be screened for Part B only after *discussion with* the Medical Monitor or delegate. The reason(s) for the decision must be documented.

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 Sponsor approval. A new participant number should be assigned.

5.6 RECRUITMENT PROCEDURES

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 drug is defined as any investigational treatment(s) or placebo intended to be administered to a study participant according to the study protocol.

All IMPs required for completion of this study (RO6889450 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. For all subsequent treatment period visit days, study drug administration will be at the study center under supervision of site staff.

6.1 TREATMENTS ADMINISTERED

Table 5 summarizes the treatments administered. Of note, the daily dose of study drug has been increased in Part B of the study (*from* protocol Version 5: [redacted] RO6889450, [redacted] RO6889450, or placebo).

Table 5 Summary of Treatments Administered

Study Part A			
Study Drug Name:		RO6889450 (IMP)	RO6889450 (placebo; IMP)
Dosage Formulation:		Hard capsules	Hard capsules
Strength:		[redacted]	N/A
Route of Administration:		Oral	Oral
Dosing Instructions:		3 capsules QD	3 capsules QD
Daily Dose of RO6889450		[redacted]	NA
Packaging and Labeling[a]		HDPE bottle	HDPE bottle
Storage Conditions		Do not store above 30°C, protect from light, keep container tightly closed.	Do not store above 30°C, protect from light, keep container tightly closed.
Study Part B (prior to Protocol Version 5)			
Study Drug Name:	RO6889450 (IMP)	RO6889450 (IMP)	RO6889450 (placebo; IMP)
Dosage Formulation:	Hard capsules	Hard capsules	Hard capsules
Strength:	[redacted]	[redacted]	N/A
Route of Administration:	Oral	Oral	Oral
Dosing Instructions:	**3 capsules QD**	**3 capsules QD**	**3 capsules QD**
Daily Dose of RO6889450	[redacted]	[redacted]	NA
Packaging and Labelinga	**HDPE bottle**	**HDPE bottle**	**HDPE bottle**
Storage Conditions	Do not store above 30°C, protect from light, keep container tightly closed.	Do not store above 30°C, protect from light, keep container tightly closed.	Do not store above 30°C, protect from light, keep container tightly closed.

Table 4 Summary of Treatments Administered (cont.)

Study Part B (from Protocol Version 5)		
Study Drug Name:	RO6889450 (IMP)	RO6889450 (placebo; IMP)
Dosage Formulation:	Hard capsules	Hard capsules
Strength:	[redacted]	N/A
Route of Administration:	Oral	Oral
Dosing Instructions:	Patients will take 3 capsules from each of two bottles (total 6 capsules) once daily, preferably in the morning, with or without food.	
[redacted] **arm**	3 capsules [redacted] and	3 capsules placebo QD
[redacted] **arm**	6 capsules QD (three from each of two bottles)	N/A
Placebo arm	N/A	6 capsules QD (three from each of two bottles)
Daily Dose of RO6889450	[redacted]	NA
Packaging and Labeling[a]		
[redacted] **arm**	1 HDPE bottle	1 HDPE bottle
[redacted] **arm**	2 HDPE bottles	N/A
Placebo arm	N/A	2 HDPE bottles
Storage Conditions	Do not store above 30°C, protect from light, keep container tightly closed.	Do not store above 30°C, protect from light, keep container tightly closed.

Abbreviations: HDPE = high density polyethylene; IMP = investigational medicinal product; N/A = not applicable; QD = once a day

[a] Study drug will be provided in HDPE bottles. Each HDPE bottle will be labeled as required per country requirement.

Study drug should preferably be taken in the morning. Study drug can be taken with or without food, regardless of the timing of meals. A minimum of 8 hours between study drug intake on one day to the next daily dose is recommended.

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

Please see the RO6889450 Investigator's Brochure 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 IMPs will be in accordance with Sponsor standard 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, and integrity of seals.
- Report any deviations or product complaints to the study monitor upon discovery.

For the placebo compliance period, the bottles are open-label and the batch number is the identifier. The qualified individual responsible for dispensing will dispense the batch number assigned to a participant by the IxRS.

Each double-blind bottle of capsules will be labeled with a unique medication number (MEDNO). The qualified individual responsible for dispensing the study drug will dispense the correct bottles of IMP to the participant at each dispensing visit by matching the MEDNOs allocated by the IxRS for that visit with the number printed on the IMP label.

Only participants enrolled in the study may receive study drug and only authorized site staff may supply or administer IMP. If the IMP dispensing visit cannot take place in the clinic (e.g., due to travel restriction due to an outbreak of COVID-19) and alternatives methods of delivery are not feasible, the IMP dispensing may be done with direct site to patient shipment (with a prior approval from relevant health authority if applicable). All IMPs 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. Any deviations or product complaints should be reported to the study monitor upon discovery.

The Investigator, Institution, or the Head of the Medical Institution (where applicable) is responsible for IMP 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 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

An IxRS will be used to randomize the participants in equal proportion to the treatment arms.

The randomization numbers will be generated by the Sponsor or its designee. Details on randomization and stratification factors are described in Section 4.1.

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 investigative site and the Sponsor Study Management Team (SMT) will be blinded.

If unblinding is necessary for participant management (e.g., in case the knowledge is needed for treatment of a SAE), the Investigator will be able to break the treatment code using IxRS. Treatment codes should not be broken except in emergency situations. 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. The Investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a SAE).

The randomization list will be made available to the individual responsible for PK sample bioanalysis and to statisticians or statistical programmers at Roche. Also, members of the iDMC will be unblinded. The Sponsor's study statistician as well as a statistical programmer will be unblinded to provide unblinded safety information to the iDMC.

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.

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.

Whenever disclosure of the identity of the test medication is necessary, adequate procedures will be in place to ensure integrity of the data.

6.4 TREATMENT COMPLIANCE

The qualified site personnel will dispense the correct bottles of IMP according to the visits outlined in the Schedule of Activities (SoA; see Section 1.3) and according to the IxRS instructions (see Section 6.2). This individual will write the date dispensed and

participant number on the IMP label. To improve compliance bottles will be marked as Bottle A and Bottle B. This individual will also record the unique batch numbers for the placebo compliance period or MEDNOs for the double-blind period received by each participant in the participant's records. Treatment compliance verification will be done using the medication adherence platform via a smartphone app (see Section 6.4.1) and will also be checked by the site.

6.4.1 Medication Adherence Platform

This trial will employ a medication adherence monitoring platform ("Platform"). The Platform will either be provided to a participant preloaded on a smartphone, or the participant may download the Platform onto their own smartphone. 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 allows 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 or not 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 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 are found to regularly not take their medication will be contacted by study staff for retraining and motivational interventions.

6.5 CONCOMITANT THERAPY

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

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

6.5.1 Rescue Medicine During Part A

If early signs of relapse requiring treatment are noticed/recorded by the Investigator, an antipsychotic should be prescribed and the participant will be immediately withdrawn from the study drug. Investigators should make reasonable effort to complete a final assessment including efficacy endpoints before starting antipsychotic medication.

6.5.2 Permitted Therapy

Concomitant therapy includes any medication, e.g., prescription drugs, OTC drugs, approved dietary and herbal supplements, nutritional supplements and any non-medication 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.

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

The use of stable, scheduled doses of benzodiazepines is permitted. The use of stable, scheduled doses of non-benzodiazepine hypnotics is permitted.

If deemed necessary by the Investigator to treat occasional anxiety, agitation, or sleep problems, lorazepam, alprazolam, or oxazepam are allowed as needed ([PRN], up to a maximum daily dose of lorazepam 6 mg, alprazolam 3 mg, or oxazepam 90 mg). If PRN treatment of more than five consecutive days is necessary, this should be discussed with the Medical Monitor. PRN doses of benzodiazepines should not be administered within 12 hours of a clinic visit.

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, provided that they have been stable for 28 days prior to screening and are intended to remain stable throughout the study up to the follow-up visits.

Participants in Part B of the study have to be on stable treatment (i.e., no medication changes or significant dose adjustments) with D2/5HT2A antagonists or D2 partial agonist for a minimum of six months prior to screening. *In cases where change in medication is not associated with the participant's psychiatric stability, treatment changes can be accepted up to three months prior to screening.*

Co-administration of RO6889450 and weak P-gp substrates, such as risperidone, amisulpride, aripiprazole, and paliperidone, though permitted may result in slight elevations of the P-gp substrate, so continued monitoring is suggested.

SARS-CoV-2 vaccines were permitted during the study (see Section 2.3).

6.5.3 Prohibited Therapy

Use of the following therapies (non-topical formulation where applicable) is prohibited during the study unless otherwise specified:

- Clinically relevant substrates of P-gp, including quinidine and loperamide.
- Cannabidiol (may affect schizophrenia symptoms [McGuire 2018]).

In Part A, all antipsychotic treatment as well as medications used to treat EPS (e.g., anticholinergics) will be discontinued before randomization. Antipsychotic medications that require longer washout periods (i.e., more than two weeks), such as cariprazine, brexpiprazole, and long-acting injectable antipsychotics (e.g., aripiprazole lauroxil, olanzapine pamoate, and haloperidol decanoate) are exclusionary at screening (see Section 5.3, and Appendix 6).

Patients receiving treatment for tardive dyskinesia (e.g., valbenazine or deutetrabenazine) are excluded (see Section 5.2). As a general rule, no new concomitant medications will be permitted, with the exception of medications to treat AEs, unless the rationale for exception is discussed with the Sponsor or designee and clearly documented between the Investigator and the Sponsor.

6.6 DOSAGE MODIFICATION

No dosage modifications are allowed in this study.

6.7 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 earlier participant withdrawal. Participants should consult with their physician on available treatment options, such as antipsychotics, to begin after the last dose of study drug.

7. DISCONTINUATION OF STUDY DRUG AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

An excessive rate of withdrawals (either participants discontinuing study drug 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.

Details on study and site closures are provided in Appendix 1 Study Governance Considerations Study.

7.1 DISCONTINUATION OF STUDY DRUG

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

- Pregnancy
- Participant 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.

7.1.1 Part A

During Part A, participants will be monitored for signs of relapse by evaluating their typical prodromal symptoms, referred to as MTS (see Section 8.1.1.3) at scheduled site visits and during phone calls. If an increase in MTS is noted during a phone call as described below for either the CGI-S or CGI-I MTS, the participant will be asked to come in for an unscheduled visit for a full evaluation by the clinician.

CGI-S-MTS

- at least an increase of 1 point on two CGI-S-MTS as compared to baseline scores

OR

- an increase of 2 points on one CGI-S-MTS as compared to the baseline score

CGI-I-MTS

- at least a CGI-I-MTS score of 5 on two CGI-I-MTS

OR

- at least a CGI-I-MTS score of 6 on one CGI-I-MTS

Participants exhibiting signs or symptoms of a psychotic relapse or considered at imminent risk of relapse by the investigator at a scheduled or unscheduled visit should be withdrawn from the study.

The following guidance is provided for the use of investigators in Part A:

- Participants that have a CGI-I ≥ 5 (minimally worse) and an increase on any of the following PANSS items: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content to a score of > 4 with an absolute increase of ≥ 2 on that specific item since randomization should be considered for treatment discontinuation. If a patient meets these criteria and is not withdrawn from the study, the investigator needs to discuss this with the Medical Monitor.

7.1.2 Part A and Part B

In Part A and Part B, patients that meet the following criteria will be discontinued from study medication:

1. hospitalization due to worsening of psychotic symptoms.
2. suicidal behavior or active suicidal ideation with specific plan and intent.
3. violent or aggressive behavior resulting in injury or property damage.
4. symptomatic with moderate or severe COVID-19 infection (as per WHO guidelines) with signs of pneumonia or hypoxia.

If, in the judgement of the Investigator, the participant is at an imminent risk of relapse, even if none of the above criteria are met, the participant should be withdrawn from the study as well.

Discontinuation of study intervention for abnormal liver function should be considered by the Investigator when a participant meets one of the conditions outlined (Section 6 of Appendix 3) or if the Investigator determines that it is in 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 baseline 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.

Participants who discontinue study drug prematurely will be asked to return to the clinic for a study completion/early termination visit (see Section 8.11.3) and may undergo

follow-up assessments (see Section 8.11.4). The primary reason for premature study drug discontinuation should be documented on the appropriate eCRF.

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.

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 and psychiatric conditions that the Investigator or Sponsor determines may jeopardize the participant's safety if he/she continues in the study.

If possible, 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 remain as part of the overall research data.

Participants who withdraw from the study will not be replaced.

See the 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 SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

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

8.1 EFFICACY ASSESSMENTS

8.1.1 Efficacy Assessments to be Completed at Site Visits

Training, guidance on rater qualifications and procedures are described separately in the Ratings Manual. The following assessments will be performed by an approved remote centralized rater:

- BNSS
- PANSS

Remote centralized raters will administer assessments live via secure videoconference. The centralized 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.

8.1.1.1 Brief Negative Symptom Scale

The BNSS (Strauss et al 2012) is a 13-item instrument designed for clinical trials that measures the severity of negative symptoms in five domains (subscales): blunted affect, alogia, asociality, anhedonia, and avolition/apathy. All ratings are based on a semi-structured interview with prompts and queries. Items are rated on a 7-point scale,

ranging from the symptom being absent (0) to severe (6). Subscale scores as well as a total score will be derived. The avolition/apathy subscore is the primary endpoint for this study. The full scale should take approximately 10-15 minutes to complete.

8.1.1.2 Positive and Negative Syndrome Scale

The PANSS is a 30-item clinician-rated instrument for assessing positive, negative and other symptoms in patients with schizophrenia (Kay et al 1987). The symptoms are rated on a 7-point scale capturing absent to extreme psychopathology and has demonstrated sensitivity to effects seen with medication. A total score will be derived with higher scores indicating greater severity of symptoms. Further classification of symptoms using a factor analysis of the PANSS will also be calculated for the following five factors: negative symptoms, positive symptoms, disorganized thought, uncontrolled hostility/excitement, and anxiety/depression. The scale takes approximately 40 minutes to administer.

A caregiver or informant identified upon enrollment of the participant should have intimate knowledge of the participant's situation and level of impairment to be able to provide accurate information as required to complete the informant checklist (IC) PANSS.

The PANSS Positive and Negative Symptoms Factor Score as described in Table 6 will be used as an entry criterion for the study (see Section 5.1).

Table 6 PANSS Positive and Negative Symptoms Factor Score

Factor	Original PANSS Item Number	PANSS Item Name
Negative symptoms	N1	Blunted affect
	N2	Emotional withdrawal
	N3	Poor rapport
	N4	Passive/apathetic social withdrawal
	N6	Lack of spontaneity and flow of conversation
	G7	Motor retardation
	G16	Active social avoidance
Factor	Original PANSS Item Number	PANSS Item Name
Positive symptoms	P1	Delusions
	P3	Hallucinatory behavior
	P5	Grandiosity
	P6	Suspiciousness
	N7	Stereotyped thinking
	G1	Somatic concern
	G9	Unusual thought content
	G12	Lack of judgement and insight

8.1.1.3 Clinical Global Impression Scales

The CGI rating scales are tools used to evaluate both the severity of illness and change from baseline (Guy 1976). The CGI-S reflects the severity of illness on a 7-point scale ranging from no symptoms (1) to very severe (7). The CGI-I is used to assess the clinical change as compared to symptoms at baseline using a 7-point scale, ranging from very much improved (1) to very much worse (7). In this study, overall clinical status will be evaluated with the CGI-S and CGI-I. Overall global impression of negative symptoms will be assessed using the CGI-S and CGI-I for negative symptoms (Haro et al 2003).

Only in part A: At screening, clinicians will gather information from the patient's past psychiatric history, caregiver feedback, and clinical judgement to determine two to three prodromal or MTS historically associated with a signal of the patient's relapse. 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. This re-assessment of the patient's prodromal symptoms will support with the ongoing clinical evaluation of relapse risk.

It takes approximately 15 to 20 minutes to complete all CGI-I and CGI-S scales.

8.1.1.4 Fagerström Test for Nicotine Dependence

The Fagerström Tolerance Scale (Heatherton et al. 1991) will be used to assess nicotine consumption during the course of the study. The Fagerström test 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. The test will only be administered to participants that are cigarette smokers and is not applicable for other forms of nicotine consumption or non-smokers.

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.

8.1.1.5 Reinforcement Learning Working Memory Task

This task assesses the ability to learn from positive reward and establish corresponding mental value representations, functions that are deficient in patients with negative symptoms (Gold et al 2008, Gold et al 2012)

In completing the RLWM task, participants have to learn to select one out of three button presses for each stimulus (one stimulus present at a time) (Gold et al 2012). The number of stimuli in the set to be learned at any one time ranges from 2, 3, 4, 5, 6. Reinforcement probabilities are deterministic, so the correct action is always correct and the incorrect one is always incorrect. The reward magnitudes associated with a correct

action will be probabilistically assigned, with reward values 1 or 2, with probability 0.25, 0.5, or 0.75 depending on the stimulus (incorrect actions will always lead to no reward). Note that encoding this reward value is not necessary for learning the task, since the best one can hope to do for any stimulus is just select the correct action; they have no control as to whether they obtain one or two points. However, the striatal reinforcement learning system is expected to nevertheless learn to represent higher expected reward values for those stimuli associated with higher probability of two points, which we can assess in the test phase below.

In addition, with lower set sizes, participants can rely on working memory, but this is subject to decay in time and capacity limitations. As set size exceeds their working memory capacity, they have to rely on incremental reinforcement learning. The paradigm can thus isolate working memory from reinforcement learning processes that are striatal dependent.

In a subsequent test/transfer phase after initial learning, learned stimulus values will be probed by having participants choose between pairs of previously observed stimuli. Instead of selecting the response that had been 'correct' for each of the individual stimuli during the learning phase, now participants will be asked to select among pairs of stimuli and to indicate their preferences (which ones they thought had led to more points). Typically, participants are more likely to select the more rewarding stimuli, and they do so more reliably as the difference between their reward values grows. This test also allows us to assess whether participants perform better at choosing the most rewarding stimuli or in avoiding the least rewarding stimuli, when each of these are paired with neutral stimuli; this difference in performance in these conditions is related to striatal dopaminergic measures in various studies.

The RLWM task takes approximately 30 minutes to complete. This assessment will not be performed in countries without validated translation. If validated translations become available, they may be used.

8.1.1.6 Effort Cost/Benefit Tradeoff Task

This task will assess the degree to which participants are willing to engage in effortful responding as a function of the probability and magnitude of potential rewards (monetary compensation). Patients with negative symptoms show reduced willingness to engage in effortful behavior probably reflecting deficits in mental value representations and/or motivation (Gold et al 2013).

There will be a low effort/low reward and a high effort/high reward condition. In the low-effort condition, participants will respond a fixed number of times (e.g., 20) to obtain a certain reward (e.g., $3). In the high-effort condition, rather than having a fixed payoff, the reward will be proportional to the number of key presses made in that same 20 second interval. The payoff will be manipulated across trials such that in some trials, they can obtain 10¢/press (in which case 30 presses would be needed to get the same

$3 as the low-effort condition, but more than 30 presses could allow them to win that much more: 100 presses would be $10). In other trials the payoff/press would be more (e.g., 20¢/press) or less (5¢/press).

This task takes approximately 30 minutes to complete. This assessment will not be performed in countries without validated translation. If validated translations become available, they may be used.

8.1.1.7 Brief Assessment of Cognition in Schizophrenia

The BACS was designed to measure cognition in schizophrenia. The domains of cognitive function measured by the BACS including verbal memory, working memory, motor speed, attention, executive functions, and verbal fluency found to be impaired in schizophrenia (Addington et al 2003; Bilder et al 2002; Censits et al 1997; Hobart et al 1999; Keefe et al 2004; Mohamed et al 1999; Nuechterlein et al 2004; Saykin et al 1991). The BACS is found to be a valid outcome measure for the effects of rehabilitation, medication, and therapy on cognitive function, and is an indicator of functional relevance with respect to independent living skills, performance-based assessments of everyday living skills, and interview-based assessments of cognition in patients with schizophrenia (Keefe et al 2004; Keefe et al 2006). The BACS will be administered by qualified site raters using the tablet-based BACS App and should take approximately 30 minutes to complete. This assessment will not be performed in countries without validated translation. If validated translations become available, they may be used.

8.1.1.8 Virtual Reality Functional Capacity Assessment Tool

The VRFCAT is a computerized measure that was developed to be a reliable, valid, and sensitive measure of functional capacity, with the potential to demonstrate real-world functional improvements associated with cognitive change. The VRFCAT presents participants with a realistic simulated environment to recreate routine activities of daily living (Ruse et al 2014). The VRFCAT uses a game engine (the “Unreal Engine”) to create a realistic, interactive, and immersive environment consisting of four mini-scenarios that follow a story, including: (1) exploring a kitchen, (2) catching a bus to a grocery store, (3) finding/purchasing food in a grocery store, and (4) returning home on a bus. To permit repeated testing while avoiding learning effects, six alternate forms were created that vary the ingredients stored in the cabinets, items on the recipe and grocery list, cost of the bus rides, cost of groceries, and money available in a wallet. Participants complete each scenario through a progressive storyboard design. The VRFCAT should take approximately 30 minutes to complete. This assessment will not be performed in countries without validated translation. If validated translations become available, they may be used.

8.1.2 Digital Biomarkers

See Section 4.2.5 for the rationale for digital biomarker assessments.

8.1.2.1 Study Phone Usage Tracker (Smartphone App)

Participants who have a suitable personal smartphone will be asked to download the Study Phone Usage Tracker App (Torous et al 2016; Wang et al 2016; Wang et al 2017). This app will record:

- Time spent on the phone and on different apps
- Ambient noise
- Location

To fully protect study participant's privacy, the data will be collected in an anonymized manner. No participant-identifying information is collected. For example, the Study Phone Usage Tracker monitors the apps the participants use and how long they use them, but never what is done in the apps. Similarly, the ambient noise recording stores the level and quality of background noise rather than a sound clip of the background noise. Patients have the option to pause location, phone usage, and ambient noise recording.

Data are encrypted and uploaded to secure servers whenever the phone is connected to WiFi. If participants have a WiFi network at home, they are encouraged to connect their smartphone to enable data transfer. If no WiFi network is available, the sensor data will be transferred during site visits.

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

Additional information will be provided in the Digital Biomarker Manual. This assessment will not be performed in countries without validated translation. If validated translations become available, they may be used.

8.1.2.2 AiCure Digital Biomarkers

AiCure provides a brief smartphone-based automated assessment of negative symptoms of schizophrenia. The assessment includes components to produce both spontaneous and evoked responses following validated methodologies in the scientific literature consisting of the following components:

Spontaneous Response Evocation: Facial Expressivity and Free Speech

This first component asks participants brief open-ended questions along with positively and negatively valenced images and asks the participant to speak about them. This component is designed to collect spontaneous facial expressivity and free speech behavior when responding to the open-ended questions and in response to positive and negative stimuli.

Elicited Verbal and Emotionally Expressive Behaviors

This second component evokes elicited behaviors. The first elicited behavior is a sustained vowel sound (e.g., saying 'aaaah'). This component is used to calculate acoustic characteristics indicative of symptom severity in schizophrenia. The second elicited behavior is creating evoked emotional expressions (e.g. happy face, sad face). This allows for quantification of evoked emotional expressivity.

Tasks are designed to be low burden, taking approximately 2-3 minutes to complete. A pop-up visualization will signal participants once throughout the day, 3 days a week during the week prior to the visits when the BNSS is administered.

The decision to install the AiCure Digital Biomarker app is strongly encouraged. The decision not to install the AiCure Digital Biomarker app will not affect the participant's eligibility for the study. Participants can at any time point decide to remove the AiCure Digital Biomarker app from their smartphone.

Additional information will be provided in the training session while using the app.

This assessment will not be performed in countries without validated translation. If validated translations become available, they may be used.

8.1.3 Efficacy Assessments to be Completed by the Participant

8.1.3.1 Defeatist Performance Attitude Scale

The DPAS is a 15-item, patient-rated assessment that evaluates expectations of failures or self-defeating beliefs related to prior failed experiences as well as illness on a 7-point Likert scale ranging from totally agree (1) to totally disagree (7). Previous research suggests a correlation in defeatist beliefs (e.g., "People will probably think less of me if I make a mistake" or "People who have good ideas are more worthy than those who do not") and negative symptoms in schizophrenia (Grant and Beck 2009). This scale takes approximately 10 minutes to complete. It will be completed by the participant during site visits.

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

Three Likert scales assessing sleep quality, mood / well-being, and cognitive functioning will be administered via the smartphone (Appendix 10). 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: "Do you think you were taking placebo or drug?" The scales will be completed by the participant at pre-specified time points that will appear random to the participant.

8.1.3.3 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 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 WiFi or if cellular data is available. If no WiFi network is available and cellular data is unavailable, the sensor data will be transferred during site visits.

The decision to install the app is strongly encouraged. 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.

This assessment will not be performed in countries without validated translation. If validated translations become available, they may be used.

8.2 SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in Section 1.3.

Safety assessments will consist of monitoring and recording AEs, including SAEs, measurement of protocol‑specified safety laboratory assessments, measurement of protocol-specified vital signs, ECGs, and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

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

Any abnormality identified at baseline should be recorded on the Medical History 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 AE eCRF.

8.2.2 Vital Signs

Vital sign measurements will include participant's temperature, systolic and diastolic blood pressure 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, blood pressure and pulse measurements will be taken again after two minutes in a standing position (orthostatic vital signs) at the time points indicated in Section 1.3.

Blood pressure 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 blood pressure measurements.

8.2.3 Electrocardiograms

Sites will be provided with ECG equipment by the central ECG analysis vendor. Twelve-lead ECG recordings will be obtained at the time points specified in the SoA (Section 1.3) with the following parameters: heart rate, PQ (PR), QRS, QT, RR and QTcF, 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 meal-time 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. In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. 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 baseline conditions; this includes but is not limited to food intake, activity level, stressors, and room temperature.

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) as well as information on T-wave and U-wave.

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. 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 will be supplied by the central laboratory 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 eCRF. 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 received as electronically produced laboratory reports submitted directly from the 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 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, or opiates, the test may be repeated to confirm washout.

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

8.2.5 Suicidal Risk Monitoring

RO6889450 is a CNS-active study drug. There has been some concern that some CNS-active study drugs may be associated with an increased risk of suicidal ideation or

behavior. Although this study drug 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, the Sponsor considers it important to monitor for such events before or during this clinical study.

Participants being treated with RO6889450 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 RO6889450 in participants who experience signs of suicidal ideation or behavior.

Families and informants of participants being treated with RO6889450 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 C-SSRS.

The C-SSRS is a tool used to assess the lifetime suicidality of a participant (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 with actual/potential lethality (Posner et al 2011). The “baseline/lifetime” version will be completed at the screening visit and a “since last visit” version will be completed at subsequent visits. This assessment takes approximately 5-10 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 to specifically 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 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) used by the participant within 28 days prior to the screening visit.

A detailed psychiatric history will be taken during the screening period. This will include information regarding specific symptoms, hospitalizations, and treatment history. 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 which will include the above mentioned demographic information along with other pertinent information as specified on the ECF. The completed ECF will be forwarded as soon as possible to the Site Clinical Team Manager (CTM) or 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 adverse events of special interest and disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs are discussed in Sections 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 AE 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:
- 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 schizophrenia
- 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 AEs at each participant's contact. All AEs, whether reported by the participant or noted by study personnel, will be recorded in the participant's medical record and on the AE eCRF as follows:

After informed consent has been obtained **but prior to initiation of study drug**, 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 drug, all adverse events, regardless of relationship to study drug, will be reported until 28 days after the last dose of study drug.

Post-study AEs and SAEs: The Investigator is not required to actively monitor participants for adverse events after the end of the AE reporting period 28 days after the last dose of study drug.

However, if the Investigator learns of any SAE (including a death) or other AEs of concern that are believed to be related to prior treatment with study drug, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study drug or study participation, 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 or caregiver/informant is the preferred method to inquire about AE occurrence.

A consistent methodology of non-directive questioning should be adopted for eliciting AE 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 AE 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 SAEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the AE 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 AE eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome and reported according to the instructions provided in Section 8.3.5.

8.3.3.2 Sponsor Follow-Up

For SAEs, non-serious AEs 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 drug 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 drug under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/Independent Ethics Committees (IEC), and Investigators.

Investigator safety reports must be prepared for SUSARs 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 Investigator's Brochure, 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, seven 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 last dose of study drug.

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 drug, 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 participant exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

8.4 TREATMENT OF OVERDOSE

The MTD of RO6889450 has been defined as [redacted] QD (based on tolerability demonstrated when administered [redacted] [Phase I SAD study] and the occurrence of only two dose limiting events [DLEs] [redacted] Phase I MAD study in healthy volunteers). Any accidental or intentional overdose or incorrect administration of study drug should be reported as an AE (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. Document the quantity of the excess dose, as well as the duration of the overdose, in the eCRF.

8.5 PHARMACOKINETICS

Blood samples for measurement of plasma concentrations of RO6889450 and derived metabolite(s) will be collected at the time points specified in Section 1.3. Plasma concentrations will be measured by a specific and validated LC-MS/MS method. Population PK analyses using nonlinear mixed effects modeling will be performed to analyze the sparse dose-plasma concentration-time data of RO6889450 and, if feasible, of the derived metabolite(s). The influence of covariates (e.g., weight and gender) on selected PK parameters (clearance and volume of distribution) will be investigated in an exploratory way. If deemed necessary, data may be pooled with data from other studies with RO6889450 (and derived metabolite[s] if available) in order to improve the parameter estimates of the model. 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

Pharmacodynamic effects will not be assessed in this study.

8.7 FURTHER ASSESSMENTS

8.7.1 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.

8.7.2 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, at screening only. The age-corrected standard score obtained will be used as pre-morbid IQ estimate. This assessment will not be performed in countries without validated translation. If validated translations become available, they may be used. Equivalent scales may be used, if available.

8.7.3 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 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. This assessment will not be performed in countries without validated translation. If validated translations become available, they may be used. Equivalent scales may be used, if available.

8.8 GENETICS

8.8.1 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]), receptors, 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 8.9.1), otherwise the specimen will be destroyed after successful analysis.

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

8.9 BIOMARKERS

8.9.1 Samples for Research Biosample Repository

8.9.1.1 Overview of the Research Biosample Repository

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

Specimens will be collected from participants who give specific consent to participate in this optional RBR. Collected specimens 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.

8.9.1.2 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 two 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 in Appendix 1).

8.10 MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.11 TIMING OF STUDY ASSESSMENTS

8.11.1 Screening and Pretreatment Assessments

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

All screening and pretreatment assessments 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 pretreatment assessments will be performed within three to five weeks prior to start of study drug on Day 1. The screening period may be extended after discussion with *the Sponsor (Medical Monitor/designee). During screening, the ECF will be completed and forwarded as soon as possible to the CTM or Monitor via the CRO ePIP for documentation and monitoring purposes. The Investigator will act as final decision maker regarding exclusion or inclusion of participants in the study.*

In Part A of the study, all antipsychotics will be washed-out for at least one week prior to baseline/Day 1 (see Appendix 6 for details on atypical antipsychotic PK). Participants in Part A will have the option of inpatient or partial hospitalization for the washout period and for an additional week if they wish.

To enter the randomized, double-blind treatment period (Part A) there must be:

- No significant new or worsening psychiatric or medical illness since screening that in the opinion of the Investigator would interfere with the participant's ability to participate in the study.
- No change in medications since screening except as allowed in the concomitant medication section.

The treatment period begins with the investigational site call into IxRS confirming the participant's eligibility as per the confirmation of eligibility at baseline (see Section 5.3).

8.11.2 Assessments During Treatment

Under no circumstances will participants who enroll in this study and 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 *should* be performed on the day of the specified visit, unless a time window is specified in the SoA. Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment, unless otherwise noted in the SoA. 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).

If the specified order of assessments cannot be followed, every effort should be made to conduct ECG and vital sign assessments prior to blood draws. Please refer to Section 8.2.2 and 8.2.3 for further guidance. Blood samples should be taken at least 2 hours prior to PROs and COAs being performed. In exceptional situations, visits may be split over two consecutive days (as per SoA). In case the baseline visit is split over two consecutive days, study treatment administration must be performed after all assessments have been performed.

On baseline/Day1 participants will be randomized to one of the treatments as shown in Section 6.1. Study drug is to be administered on Day 1 as described in Section 6.1, only after all baseline procedures and assessments are completed. Subsequently, dosing will continue as once daily, preferably in the morning, throughout the treatment period.

During the outpatient periods, frequent telephone contacts with the participants by a clinician are planned to monitor for the emergence of any clinically significant AEs, including signs of relapse.

8.11.3 Assessments at Study Completion/Early Termination Visit

Participants who complete the study or discontinue from the study early are to return to the clinic for an end-of-treatment (EOT) visit with assessments as defined in the SoA (Section 1.3). They are then also to return for the required follow-up visits as described below.

8.11.4 Follow-Up Assessments

Follow-up phone calls will be made 7 and 14 days after the last dose of study drug or after early termination. An additional on-site follow-up visit will be performed 28 days after the last dose of study drug or after early termination.

After the study completion/early termination visit, AEs should be followed as outlined in Sections 8.3.1 and 8.3.3.

9. STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The primary efficacy analysis for this trial will compare each dose of RO6889450 with placebo at Week 12 for the primary endpoint. The following null (H_0) and alternative (H_1) hypotheses will be tested at a one-sided α=0.05 level:

- H_0: $MEAN_{RO6889450} \leq MEAN_{placebo}$ versus
- H_1: $MEAN_{RO6889450} > MEAN_{placebo}$

for which the $MEAN_{RO6889450}$ and $MEAN_{placebo}$ refer to the mean change from baseline for RO6889450 and placebo, respectively. In Part B, doses will be tested sequentially, starting with the higher and followed by the lower dose arm to maintain Type I error at 5% one-sided.

9.2 SAMPLE SIZE DETERMINATION

Assuming a true effect size of 0.5, a number of 50 participants per arm will provide 80% power to see an effect with a one-sided type I error of 0.05. Thus, the goal is to have 50 evaluable participants per arm in Part A. Allowing for about 20% of the participants randomized not completing 12 weeks of treatment, approximately 125 participants will be randomized to Part A of the study. [redacted]

In Part B, 50 participants per treatment arm will provide 80% power for an effect size of 0.5 and a one-sided type I error of 0.05. Allowing for about 25% of the participants randomized not completing 12 weeks of treatment, the goal is to have approximately 200 participants over all three dose groups, leading to 50 evaluable participants per treatment arm. *In case of an unexpectedly high proportion of participants not completing 12 weeks of treatment (i.e. more than 25%), the number of randomized participants may be increased to achieve 150 patients completing 12 weeks of treatment.*

These 200 participants will be recruited outside Japan. In addition to these 200 participants, approximately 20 participants will be recruited in Japan, leading to approximately additional 5 evaluable participants per treatment arm. The primary analysis will be based on all participants recruited outside Japan and in Japan and will be performed when all patients from outside Japan and in Japan complete the study.

Based on data from previously conducted studies in negative symptoms, the standard deviation for the change from baseline in the BNSS Avolition/Apathy Subscale (consisting of the sum of the two items 'Avolition/Apathy: Behavior' and 'Avolition/Apathy: Internal Experience') at Week 12 is about 2.8. Hence, an effect size of 0.5 translates to a reduction (versus placebo) of 1.4 points for the primary endpoint. With an anticipated sample size of 50 participants per arm, statistical significance at the one-sided type I error of 0.05, any observed reductions (versus placebo) by

approximately 0.92 or more points is expected to be statistically significant. For these calculations, the BNSS items are assumed to be rated on a 7-point (0–6) scale, with anchor points ranging from the symptom's being absent (0) to severe (6).

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined in Table 7.

Table 7 Analysis Populations

Population	Description
Modified intent-to-treat (ITT)	All randomized participants who have received at least one dose of study drug will be included in the efficacy population.
Per-protocol	All randomized participants who finished 12 weeks of treatment without any major protocol violations and acceptable compliance
Safety	Same as modified ITT population.
Pharmacokinetic	All participants who have received at least one dose of study drug 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 that 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 and secondary efficacy analyses will be based on the efficacy population defined in Table 7.

For the primary analysis of the primary endpoint, the model $Y_{ijk} = \mu + b_i + \tau_k + t_j + (\tau t)_{kj} + \varepsilon_{ijk}$ will be used. Therein Y_{ijk} denotes the change from baseline in participant i at visit j, μ denotes the general mean, τ_k is the fixed effect of treatment k, t_j is the fixed effect of visit j, and b_i is the baseline value of the variable analyzed for participant i. The model also includes the treatment-by-visit interactions $(\tau t)_{kj}$. The random errors ε_{ijk} are assumed to be independent across different participants, while within each participant an unspecified

covariance structure will be modelled. Albeit not mentioned in the model equation, factors other than baseline used for stratification at the time of randomization will be added to the model. Baseline of the variable analyzed will be included as a continuous covariate.

Least squares means per treatment arm 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 arm and placebo will be estimated and also reported with 2-sided 90% confidence intervals. The comparison at Week 12 will be used to test the statistical hypothesis described in Section 9.1.

Analysis methods for efficacy endpoints are summarized in Table 8.

Table 8 Efficacy Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Primary:	
• Change from baseline at Week 12 in the BNSS avolition/apathy subscore (sum of items “behavior” and “internal experience”)	• Repeated Measures Model as described in Section 9.4.2.
Secondary:	
• CGI-I and CGI-I negative symptoms scores • CGI-S and CGI-S negative symptoms scores	• Percent responders and percent deteriorating
• Change from baseline in PANSS total and symptom factor scores • Change from baseline in BNSS total and subscores • Change from baseline in DPAS scores	• Similar models as described in Section 9.4.2 will be used for change from baseline endpoints of approximately continuous variables (e.g., PANSS, BNSS, DPAS, etc).
• 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 vital signs • 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, coagulation and urinalysis test results	• AEs will be presented as frequency tables with the number and percentage of participants experiencing AEs. • Summary statistics of raw values as well as changes from baseline will be presented for continuous safety endpoints. • Laboratory abnormalities will be presented as frequency tables with the number and percentage of participants experiencing these.
• To evaluate the pharmacokinetics (PK) of RO6889450 and RO6889450-derived metabolite(s).	• Concentration per time point • AUC_{ss} of RO6889450 and, if feasible, of RO6889450-derived metabolite(s) • C_{max} of RO6889450 and, if feasible, of RO6889450-derived metabolite(s) • Other PK parameters as appropriate

9.4.3 Safety Analyses

All safety analyses will be based on the safety analysis population grouped according to the treatment assigned at randomization. Analysis methods are summarized in Table 9.

Table 9 Safety Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Adverse events	The original terms recorded on the eCRF by the Investigator for AEs will be coded by the Sponsor. AEs will be summarized by mapped term and appropriate thesaurus level.
Clinical laboratory tests	All clinical laboratory data will be stored on the database in the units in which they were reported. Participant listings and summary statistics at each assessment time will be presented using the International System of Units (SI units; Système International d'Unités). Laboratory data not reported in SI units will be converted to SI units before processing. Laboratory test values will be presented by individual listings with flagging of values outside the normal ranges.
Vital signs	Vital signs data (including orthostatic changes) will be presented by individual listings with flagging of values outside the normal ranges and flagging of abnormalities. In addition, tabular summaries or averaged graphs will be used, as appropriate.
ECG data analysis	ECG data will be presented by individual listings. In addition, tabular descriptive summaries for the change from baseline in ECG intervals: heart rate, 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 assigning preferred terms. Concomitant medications will be presented in summary tables and listings.
C-SSRS	C-SSRS data will be presented by individual listings.
ESRS-A	ESRS-A data will be presented by individual listings.

9.4.4 Pharmacokinetic Analyses

Population PK analyses using nonlinear mixed effects modeling will be performed as described in Section 8.5.

The results of the analysis will be reported separately from the CSR.

9.5 INTERIM ANALYSES

The Sponsor may choose to conduct an interim efficacy analysis in Part A. 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. The interim analysis will be performed and interpreted by members of the Sponsor 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.

The results of this analysis may support initiation of Part B enrollment during Part A if a positive results threshold is met as defined in the SAP. In case of very slow recruitment, Part A may be stopped and/or Part B may be started without the interim analysis.

The Sponsor may choose to conduct up to two additional interim efficacy analyses of Part B to determine the chance of final success. The decision to conduct an optional interim analysis and its timing will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by members of the Sponsor study team who will be unblinded at the treatment group level. The results of such an analysis may support an early termination of Part B. Access to treatment assignment information will follow the Sponsor's standard procedures.

The planned interim analyses will be described in detail separately. An iDMC will review unblinded safety and efficacy (as appropriate) data, as outlined in the "iDMC charter". Additional ad-hoc meetings may be convened to evaluate safety.

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 drug 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) Appendix 3 (procedures of recording), Appendix 4 (clinical laboratory tests), and Appendix 5 (contraceptive guidance and collection of pregnancy information). Additional study-related appendices are in order of appearance in the protocol: Appendix 6 Atypical Antipsychotic Pharmacokinetics, Appendix 7 Antipsychotic Equivalencies, Appendix 8 Calculation of Body Mass Index, Appendix 9 Evaluation to Sign Consent (example form), and Appendix 10 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 European Union(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/ ethics committee (EC) before the study is initiated.

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 (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. During the consent process, the ability to comply with the study protocol must be assessed using the Evaluation to Sign Consent (see Appendix 9) or similar local process. 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.

Participants must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. 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.

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 are required to sign a new ICF.

In this study, the caregiver will be asked to provide information useful to assess patient eligibility and to complete clinician rated scales. A separate written informed consent will be obtained from this informant.

Consent to Participate in the Research Biosample Repository

A separate ICF will be required to document a participant's agreement to allow any remaining specimens to be used for optional exploratory research. 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 specimens 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 optional RBR specimens. 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 participant who is participating in the research, the participant's specimens 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

Sampling for the RBR 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 specimens for the RBR have the right to withdraw their specimens at any time for any reason. If a participant wishes to withdraw consent to the testing of his or her specimens, 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 BP40283 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a participant’s withdrawal from the RBR does not constitute withdrawal from Study BP40283. 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 that 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.

Confidentiality for Research Biosample Repository

Data generated from RBR specimens 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 specimens 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 specimen 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 specimen data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

Monitoring and Oversight Research Biosample Repository

Specimens 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 specimens 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., last participant, last visit [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 eCRF.

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

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 eCRF 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 to capture 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). Data will be transmitted electronically to a centralized database at the eCOA vendor. The data can be reviewed by site staff via secure access. 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. Food and Drug Administration (FDA) regulations for electronic records (21 CFR Part 11). The eCOA device data are available for view via secure access only. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have access only to data transferred by the eCOA vendors. 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 and raters will use paper booklets to capture COA data. All item-level, score data will be entered into EDC. All original forms on which participants and raters first record 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 and Sponsor designee 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 unless local regulations or institutional policies require a longer retention period. 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.

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.

2.3.4. 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.

3. Study and Site Closure

The Sponsor (or designee) has the right to suspend or terminate this study at any time. Reasons 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 drug 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:

- Any deterioration in a laboratory value (hematology, clinical chemistry, coagulation or urinalysis) or other clinical test (e.g., ECG, X−ray) that is associated with symptoms or leads to a change in study drug or concomitant treatment or discontinuation from study drug.
- 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 drug 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 drug (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. 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 that 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 eCRF.

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 Investigator will make an assessment of severity for each AE and SAE reported during the study and assign it to one of the categories provided in Table 1 (as a guidance for assessing adverse event severity).

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe, or according to a pre-defined grading criteria [e.g., National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] criteria); 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 drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug.
- Course of the event, considering especially the effects of discontinuation of study drug
- Known association of the event with the study drug 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 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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 drug:

- Serious adverse events
- Non-serious adverse events of special interest (NSAESI)
- Pregnancies (see Section 8.3.5)
- Overdoses, medication errors, drug abuse, or drug misuse associated with a SAE (see Appendix 2, Section 5.2 for details on reporting requirements)

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 Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, 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 party immediately (i.e., no more than 24 hours after learning of the event).

Events that Occur after Study Drug 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 drug (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 electronic data capture (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 party 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 and if the event is believed to be related to prior study drug, 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 any quantity that is higher than the assigned dose in any arm.
- Intentional overdose: intentional administration of a drug in any quantity that is higher than the assigned dose in 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. All special situations associated with RO6889450 or matching placebo, 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.

For RO6889450 or matching placebo, 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; see Appendix 2, Section 5.1). For RO6889450 or matching placebo, 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.

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 using the following reference document{s}:

- RO6889450 Investigator's Brochure

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.

An iDMC will monitor the incidence of these expected events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to Health Authorities.

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 three 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 drug (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 and bilirubin 5 times the 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 drug (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 blood pressure), 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 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.

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 or social management
- Planned hospitalization required by the protocol (e.g., for wash-out of previous medication)

- 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:

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

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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, and urine pregnancy test, will be performed by the central laboratory.

Local laboratory results may be utilized in the event that the central laboratory results are not available in time for either study drug 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 is 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, and urine pregnancy test, 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, other cells).
Clinical Chemistry and Lipids	• Sodium, potassium, chloride, bicarbonate, glucose, urea, creatinine, protein, albumin, phosphate, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, urate, lactate dehydrogenase, glycated hemoglobin, fructosamine, C reactive protein (CRP). • Prolactin (all patients), follicle stimulating hormone (FSH, post-menopausal females, as applicable) • Cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides.
Coagulation	• PT, aPTT and INR
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), HBsAg, HCV antibody. In cases where HCV was successfully treated, a positive HCV serology result can be followed by HCV RNA testing.
Pregnancy Test	• All WOCBP (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 (confirmed by a positive repeated sample), 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, WBCs, casts, crystals, epithelial cells, and bacteria.
Other Screening Tests	• Drugs of abuse will be measured in urine: cannabinoids, amphetamines, methamphetamines, opiates, buprenorphine, methadone, cocaine, benzodiazepines, and barbiturates. • Alcohol levels will be tested using a urine dipstick test.

Laboratory Assessments	Parameters
Antipsychotic drug level	• *Blood samples will be tested for the antipsychotic(s) noted at screening. Testing of blonanserin and perospirone cannot be performed by the central laboratory. Therefore, no blood samples to assess antipsychotic drug levels will be drawn for participants being currently treated with blonanserin and/ or perospirone. Participants currently treated with other antipsychotics in addition to blonanserin or perospirone will have blood samples taken to assess antipsychotic blood levels. Antipsychotic medication compliance of participants taking blonanserin or perospirone will be monitored via informant report and recorded in the eCRF.*

The results of each test will be transferred to Roche electronically by the laboratory vendor.

Investigators must document their review of each laboratory safety report.

Additional Statistical Considerations for Clinical Laboratory Data

- Standard Reference Ranges and Transformation of Data

Roche standard reference ranges, rather than the reference ranges of the Investigator, will be used for all parameters. For most 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 alkaline phosphatase 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, 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 each laboratory parameter. 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.

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

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 postovulation methods) and withdrawal are not acceptable methods of contraception. Female participants of childbearing potential are

eligible to participate if they agree to use an effective method of contraception consistently and correctly as described in Table 1 below.

Table 1 Acceptable 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
Less Effective Contraceptive Methods That Are User Dependent
• Male or female condom with or without spermicide • Cap, diaphragm, or sponge with spermicide
Highly Effective Methods That Are User-Independent[a]
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • 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.

a) 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.

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 drug 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 abortion not associated with 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 drug 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
Atypical Antipsychotic Pharmacokinetics

Generic	Brand	Half-life	Washout duration needed	Testing Available from Central Lab	Permitted in Part A* (washout time compatible)	Permitted in Part B** (IxRS stratification)
Aripiprazole	Abilify[1] Abilify Maintena Aristada	~75 hours, metabolite: ~94 hours PM: ~146 hours LAI: 30-57 days	2 weeks LAI: 40 weeks	X	X LAI not permitted	D2 partial agonist
Asenapine	Saphris[2]	~24 *hours* (mean)	1 week	X	X	D2/5HT2A antagonists
Brexpiprazole	Rexulti[3]	91 hours	3 weeks	X	Not permitted	D2 partial agonist
Blonanserin	Lonasen	~95.5 hours	approximately 20 days	X	Not permitted	D2/5HT2A antagonists
Cariprazine	Vraylar[4]	2-4 days, metabolite: 1-3 weeks	15 weeks	X	Not permitted	D2 partial agonist
Chlorpromazine[5]	Thorazine	30 hours	1 weeks	X	X	D2/5HT2A antagonists
Clozapine	Clozaril	*Not permitted during the study. Not permitted within 5 years prior to screening for treatment of schizophrenia and within 12 months prior to screening for treatment of insomnia and dyskinesia (< 200 mg/day).*				
Fluphenazine[6]	Prolixin	~15 hours LAI: 6.8-9.6 days	1 weeks LAI: 7 weeks	X	X LAI not permitted	D2/5HT2A antagonists
Haloperidol[7]	Haldol	IM: 20 hours IV: 14-26 Hours PO: 14-37 hours LAI: 3 weeks	IM/IV/PO: 1 week LAI: 15 weeks	X	X LAI not permitted	D2/5HT2A antagonists
Iloperidone	Fanapt[8]	EM: 18 hours, metabolites: 23-26 hours PM: 33hrs, metabolites: 31-37 hours	1 week	X	X	D2/5HT2A antagonists

Generic	Brand	Half-life	Washout duration needed	Testing Available from Central Lab	Permitted in Part A* (washout time compatible)	Permitted in Part B** (IxRS stratification)
Loxapine	Adasuve, Loxitane[9]	~8 hours	1 week	X	X	D2/5HT2A antagonists
Lurasidone HCl	Latuda[10]	~18 hours (mean)	1 week	X	X	D2/5HT2A antagonists
Molindone[11]	Moban	2 hours	1 week	X	X	D2/5HT2A antagonists
Olanzapine	Zyprexa[12] Zyprexa Relprevv	21-54 hours LAI: 30 days	2 weeks LAI: 20 weeks	X	X LAI not permitted	D2/5HT2A antagonists
Paliperidone	Invega[13] (ext-rel tabs)	~23 hours	1 week LAI: 35 weeks	X	X LAI not permitted	D2/5HT2A antagonists
Perphenazine	Trilafon[14]	9-12 hours, metabolite: 10-19 hours	1 week	X	X	D2/5HT2A antagonists
Prochlorperazine[15]	Compazine	~9 hours	1 week	X	X	D2/5HT2A antagonists
Perospirone	Lullan	1 - ~8 hours	approximately 40 h	X	X	D2/5HT2A antagonists
Quetiapine fumarate	Seroquel[16] Seroquel XR[17]	~6 hours ~7 hours (quetiapine), metabolite: 12 hours	1 week	X	X	D2/5HT2A antagonists
Risperidone	Risperdal[18] Risperdal Consta	EM: 3 hours, PM: 20 hours LAI: 3-6 days	1 week LAI: 4 weeks	X	X LAI not permitted	D2/5HT2A antagonists
Trifluoperazine[19]	Stelazine	24 hours	1 week	X	X	D2/5HT2A antagonists
Ziprasidone HCl	Geodon[20]	~7 hours	1 week	X	X	D2/5HT2A antagonists

Key: EM = extensive metabolizers; ext-rel = extended-release; PM = poor metabolizers, LAI = long-acting injectable

Not an inclusive list of medications (Rev. 1/2018).

(https://media.empr.com/documents/22/psyc_aap_0118_5255.pdf)

* Antipsychotics (AP) that require a washout of >2 weeks (i.e., LAIs, brexpiprazole, cariprazine) will not be permitted in Part A. In Part A, AP treatment does not need to be stable for six months prior to enrollment as

long as treatment changes are not related to a psychotic exacerbation. AP levels at screening in Part A are intended to be used by the investigator as one of several elements to assess the participant's compliance, reliability and expected adherence to the study protocol. Patients without detectable blood levels of AP medication (or active metabolites) may be enrolled in Part A if they have not taken AP medication for a short time prior to screening (e.g., a period of several weeks). For patients without AP levels at baseline, the washout period may be skipped if considered appropriate by the investigator after discussion with the medical monitor or sponsor and a 1 week placebo compliance period monitored with the AiCure Adherence App may be considered appropriate. If a patient is taking one of the long-acting treatments marked as not permitted in Appendix 6 at the time of screening, the patient is not eligible since the treatment requires a washout period longer than the protocol allows. These treatments should not be stopped for the purpose of entering the study. If a patient has taken any of these medications in the 6 months prior to screening and stopped them for reasons unrelated to the study the patient may be eligible upon consultation with the medical monitor.

** Participants in Part B will be stratified based on their antipsychotic treatment (1:1 stratification ratio between D2/5HT2A antagonists and D2 partial agonist). In Part B, the screening sample is used as proxy of treatment compliance and if no blood concentration of the prescribed AP medication (or active metabolites) are detected, the participant should not be enrolled.

1. Abilify [package insert]. Rockville, MD: Otsuka Pharmaceutical Co. 2014
2. Saphris [package insert]. Parsippany, NJ: Actavis. 2015
3. Rexulti [package insert]. Rockville, MD: Otsuka Pharmaceutical Co. 2018
4. Vraylar [package insert]. Parsippany, NJ: Actavis. 2015
5. "Chlorpromazine Hydrochloride". The American Society of Health-System Pharmacists. Archived from the original on 8 December 2015.
6. "Fluphenazine decanoate". The American Society of Health-System Pharmacists. Archived from the original on 2015-12-08
7. Kudo S, Ishizaki T. Pharmacokinetics of haloperidol: an update. Clin Pharmacokinet. 1999;37(6):435-56.
8. Fanapt [package insert]. Rockville, MD: Vanda Pharmaceuticals Inc. 2009
9. Adasuve [package insert]. Mountain View, CA. Alexza Pharmaceuticals, Inc. 2012.
10. Latuda [package insert]. Fort Lee, NJ: Sunovion Pharmaceuticals Inc. 2010
11. Zetin M, Cramer M, Garber D, et al. Bioavailability of oral and intramuscular molindone hydrochloride in schizophrenic patients. Clin Ther. 1985;7(2):169-75.
12. Zyprexa [package insert]. Indianapolis, IN: Eli Lilly and Co. 2009.
13. Invega [package insert]. Titusville, NJ: Janssen Pharmaceuticals Inc. 2010.
14. Trilafon [package insert]. Kenilworth, NJ: Schering Corporation. 2002.
15. Toxnet: Toxicology Data Network: Prochlorperazine. https://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+3171
16. Seroquel [package insert]. Wilmington, DE: AstraZeneca. 2003
17. Seroquel XR [package insert]. Wilmington, DE: AstraZeneca. 2009
18. Risperdal [package insert]. Titusville, NJ: Janssen Pharmaceuticals Inc. 2009

19. American Psychiatric Association. Practice guideline for the treatment of patients with schizophrenia, second edition. Am J Psychiatry. 2004; 161(Suppl):1-56.
20. Geodon [package insert]. New York, NY: Pfizer Inc. 2008

Appendix 7
Antipsychotic Equivalencies

	Possible Market Dose Strength: mg/tab or cap	Equivalent Marketed Dose of Antipsychotics: mg/day (oral)						
Risperidone	**0.25, 0.5, 1, 2, 3, 4, 5**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**
Aripiprazole	2, 5, 10, 15, 20, 30		5		10	15	20	30
Aripiprazole (Abilify Maintena) (LAI)	300 mg, 400 mg vials, i.m. (monthly)					300	400	
Aripiprazole Lauroxile (LAI)	441, 662, 882 mg, i.m. (monthly)				441	662	882	
Asenapine	5, 10			5		10		20
Brexpiprazole	0.25, 0.5, 1, 2, 3, 4		0.5	1		2		4
Blonanserin	2, 4, 8		4		8	12	16	24
Cariprazine	1.5, 3, 4.5, 6			1.5		3		6
Chlorpromazine	10, 25, 50, 100, 200	50	100	150	200	300	400	600
Fluphenazine	1, 2.5, 5, 10	1	2		4	6	8	12
Fluphenazine decanoate (LAI)	25						25	50
Haloperidol	0, 1, 2, 5, 10				3	5	6	10
Haloperidol decanoate (LAI)	50, 100				50		100	150
Iloperidone	1, 2, 4, 6, 8, 10, 12		4		8	12	16	24
Loxapine	5, 10, 25, 50	5	15	20	30	45	65	95
Lurasidone	40, 80					40		80
Molindone	5, 10, 25, 50	5	10	15	25	35	50	75
Olanzapine	2.5, 5, 7.5, 10, 15, 20		2.5	5	7.5	10	15	20
Olanzapine pamoate (LAI, bi-weekly)	210 mg, 310 mg, 405 mg vials					150	210	300
Olanzapine pamoate (LAI, monthly)	310 mg, 405 mg vials					300	405	
Paliperidone	1.5, 3, 6, 9, 12		3		6	9	12	15
Paliperidone palmitate (LAI)	39, 78, 117, 234		39		78	117		234
Perphenazine	2, 4, 8, 16	2	6	8	12	16	24	32
Perospirone	4,8,16	4	8	12	16	24	32	48
Prochlorperazine	5, 10, 25		5		10	15	25	35
Quetiapine	25, 50, 100, 200, 300, 400	75	150		300	450	600	900
Risperidone (LAI)	12.5, 25, 37.5, 50			12.5		25	37.5	50
Trifluoperazine	1, 2, 5, 10		5		10	15	20	30
Ziprasidone	20, 40, 60, 80		20	40	60		120	160

LAI = long-acting injectable

Appendix 8
Calculation of Body Mass Index

Formula for calculation of BMI

$$\text{BMI} = \frac{\text{Weight (kg)}}{\text{Height (m)}^2}$$

Unit Conversion: 1 kg = 2.2 lbs

1 inch = 2.54 cm

Example: BMI of a participant being 1.70 m tall and weighing 80 kg:

$$\frac{80 \text{ kg}}{(1.70 \text{ m})^2} = 27.7 \text{ kg/m}^2$$

The participant's standing height will be measured in bare feet standing with his/her heels and back in contact with the vertical bar of a wall mounted measuring device. The head is held so the participant looks straight forward. A level will be placed on the participant's head to ensure that the participant is looking straight forward. The point at which the lower surface of the level intersects with the vertical measuring device will be the standing height. BMI calculation will be rounded to the unit, so a BMI of 17.50 or 40.49 will be rounded to 18 and 40, respectively.

Appendix 9
Evaluation to Sign Consent (example form)

Evaluation to Sign Consent (ESC) *Form Version: 1/15/16 JMP*

MPRCID#: ___ ___ ___ ___ ___ ___ ___ **Program ID:** ___ ___ ___ **Date of Rating:** ____/____/____

Subject Initials: ___ ___ **Rater ID:** ___ ___ **Rater Initials:** ___ ___

Protocol ID#: _____ **Protocol Name:** _____

PROCEDURE:
Make a subjective judgement regarding item 1 below. Ask the patient questions 2-6. The evaluator may select the language to use in asking the questions in order to help the patient understand them.

ITEMS: **SCORE**

1. Is the patient alert and able to communicate with the examiner? _____
   yes = 2 no = 0

2. Ask the patient to name at least two (2) potential risks incurred as a result of participating in the study. **0=not able to list potential risks, 1= able to list one risk, 2 =able to list two risks** _____

_____

_____

3. Ask the patient to name at least two (2) things that will be expected of him/her in terms of patient cooperation during the study. **0=not able to list expectations, 1= able to list one expectation, 2=able to list two expectations** _____

_____

_____

4. Ask the patient to explain what he/she would do if he/she decides that they no longer wish to participate in the study. **0=doesn't know, 1=answers but not the most appropriate response, 2=talk to any staff member** _____

_____

_____

5. Ask the patient to explain what he/she would do if he/she is experiencing distress or discomfort. **0=doesn't know, 1=answers but not the most appropriate response, 2=talk to any staff member** _____

_____

_____

6. Ask the patient to explain how medications (or treatments) are assigned during the study. **0=doesn't know, 1=answers but not the most appropriate response, 2=able to explain randomization procedures** _____

_____

_____

SIGNATURE:
I hereby certify that the above patient is alert, able to communicate and able to give acceptable answers to items 2,3,4,5 and 6 above.

Total Score _____

_____ __ __/__ __/__ __ __ __
(Evaluator Signature) (Date signed)

Appendix 10
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 84 ±2)

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

Placebo ☐

Study drug ☐