Official Title: **A NON-RANDOMIZED OPEN LABEL, ADAPTIVE, PARALLEL GROUP, HUMAN POSITRON EMISSION TOMOGRAPHY (PET) STUDY TO ASSESS OCCUPANCY OF BRAIN α5-CONTAINING $GABA_A$ RECEPTORS OF RO7017773 USING [^{11}C] Ro15-4513 FOLLOWING SINGLE ORAL DOSES IN HEALTHY PARTICIPANTS**

NCT Number: NCT03507569

Document Date: Protocol
Version 1: 08 January 2018
Version 2: 08 March 2018

PROTOCOL

TITLE:	**A NON-RANDOMIZED OPEN LABEL, ADAPTIVE, PARALLEL GROUP, HUMAN POSITRON EMISSION TOMOGRAPHY (PET) STUDY TO ASSESS OCCUPANCY OF BRAIN α5-CONTAINING $GABA_A$ RECEPTORS OF RO7017773 USING [^{11}C] Ro15-4513 FOLLOWING SINGLE ORAL DOSES IN HEALTHY PARTICIPANTS**
PROTOCOL NUMBER:	BP40257
VERSION:	2
EUDRACT NUMBER:	2017-004400-22
TEST PRODUCT:	RO7017773
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 08 January 2018
DATE AMENDED	Version 2: See electronic date stamp below

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	08-Mar-2018 20:34:07

PROTOCOL ACCEPTANCE FORM

TITLE:	**A NON-RANDOMIZED OPEN LABEL, ADAPTIVE, PARALLEL GROUP, HUMAN POSITRON EMISSION TOMOGRAPHY (PET) STUDY TO ASSESS OCCUPANCY OF BRAIN α5-CONTAINING $GABA_A$ RECEPTORS OF RO7017773 USING [11C] RO15-4513 FOLLOWING SINGLE ORAL DOSES IN HEALTHY PARTICIPANTS**
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TEST PRODUCT:	RO7017773
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 2:
RATIONALE

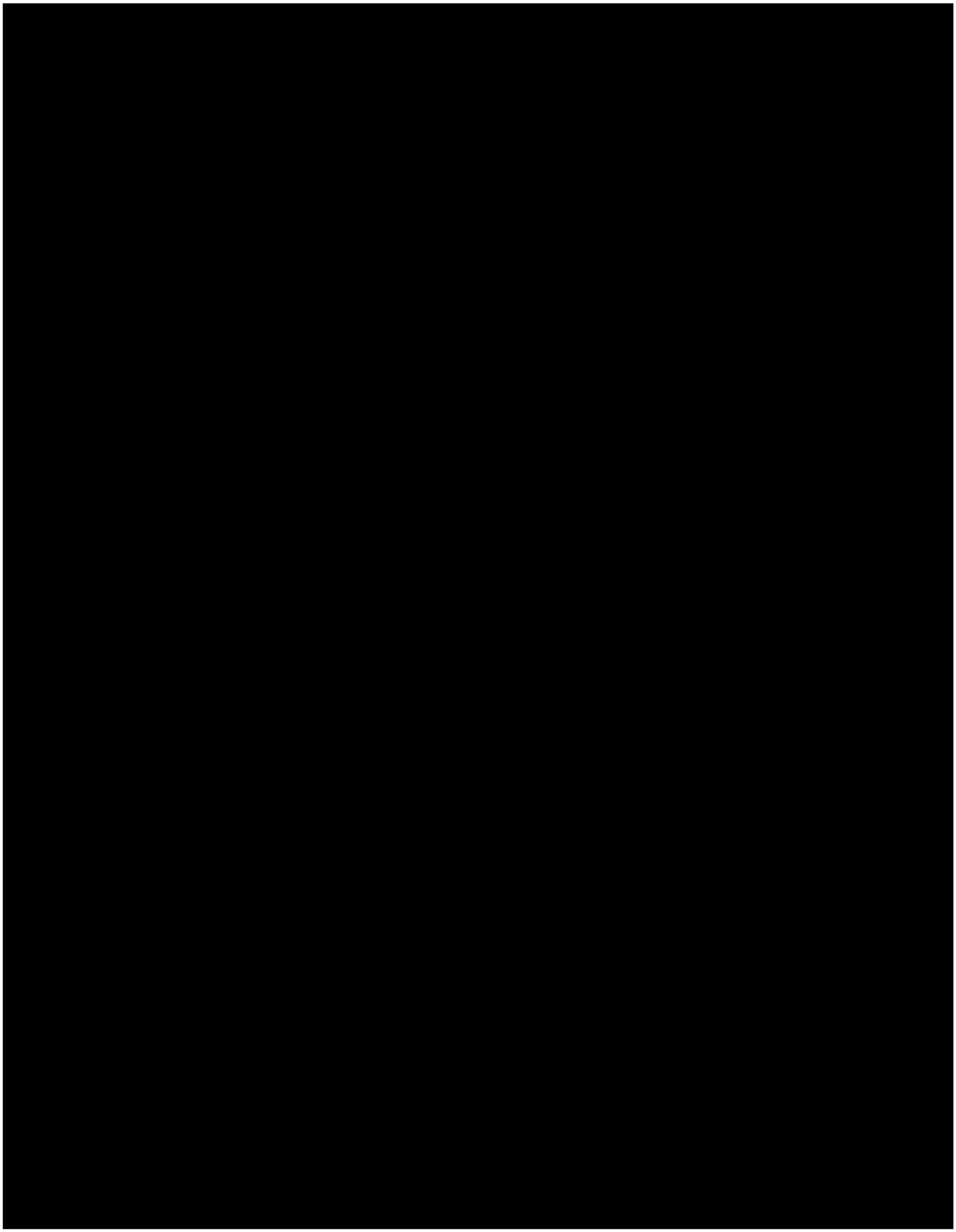
Protocol BP40257 version 1 has been amended to incorporate the following changes:

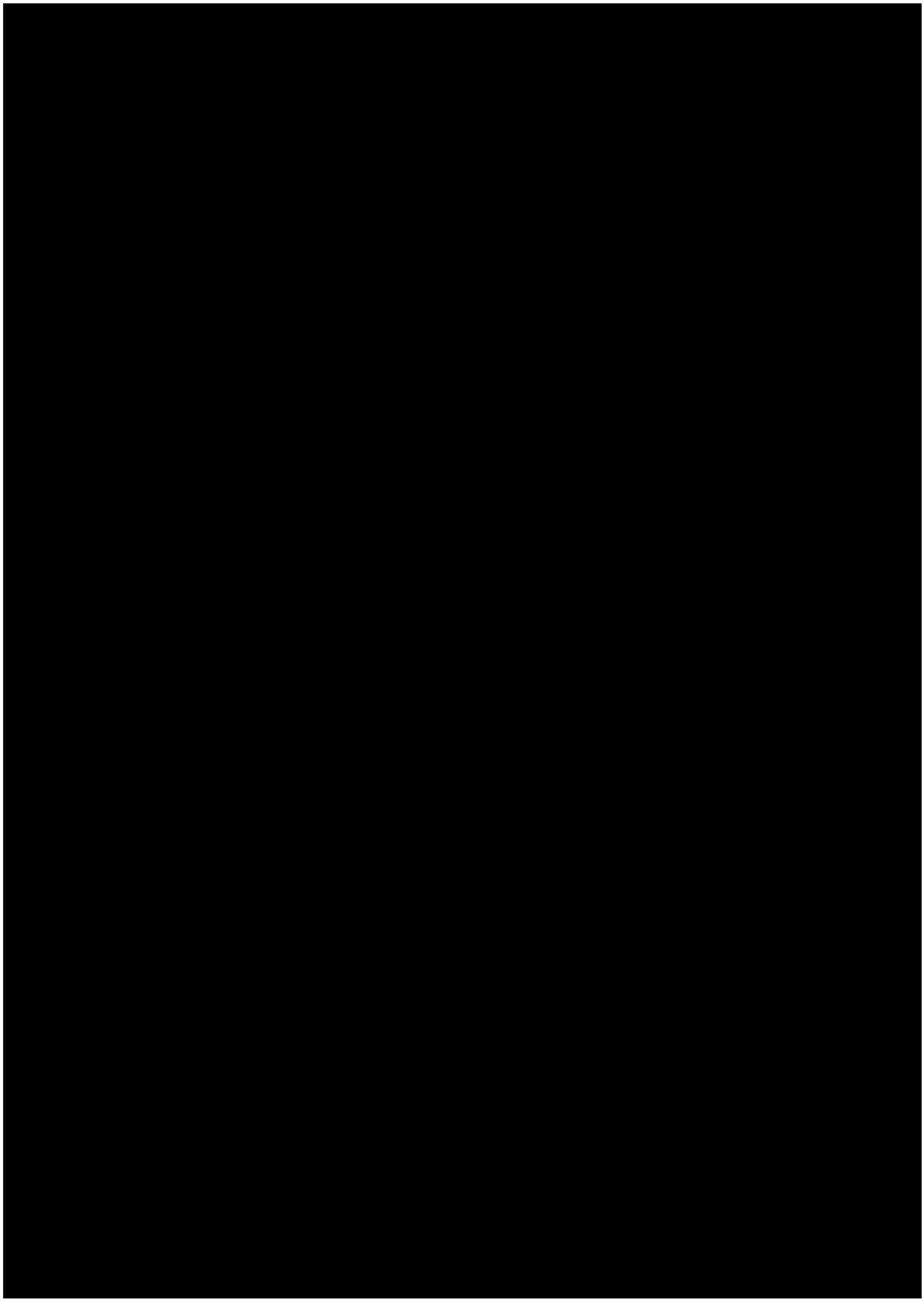
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

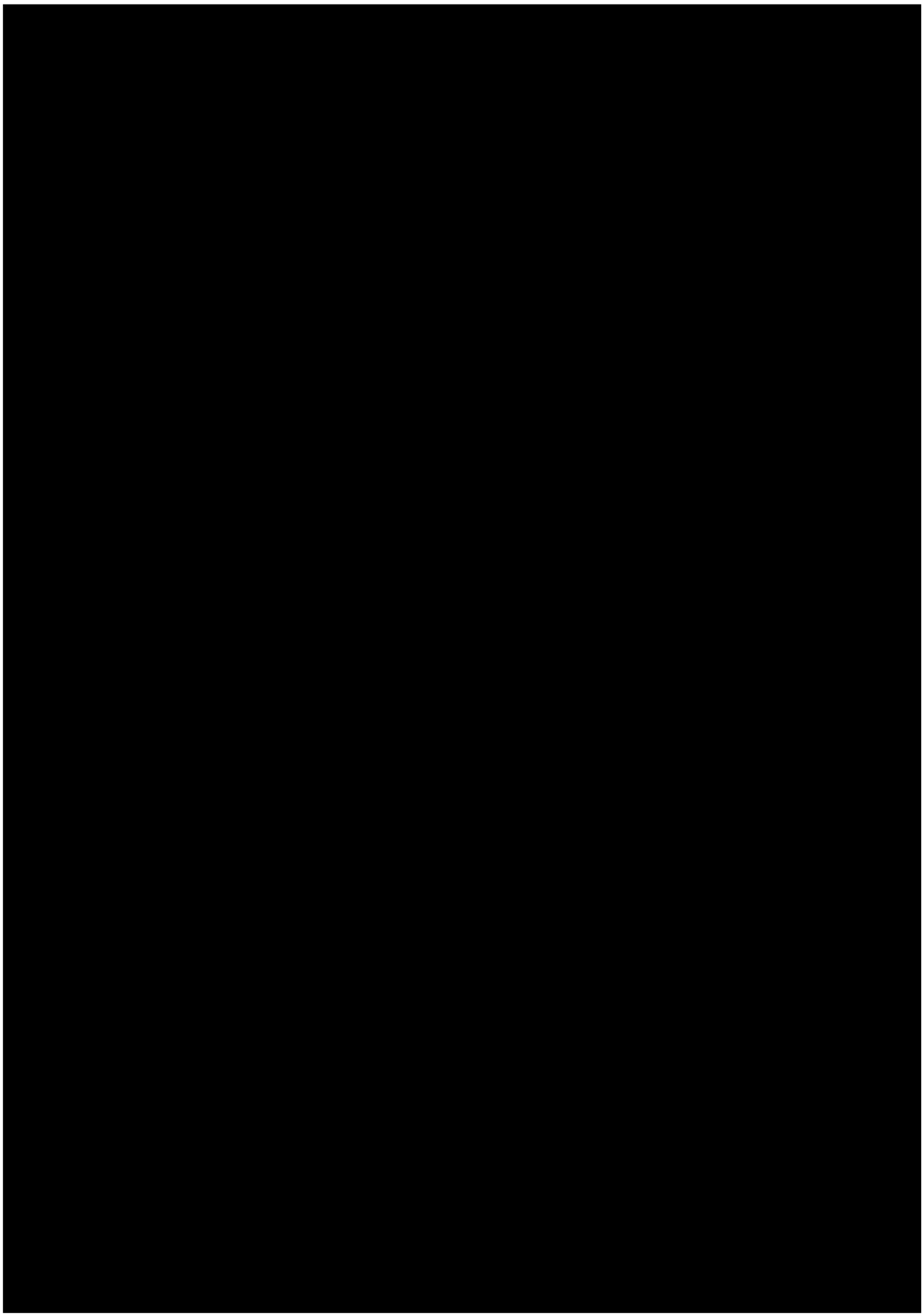
- [redacted]

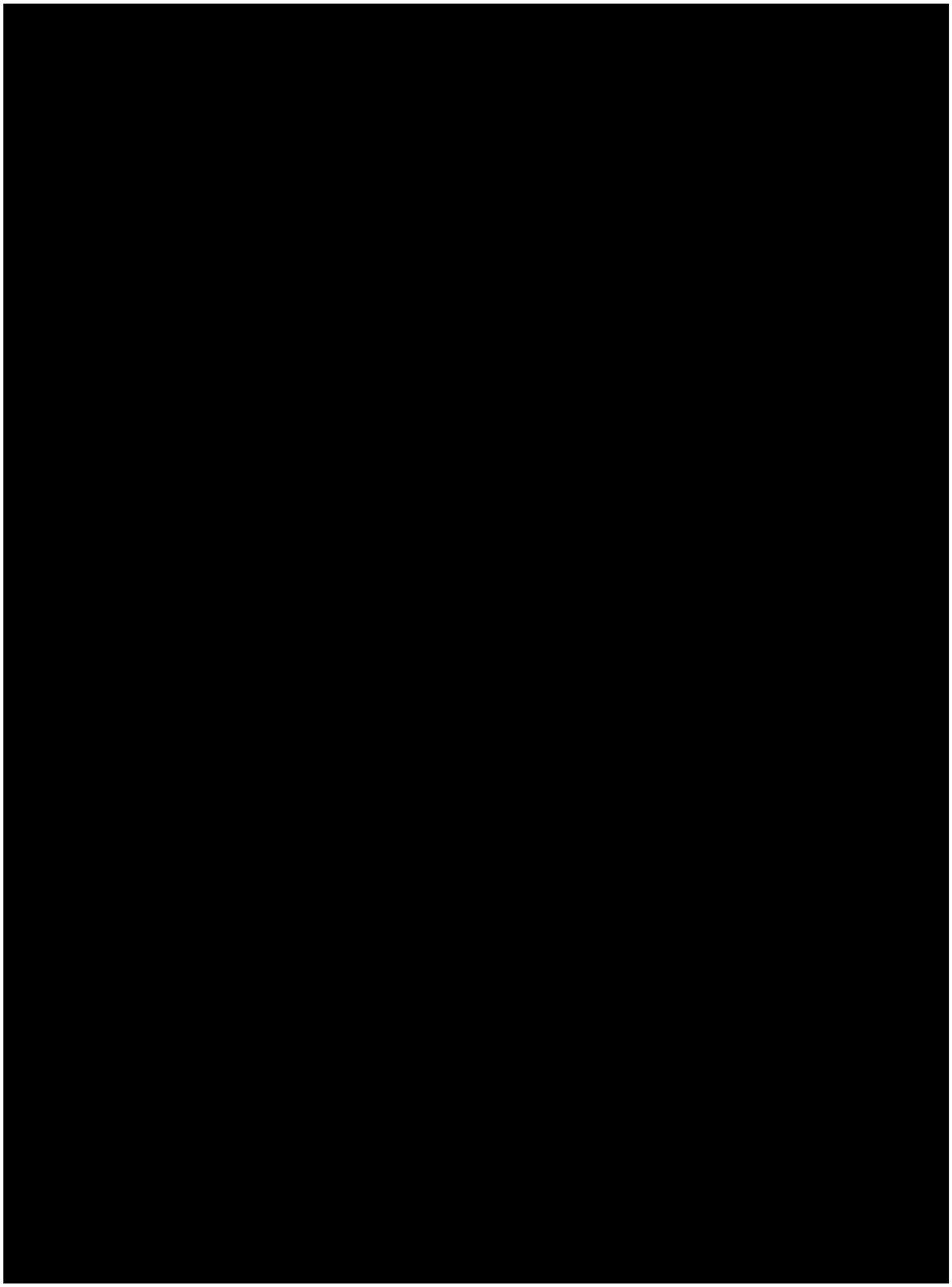
Additional minor changes have been made to improve clarity and consistency. Substantial new information appears in italics. This amendment represents cumulative changes to the original protocol.

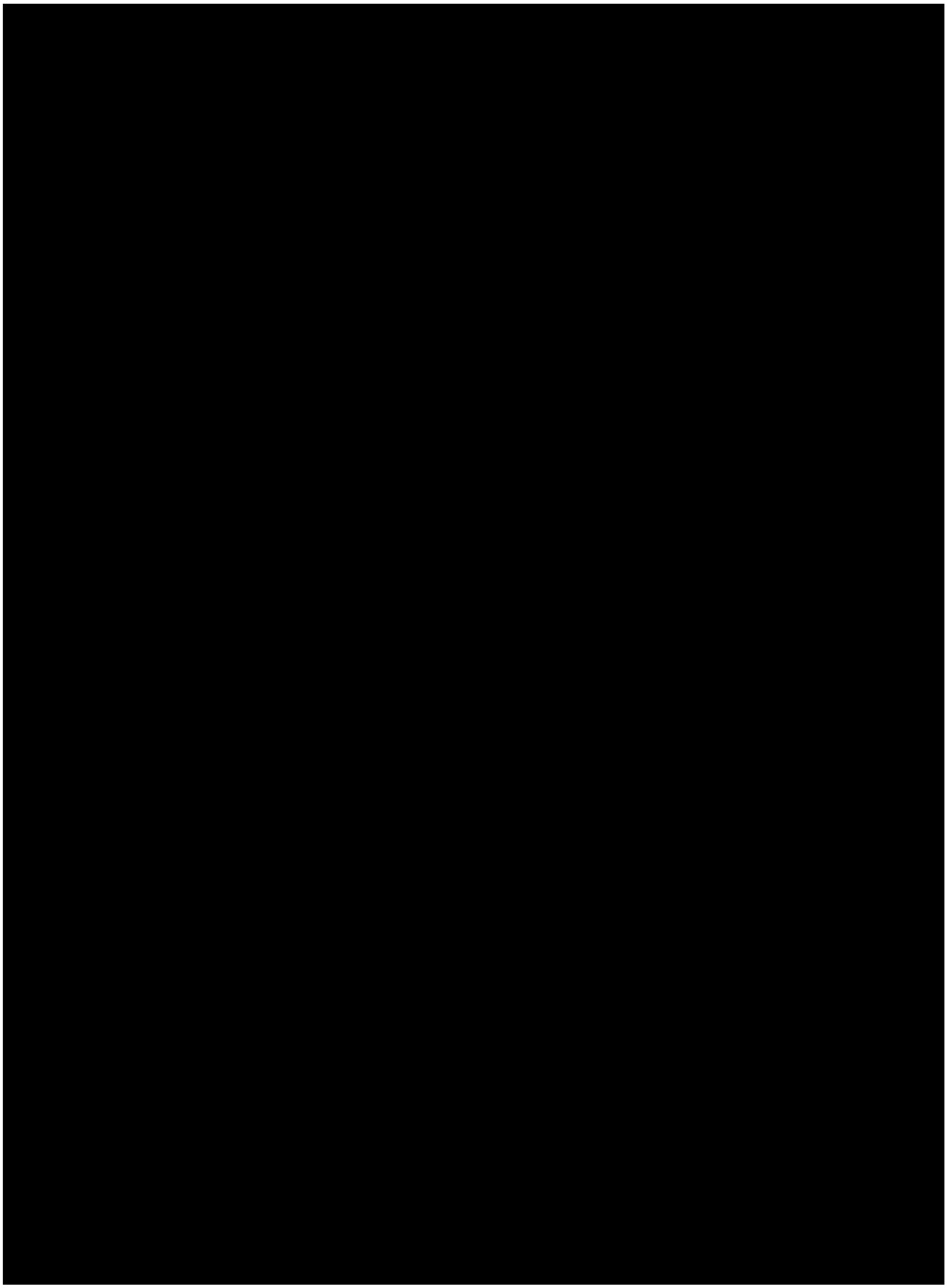
PROTOCOL AMENDMENT, VERSION 2:

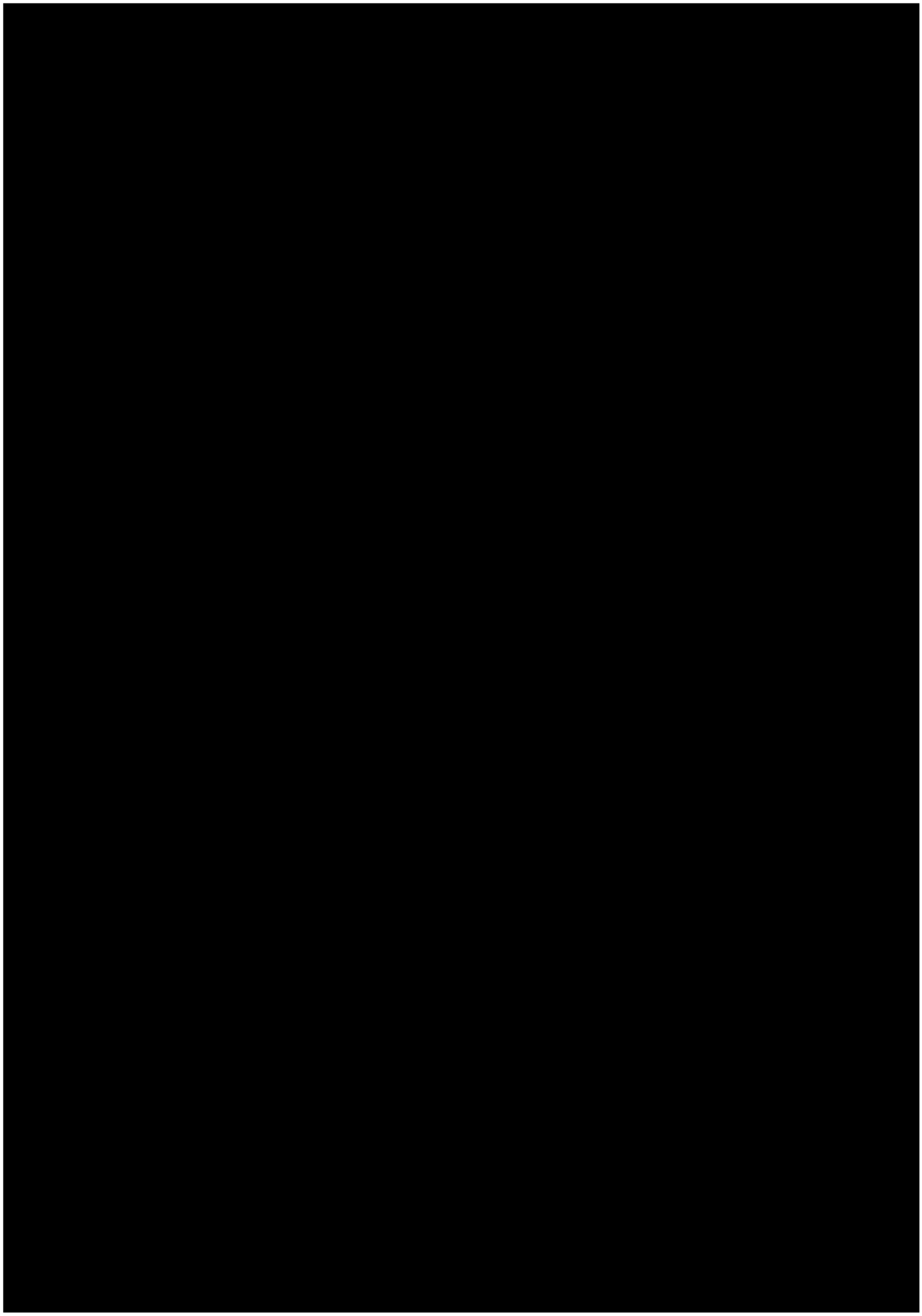


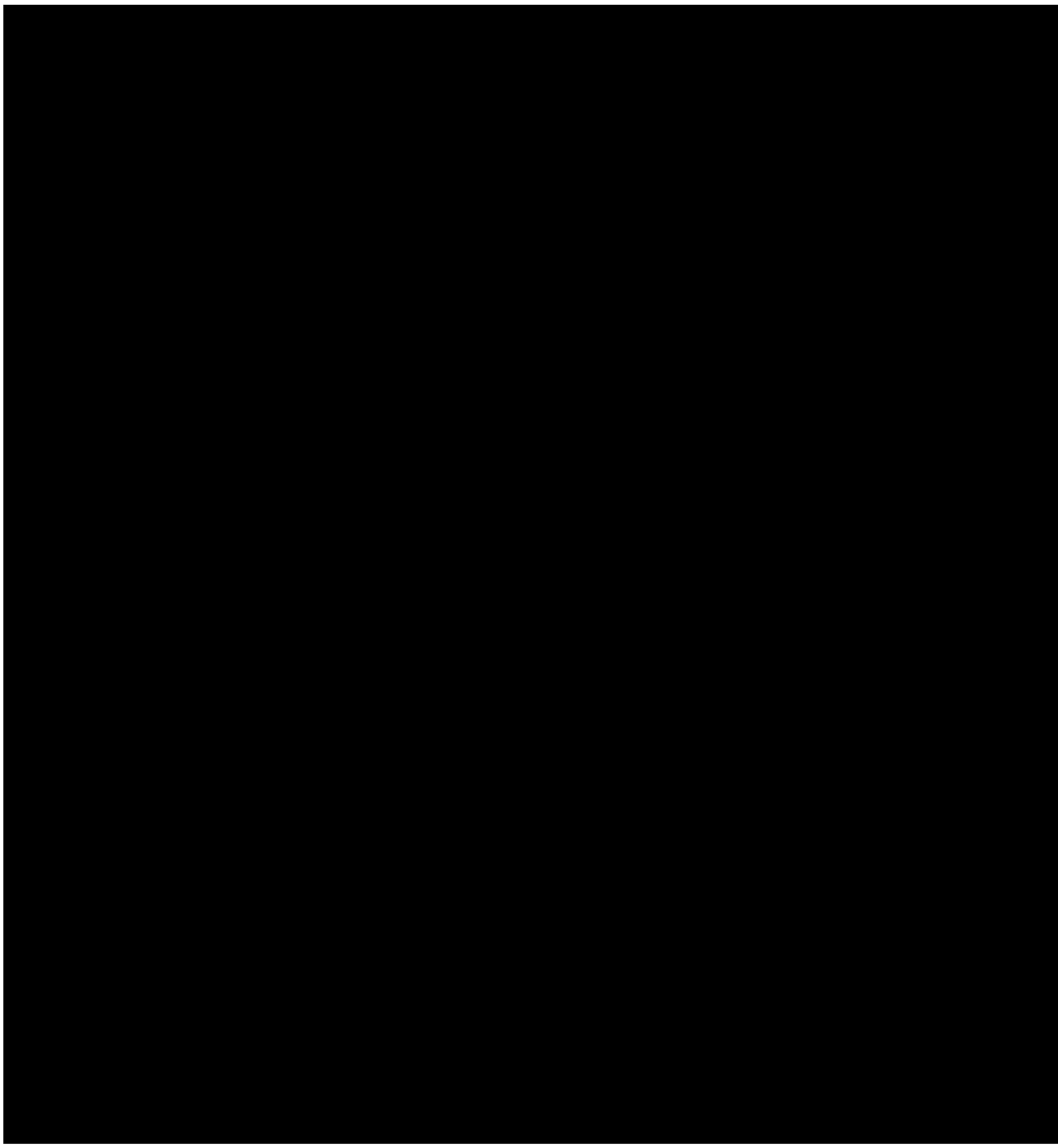












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[redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADP	Adenosine diphosphate
AE	Adverse event
aPTT	Activated partial thromboplastin time
ASD	Autism Spectrum Disorder
AUC	Area under the curve
BP	Blood pressure
CL	Clearance
CNS	Central nervous system
CRO	Contract research organization
CSR	Clinical study report
CT	Computed tomography
CYP	Cytochrome
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EU	European Commission
FSH	Follicle-stimulating hormone
GLP	Good Laboratory Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICRP	International Committee for Radiological Protection
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IND	Investigational new drug (application)
INR	International normalized ratio
IRB	Institutional review board
IV	Intravenous
LPLO	Last participant, last observation
MAD	Multiple-ascending doses
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose

NOAC	Non-vitamin K antagonist oral anticoagulant
NOAEL	No-observed-adverse-effect level
NSAESI	Non-serious adverse event of special interest
OTC	Over-the-counter
PAM	Positive allosteric modulator
PD	Pharmacodynamic
PK	Pharmacokinetic
QRS	QRS complex
QT	QT interval
QTc	QT corrected for heart rate
QTca	Individual probabilistic corrected QT
QTcF	QT corrected for heart rate using the Fridericia's correction factor
RBC	Red blood cell
RO	Receptor occupancy
ROI	Region of interest
RR	RR interval
SAD	Single-ascending dose
SAE	Serious adverse event
SoA	Schedule of activities
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reactions
TQT	Thorough QT
ULN	Upper limit of normal
V	Volume
V/F	Apparent volume of distribution
VPA	Valproic acid
WBC	White blood cell

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**A NON-RANDOMIZED, OPEN LABEL, ADAPTIVE, PARALLEL GROUP, HUMAN POSITRON EMISSION TOMOGRAPHY (PET) STUDY TO ASSESS OCCUPANCY OF BRAIN α5-CONTAINING $GABA_A$ RECEPTORS OF RO7017773 USING [^{11}C] RO15-4513 FOLLOWING SINGLE ORAL DOSES IN HEALTHY PARTICIPANTS**
SHORT TITLE	**OPEN LABEL, ADAPTIVE, PARALLEL GROUP PET STUDY USING RO7017773 AND [^{11}C] RO15-4513**
PROTOCOL NUMBER:	BP40257
VERSION:	2
TEST PRODUCT:	RO7017773
PHASE:	I

RATIONALE

This study aims to quantify the level of receptor occupancy of RO7017773 using PET tracer [^{11}C]Ro15-4513 after varying single oral doses of RO7017773. The measurement of brain receptor occupancy (RO) obtained using positron emission tomography (PET) is critically important to characterize pharmacokinetic (PK)-RO relationship and will [redacted]

This will be the first study assessing $GABA_A$ α5 receptor occupancy following single doses of RO7017773 in healthy participants using PET and the [^{11}C]Ro15-4513 PET tracer. The study will estimate the doses of RO7017773 which displaces the binding of the radiolabeled $GABA_A$ α5 ligand [^{11}C]Ro15-4513 to the receptors in the brain.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the relationship between RO7017773 plasma concentration and brain occupancy of $GABA_A$ receptor subtypes (containing the α5 subunit) after single oral doses of RO7017773 using [^{11}C]Ro15-4513 PET tracer.	• Occupancy of brain α5-containing $GABA_A$ receptors by RO7017773 in selected regions of interest (ROIs). • RO7017773 plasma concentrations.
Secondary	
• To assess the safety and tolerability of single oral doses of RO7017773.	• Incidence and severity of AE. • Changes in vital signs, physical findings, ECG parameters, and clinical laboratory results during and following RO7017773 administration.
Tertiary/Exploratory	
• [redacted]	• [redacted]

OVERALL DESIGN

Study Design

This is a single dose (SD), non-randomized, open-label, adaptive, parallel group study with the purpose of investigating the occupancy of α5-containing $GABA_A$ receptors by RO7017773 in healthy participants.

Healthy participants will be admitted to the clinical research unit on Day –1 of each imaging session. On Day 1 of the first imaging session, participant will have a baseline PET scan and will be discharged after its completion. At the second imaging session, participant will receive a single dose of RO7017773, [redacted]. The timings of PET scans and PK sampling may change based on review of emerging data *or study logistical requirements*. Participants will be discharged at least 48 hours after RO7017773 administration (at the discretion of the Investigator) when all assessments have been completed. [redacted].
For each participant, the imaging session 2 (on-treatment PET scans 1 and 2) will be at least 7 days after imaging session 1 (baseline scan).

At the start of each PET scan, participants will receive an intravenous dose of the radiolabeled tracer [^{11}C]Ro15-4513. During imaging session 2, a single oral dose of RO7017773 will be administered before the first on-treatment PET scan. Up to [redacted] dose levels, between [redacted] are anticipated to be tested allowing the extent and duration of brain $GABA_A$-α5 receptor occupancy of varying single oral doses of RO7017773 in healthy participants to be measured using the [^{11}C]Ro15-4513 PET tracer. [redacted]
-Participants will receive no more than 2 doses of RO7017773 (e.g., in case an on-treatment PET/CT scan needs to be re-scheduled *for technical or logistical reasons*), and 3 doses of the radiolabeled ligand, [^{11}C]Ro15-4513, throughout the study. Participants will attend the clinical research unit for a safety follow-up visit 5 to 10 days after the last dose of RO7017773.

[redacted]

This study will have an adaptive design to adequately evaluate the exposure versus RO relationship. The doses to be tested in the subsequent cohorts of participants will be selected after review by the Investigator, PET specialist and Sponsor of the available RO, PK, PK-RO, safety and tolerability data at the previous dose levels. The doses will be selected *in order to obtain a wide enough range of receptor occupancies to allow adequate model parameter estimation of the RO7017773 exposure-RO relationship* ~~based on RO7017773 concentrations that will span as much of the occupancy range as possible~~. If a dose level causes any safety concerns, the same or a higher dose level will not be tested in any other participants. Following review of available data from the previous dose level(s), timing of on-treatment PET scans and PK sampling may also change.

Treatment Groups and Duration

- Screening: Up to 4 weeks
- Imaging Session 1 (baseline PET scan): Day –1 to Day 1
- Imaging Session 2 (on-treatment PET scan): Day -1[1)] to [redacted]
- Safety follow-up: 5 to 10 Days after last dose

[1)]Admission for imaging session 2 will be at least 6 days after the baseline PET scan.

All participants will receive a single dose of the IMP RO7017773. The PET tracer [^{11}C]Ro15-4513 is non-IMP.

Length of Study

The total duration of the study for each participant will be up to 8 weeks.

End of Study

A participant is considered to have completed the study if he/she has completed the safety follow-up visit. The end of the study is defined as the date when the last participant last observation (LPLO) occurs. LPLO is expected to occur approximately 5 to 10 days after the last participant last dose of RO7017773.

PARTICIPANT POPULATION

The participants of this study are healthy volunteers between 23 and 55 years of age, inclusive, who fulfill all the inclusion criteria.

Inclusion Criteria

Informed Consent

1. Able and willing to provide written informed consent and to comply with the study protocol according to ICH and local regulations.

Age

2. Healthy participants aged 23 to 55 years of age, inclusive, at the time of signing the informed consent.

Type of Participants and Disease Characteristics

3. Healthy, as judged by the Investigator.

   Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, serology and urinalysis.

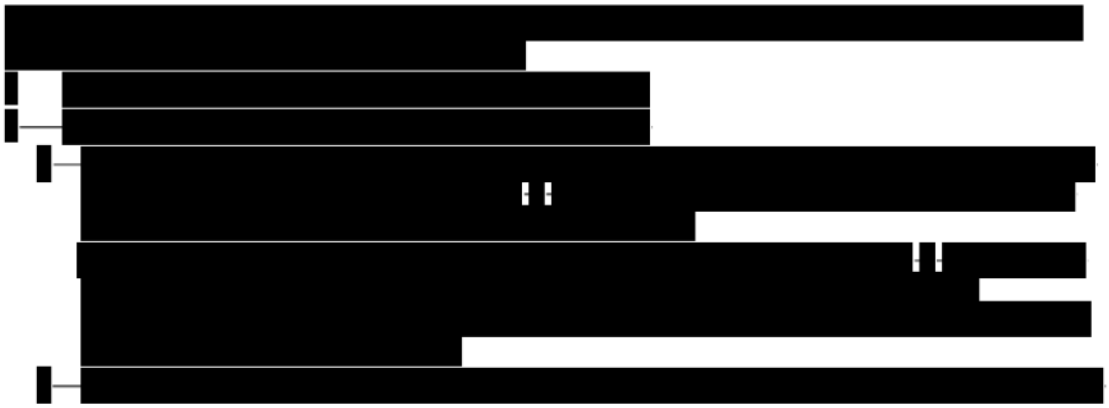
Weight

4. Body Mass Index (BMI) of 18 to 30 kg/m^2, inclusive at screening.

Sex

5. Male and female participants

a) Female Participants



b) Male Participants

During the treatment period and for at least 90 days after the last dose of study drug, agreement to:

- Remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom, with partners who are WOCBP, or pregnant female partners, to avoid exposing the embryo *to study treatment*.
- Refrain from donating sperm 90 days *after the last dose*.

The contraception and abstinence requirements are intended to prevent exposure of an embryo to the study treatment. The reliability of sexual abstinence for male ~~and/or 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

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

Medical Conditions

1. Any condition or disease detected during the medical interview/physical examination that would render the participant unsuitable for the study, place the participant at undue risk or interfere with the ability of the participant to complete the study, as determined by the Investigator.
2. History or evidence of any medical condition potentially altering the absorption, metabolism or elimination of drugs. This includes a surgical history of the gastrointestinal tract affecting gastric motility or altering the gastrointestinal tract.
3. History of any clinically significant gastrointestinal, renal, hepatic, bronchopulmonary, neurological, psychiatric, cardiovascular, endocrinological, hematological or allergic disease, metabolic disorder, ~~hypofertility,~~ cancer or cirrhosis.
4. History of convulsions (other than benign febrile convulsions of childhood) including epilepsy, or personal history of significant cerebral trauma or CNS infections (e.g., meningitis).
5. Clinically significant abnormal finding from the MRI performed after the initial screening examination.
6. A history of clinically significant hypersensitivity (e.g., drugs, excipients) or allergic reactions.
7. Any major illness within one month before the screening examination or any febrile illness within one week prior to screening and up to first study drug administration.
8. Abnormal blood pressure, i.e., systolic blood pressure (SBP) greater than 140 or less than 90 mm Hg, and diastolic blood pressure (DBP) greater than 90 or less than 50 mm Hg.

9. Abnormal pulse rate, resting pulse rate greater than 100 or less than 40 bpm.
10. History or presence of clinically significant ECG abnormalities before study drug administration (e.g., PQ/PR interval > 210 ms , QTcF > 450 ms (> 470 ms females) or cardiovascular disease (e.g., cardiac insufficiency, coronary artery disease, cardiomyopathy, congestive heart failure, family history of congenital long QT syndrome, family history of sudden death).
11. Clinically significant abnormalities in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis). In the case of uncertain or questionable results, tests performed during screening may be repeated before randomization to confirm eligibility.
12. Participants who, in the Investigator's judgment, pose a suicidal or homicidal risk, or any participant with a history of suicidal or homicidal attempts.

Prior/Concomitant Therapy

13. Participants likely to need concomitant medication during the study period (including for dental conditions).

Prior/Concurrent Clinical Study Experience

14. Participation in an investigational drug or device study within 90 days prior to screening, as calculated from the day of follow-up from the previous study, or more than 4 times a year.
15. Previous inclusion in a research and/or medical protocol involving PET or radiological investigations (within the last 12 months).

Diagnostic Assessments

16. Positive test for drugs of abuse or alcohol.
17. For WO*N*CBP, a positive pregnancy test.
18. Show evidence of human immunodeficiency virus (HIV) infection and/or positive human HIV antibodies.
19. Positive result on hepatitis B (HBV) or hepatitis C (HCV), presence of hepatitis B surface antigen (HBsAg) or positive hepatitis C antibody test result at screening or within 3 months prior to starting study treatment.

Other Exclusions

20. Dietary restrictions that would prohibit the consumption of standardized meals.
21. Any suspicion or history of alcohol abuse and/or suspicion of regular consumption of drug of abuse or previous history of or treatment for a dependence disorder.
22. Participants who regularly smoke more than 5 cigarettes daily or equivalent and unable or unwilling not to smoke during the in-house period.
23. Participants who have donated over 500 mL of blood or blood products or had significant blood loss within 3 months prior to screening.
24. Participants under judicial supervision, guardianship or curatorship.
25. Presence of a cardiac pacemaker or other electronic device; ferromagnetic metal foreign bodies in vulnerable positions; presence of certain tattoos that might make it unsafe for an MRI; participant working as a machinist, welder or metal worker; claustrophobia; as assessed by a standard pre MRI questionnaire.
26. *Occupational radiation exposure or radiation exposure* ~~Exposure to ionising radiation in~~ *from* medical *diagnostic or treatments* ~~research~~ over the past 12 months, *that would result in a dose in excess of 10 mSv* ~~which~~ *when* combined with *the planned exposure from* this study ~~would result in an effective dose in excess of 10 mSv~~.
27. Contraindication for arterial cannulation; Allen's test indicating potential risk in placement of the arterial cannula.

NUMBER OF PARTICIPANTS

It is anticipated that a maximum of 15 participants will be enrolled in the study. At each anticipated dose level, up to 2 to 3 participants may be enrolled with 2 participants per cohort.

CONCOMITANT MEDICATIONS

Permitted Therapies

- [redacted]
- Acetaminophen/paracetamol is allowed up to a maximum dose of 2 g/day up to 48 hours prior to dosing and after the in-house period, but should not exceed 4 g total during the week prior to dosing.

Prohibited Therapies

Use of the following therapies is prohibited during the study and for at least 30 days or at least 5 half-lives of the medication prior to initiation of study treatment (whichever is longer), unless otherwise specified below:

- Any prescribed or over-the-counter medication (including herbal products, vitamin, mineral, energy drinks and dietary supplements).
- [redacted]
- [redacted]
- [redacted]
- Acetylsalicylic acid and other anti-platelet and anti-coagulation medication, e.g., adenosine diphosphate (ADP) receptor inhibitors, heparin, warfarin and non-vitamin K antagonist oral anticoagulants (NOACs).

1.3 SCHEDULE OF ACTIVITIES

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

Table 1 Schedule of Activities – Main Table

Visit	Screening	Imaging Session 1 (baseline)		Imaging Session 2 (on-treatment)[a]				Follow Up Visit[b]
Day(s) (relative to PET scans)	Up to -28	-1	1	-1	1	2	3	5-10 days
Informed Consent	X							
Medical History	X							
Physical Examination	X							X
Height & weight[c]	X	X		X				X
Admission		X		X				
In-house Period		X	X	X	X	X	X	
Discharge			X				X	
Vital Signs[d]	X	X	X[e]	X	5	X	X	X
ECG-12 lead[f]	X	X	X[e]	4[g]	4	X	X	X
Serology	X							
Pregnancy Test[h]	X	X		X				X
Hormone Panel[i]	X							
Alcohol Breath Test	X	X		X				
Urine Drugs of abuse	X	X		X				
Urinalysis	X	X		X				X
Blood Chemistry	X	X		X				X
Hematology	X	X		X				X
Coagulation	X							
Standardised meal		X	X	X	X	X	X	
MRI Scan[j]	X							
Allen's test	X	X	X	X	X			
[redacted]								
Administration of RO7017773[l]					X			
Injection [^{11}C]Ro015-4513			X		2			
[redacted]								
Arterial blood sampling for [^{11}C]Ro015-4513 radioactivity measurement			X		X			
Previous and Concomitant Treatments	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X

a) For each participant, imaging session 2 (on-treatment PET/CT scans) will occur approximately 7 days after imaging session 1 (baseline scan).

b) Safety and follow-up visit to be done 5 to 10 days after the RO7017773 administration.

c) Height at screening only, when body mass index (BMI) will be derived.

d) Vital signs will include blood pressure, pulse rate and body temperature. Temperature will be recorded on Day 1 of imaging session 2 only. All measurements will be taken after the participant has rested in a supine position for at least 5 minutes.

Table 1 Schedule of Activities – Main Table (cont.)

e) Prior to the PET scan and before discharge from the unit.

f) Triplicate 12-lead ECGs will be collected after the participant has rested in a supine position for at least 10 minutes.

g) ECGs will be time-matched on Day 1 and Day -1 of imaging session 2 (see Detailed table).

h) ~~Pregnancy test for females of childbearing potential only.~~ Serum test at screening, urine test at Day –1 of imaging session 1 and 2 and follow-up. The screening pregnancy test can be used for the MRI scan if done on the day of the MRI scan otherwise an additional urine test on day of MRI scan will be performed.

i) Hormonal panel is for post-menopausal women only.

j) Participants will complete an MRI questionnaire before the scan, to exclude unsuitable and unwilling participants. The structural MRI scan may be done at a separate visit, provided the results are available before the baseline PET scan. The MRI scan should be performed within 60 days of screening.

[redacted]

l) RO7017773 will be administered orally with water, in the morning of Day 1 of imaging session 2 after an overnight fast of at least 10 hours. Water will be allowed ad libitum until 1 hour prior to dosing and from 1 hour post-dosing. *Occasionally, a technical failure (such as unsuccessful tracer synthesis) or study logistical requirements may require one or both on-treatment PET scans to be rescheduled.*

[redacted]

Table 2 Schedule of Activities – Imaging Session 2, Detailed Table

	Imaging Session 2 (on-treatment)													
	Day -1				Day 1									
Times relative to RO administration	**Predose equivalent**	**2h**	**6h**	**11h**	Predose	0h	2h	3.5h	4.5h	5h	6h	9h	10.5h	11h
Administration of RO7017773						X								
Injection [^{11}C]Ro015-4513								X				X		
[redacted]														
Vital Signs (blood pressure and pulse rate)					X		X		X		X			X
Temperature					X		X				X			
ECG-12 lead	X	X	X	X	X		X				X			X
[redacted]														

2. INTRODUCTION

[redacted]

2.1 STUDY RATIONALE

This study aims to quantify the level of receptor occupancy of RO7017773 using PET tracer [^{11}C]Ro15-4513 after varying single oral doses of RO7017773. The measurement of brain receptor occupancy (RO) obtained using positron emission tomography (PET) is critically important to characterize PK-RO relationship and [redacted]

[redacted]. Each participant will undergo a baseline PET/CT scan and two on-treatment PET/CT scans, allowing the extent and duration of brain $GABA_A$-α5 receptor occupancy of varying single oral doses of RO7017773 in healthy volunteers to be measured using the [^{11}C]Ro15-4513 PET tracer. The study will estimate the doses of RO7017773 which displaces the binding of the radiolabeled $GABA_A$ α5 ligand [^{11}C]Ro15-4513 to the receptors in the brain.

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

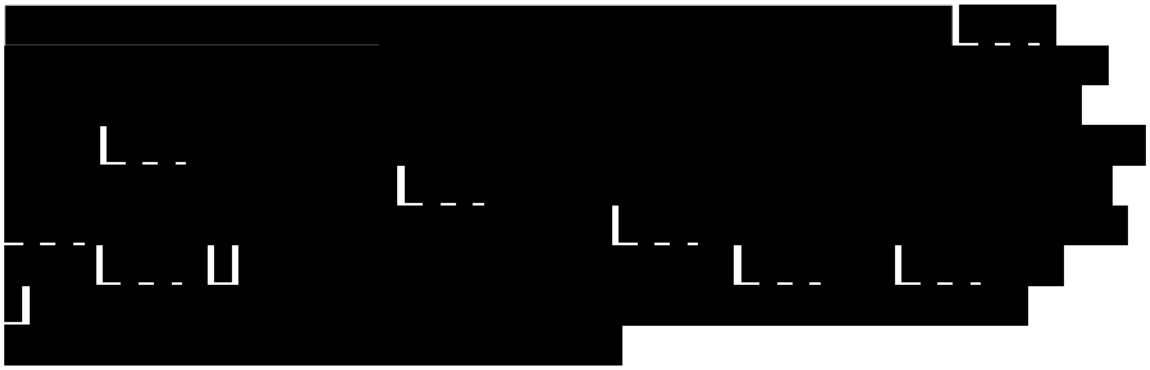
2.2 BACKGROUND

[redacted]

[redacted]

2.2.1 Background on RO7017773

[redacted]



[redacted]

[redacted]

[redacted]

[redacted]

A detailed description of the chemistry, pharmacology, efficacy and safety of RO7017773 is provided in the Investigator's Brochure (RO7017773 Investigator's Brochure).

2.2.2 Background on PET Tracer [^{11}C]Ro15-4513

In this study, the PET ligand [^{11}C]Ro15-4513 (non-Investigational Medicinal Product [NIMP]) will be given to participants at the start of each PET/CT scan, to quantify the level of receptor occupancy at α5-containing $GABA_A$ receptors after single oral doses of RO7017773.

[^{11}C]Ro15-4513 is a partially selective ligand for the $GABA_A$ α5 receptor subtype with relatively higher in vitro affinity for the α5 subunit-containing $GABA_A$ receptor than for other α subunits. Ro15-4513 has 10-20-fold higher in vitro affinity for α5 subunit-containing $GABA_A$ receptors (Ki=0.7 nmol/l) compared with α1, α2, and α3 subunit-containing receptors (Ki=7–10 nmol/l).

[redacted]

[redacted] In previous PET studies, binding of [^{11}C]Ro15-4513 was predominantly seen in the hippocampus, amygdala, anterior cingulate cortex, and insular cortex, consistent with the evidence that it is selectively labelling $GABA_A$ receptors containing the α5 subunit (Myers et al 2017). No adverse effects of the PET tracer have been reported to date.

2.3 BENEFIT/RISK ASSESSMENT

This will be the first study assessing $GABA_A$ α5 receptor occupancy following single doses of RO7017773 in healthy participants. Each participant will undergo a baseline PET/CT scan and two on-treatment PET/CT scans, allowing the extent and duration of brain $GABA_A$-α5 receptor occupancy of varying single oral doses of RO7017773 in healthy participants to be measured using the [^{11}C]Ro15-4513 PET tracer. This information will be used for [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

No therapeutic benefit is anticipated for participants of this study, as is common for most Phase 1 studies involving healthy participants. [redacted]

[redacted]

During the conduct of the study, participants will be resident at the clinical research unit for the entire treatment duration and for at least 48 hours after the last dose. PET/CT scans will be conducted at a separate imaging center where participants will be closely

supervised by clinical personnel. Safety and tolerability will be monitored closely; tolerability will be assessed by recording adverse events and close observation of the participants. In addition, laboratory safety parameters will be monitored as well as vital signs (blood pressure, temperature and pulse rate) and ECGs be recorded.

The PET tracer [^{11}C]Ro15-4513 has been used in previous studies in healthy participants to quantify the level of occupancy at α5 containing $GABA_A$ receptors after a single dose of study drug. [redacted] The amount of tracer that will be given to an individual for a PET/CT scan will be less than 10 μg.

[redacted]

[redacted]

Magnetic resonance images (MRI) delineating brain anatomy will be acquired in this study to aid PET image analysis. There are no known risks to participants associated with MRI scanning, provided that they have no contraindications to MRI as listed in the exclusion criteria. Potential risks associated with metallic implants will be mitigated by administration of a questionnaire and careful screening.

Clinically appropriate strategies to minimize risk to participants have been built into the protocol through the means of eligibility criteria, monitoring strategies, and management guidelines. Furthermore, [redacted] be available prior to initiating the PET study at the respective dose levels.

The potential risks for any healthy participants due to the treatment of RO7017773 or study-related procedures are considered minimal and are outweighed by the potential to develop a new treatment for ASD. Further information about the known and expected benefits in the context of potential risks and reasonably expected adverse events of RO7017773 is provided in the Investigator's Brochure (RO7017773 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	
• To assess the relationship between RO7017773 plasma concentration and brain occupancy of $GABA_A$ receptor subtypes (containing the α5 subunit) after single oral doses of RO7017773 using [^{11}C]Ro15-4513 PET tracer.	• Occupancy of brain α5-containing $GABA_A$ receptors by RO7017773 in selected regions of interest (ROIs). • RO7017773 plasma concentrations.
Secondary • To assess the safety and tolerability of single oral doses of RO7017773.	• Incidence and severity of AE. • Changes in vital signs, physical findings, ECG parameters, and clinical laboratory results during and following RO7017773 administration.

Objectives	Endpoints
Tertiary/Exploratory	
• [redacted]	• [redacted]

4. STUDY DESIGN

4.1 OVERALL DESIGN

[redacted] This is a single dose (SD), non-randomized, open-label, adaptive, parallel group study with the purpose of investigating the occupancy of α5-containing $GABA_A$ receptors by RO7017773 in healthy participants.

Healthy participants will be admitted to the clinical research unit on Day –1 of each imaging session. On Day 1 of the first imaging session, participant will have a baseline PET/CT scan and will be discharged after its completion. [redacted] The timings of PET scans and PK sampling may change based on review of emerging data *or study logistical requirements*. Participants will be discharged at least 48 hours after RO7017773 administration (at the discretion of the Investigator) when all assessments have been completed. Participants stay in the clinical unit may be extend*ed* based on review of [redacted].

For each participant, the imaging session 2 (on-treatment PET/CT scans 1 and 2) will be at least 7 days after imaging session 1 (baseline scan).

At the start of each PET/CT scan, participants will receive an intravenous dose of the radiolabeled tracer [^{11}C]Ro15-4513. Thus, during the study, each participant will receive three doses of the radiolabeled tracer: one IV dose at imaging session 1 (at the beginning of the baseline PET/CT scan) and two IV doses at imaging session 2 (at the beginning of each on-treatment PET/CT scan; see Section 6.1).

During imaging session 2, a single oral dose of RO7017773 will be administered before the first on-treatment PET/CT scan (see Section 6.1). [redacted].
At each anticipated dose level, up to 2 to 3 participants are expected to be enrolled (see Section 9.2).

If one, or both, on-treatment PET/CT scans need to be rescheduled, (e.g., due to a technical failure *or logistical reasons*), participants may receive a second dose of RO7017773 (at least 72 h after their initial dose). *In such cases, the entire imaging session may be repeated at a later date. The subject may be discharged and readmitted to the research unit between doses. Admission (Day –1) procedures will be repeated on each admission.* Participants

will receive no more than 2 doses of RO7017773, and 3 doses of the radiolabeled ligand, [^{11}C]Ro15-4513, throughout the study. Participants will attend the clinical research unit for a safety follow-up visit 5 to 10 days after the last dose of RO7017773.

[redacted]

This study will have an adaptive design to adequately evaluate the exposure versus RO relationship. [redacted] The doses will be selected *in order to obtain a wide enough range of receptor occupancies to allow adequate model parameter estimation of the RO7017773 exposure-RO relationship* ~~based on RO7017773 concentrations that will span as much of the occupancy range as possible~~.

4.1.1 Length of the Study

The total duration of the study for each participant will be up to 8 weeks divided as follows:

- Screening: Up to 4 weeks
- Imaging Session 1 (baseline PET/CT scan): Day –1 to Day 1
- Imaging Session 2 (on-treatment PET/CT scan): Day -1[1)] to [redacted]
- Safety follow-up: 5 to 10 Days after last dose.

[1)]Admission for imaging session 2 will be at least 6 days after the baseline PET/CT scan *if arterial sampling required.*

4.1.2 Selection of Dose Levels for Subsequent Cohorts and Timing of PET/CT scans and PK sampling S

The choice of the next dose level(s) will be made following review, by the Investigator, the PET specialist and Sponsor, of RO data at the previous dose level(s), and all available PK, PK-RO data, safety and tolerability data as outlined in Appendix 6 and in Section 4.3.

If a dose level causes any safety concerns, the same or a higher dose level will not be tested in any other participants (see Section 2.3).

[redacted]

4.1.3 Communication Strategy

There will be review of available safety, PK and occupancy data (see Section 4.1.2) prior to initiation of the next dose. A Dose Selection Meeting will be conducted between the Sponsor study team, the PET specialist and Investigator prior to dosing of the next cohort. There will be at least one week between each dose level in order to permit adequate time for collation and review of emerging data before the next dose is administered.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study rationale is provided in Section 2.1.

4.2.1 Rationale for Study Population

The participants of this study are healthy male and female *(women of non-childbearing potential)* participants aged 23 to 55 years (inclusive), chosen because of the absence of confounding diseases, which will enable a clearer and more consistent assessment of drug disposition, biological activity and safety profile. In addition, healthy participants are unlikely to require concomitant medications which could interfere with study drugs.

4.2.2 Rationale for PK sampling

Blood samples for determination of RO7017773 in plasma will be collected prior and just after each on-treatment PET/CT scans to inform the PK-RO model.

[redacted]

4.2.4 Rationale for PET Imaging

PET is a non-invasive imaging technique based on the external detection and recording of the decay of positron emitters incorporated in biological molecules introduced in a participant. Molecules of biological interest are labeled with short-lived positron emitter isotopes of biological nuclei (in this study [^{11}C]), providing radioligands with high specific activity and preserved biochemical properties. The PET instruments make it possible to

obtain time varying three-dimensional maps of the absolute radioactivity concentration distribution. By applying ligand kinetic principles to these PET data, it is then possible to estimate absolute values of the physiological parameters that determine the interactions and fate of the labeled molecule. In humans, radioligands are usually administered in minute amounts (typical mass dose is the low µg range). Because of the low radiation doses that are necessary (<10 mSv), PET can be safely used for clinical research purposes.

4.2.5 Rationale for MRI Imaging

A structural MRI scan of the brain will be acquired for each participant to provide an anatomical image to aid PET image analysis.

4.3 DOSE JUSTIFICATION

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted].

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed the safety follow-up visit.

The end of the study is defined as the date when the last participant last observation (LPLO) occurs. LPLO is expected to occur approximately 5 to 10 days after the last participant last dose of RO7017773.

5. STUDY POPULATION

The study population rationale is provided in Section 4.2.1.

The participants of this study are healthy volunteers between 23 and 55 years of age, inclusive, who fulfill all the inclusion criteria listed in Section 5.1.

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

5.1 INCLUSION CRITERIA

Informed Consent

1. Able and willing to provide written informed consent and to comply with the study protocol according to ICH and local regulations.

Age

2. Healthy participants aged 23 to 55 years of age, inclusive, at the time of signing the informed consent.

Type of Participants and Disease Characteristics

3. Healthy, as judged by the Investigator.

   Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, serology and urinalysis.

Weight

4. Body Mass Index (BMI) of 18 to 30 kg/m^2, inclusive at screening.

Sex

5. Male and female participants

a) Female Participants

[redacted]

b) Male Participants

During the treatment period and for at least 90 days after the last dose of study drug, agreement to:

- Remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom, with partners who are women of childbearing potential (WOCBP, as defined in Section 1 of Appendix 5), or pregnant female partners, to avoid exposing the embryo *to study treatment*.
- Refrain from donating sperm *for* 90 days *after the last dose*.

The contraception and abstinence requirements are intended to prevent exposure of an embryo to the study treatment. The reliability of sexual abstinence for male ~~and/or 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 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. Any condition or disease detected during the medical interview/physical examination that would render the participant unsuitable for the study, place the participant at undue risk or interfere with the ability of the participant to complete the study, as determined by the Investigator.
2. History or evidence of any medical condition potentially altering the absorption, metabolism or elimination of drugs. This includes a surgical history of the gastrointestinal tract affecting gastric motility or altering the gastrointestinal tract.
3. History of any clinically significant gastrointestinal, renal, hepatic, bronchopulmonary, neurological, psychiatric, cardiovascular, endocrinological, hematological or allergic disease, metabolic disorder, ~~hypofertility,~~ cancer or cirrhosis.

4. History of convulsions (other than benign febrile convulsions of childhood) including epilepsy, or personal history of significant cerebral trauma or CNS infections (e.g., meningitis).
5. Clinically significant abnormal finding from the MRI performed after the initial screening examination.
6. A history of clinically significant hypersensitivity (e.g., drugs, excipients) or allergic reactions.
7. Any major illness within one month before the screening examination or any febrile illness within one week prior to screening and up to first study drug administration.
8. Abnormal blood pressure, i.e, systolic blood pressure (SBP) greater than 140 or less than 90 mm Hg, and diastolic blood pressure (DBP) greater than 90 or less than 50 mm Hg.
9. Abnormal pulse rate, resting pulse rate greater than 100 or less than 40 bpm.
10. History or presence of clinically significant ECG abnormalities before study drug administration (e.g., PQ/PR interval $>$ 210 ms , QTcF $>$ 450 ms ($>$ 470 ms females) or cardiovascular disease (e.g., cardiac insufficiency, coronary artery disease, cardiomyopathy, congestive heart failure, family history of congenital long QT syndrome, family history of sudden death).
11. Clinically significant abnormalities in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis). In the case of uncertain or questionable results, tests performed during screening may be repeated before randomization to confirm eligibility.
12. Participants who, in the Investigator's judgment, pose a suicidal or homicidal risk, or any participant with a history of suicidal or homicidal attempts.

Prior/Concomitant Therapy

13. Participants likely to need concomitant medication during the study period (including for dental conditions).

Prior/Concurrent Clinical Study Experience

14. Participation in an investigational drug or device study within 90 days prior to screening, as calculated from the day of follow-up from the previous study, or more than 4 times a year.
15. Previous inclusion in a research and/or medical protocol involving PET or radiological investigations (within the last 12 months).

Diagnostic Assessments

16. Positive test for drugs of abuse or alcohol.
17. For WO*N*CBP, a positive pregnancy test.
18. Show evidence of human immunodeficiency virus (HIV) infection and/or positive human HIV antibodies.

19. Positive result on hepatitis B (HBV) or hepatitis C (HCV), presence of hepatitis B surface antigen (HBsAg) or positive hepatitis C antibody test result at screening or within 3 months prior to starting study treatment.

Other Exclusions

20. Dietary restrictions that would prohibit the consumption of standardized meals.
21. Any suspicion or history of alcohol abuse and/or suspicion of regular consumption of drug of abuse or previous history of or treatment for a dependence disorder.
22. Participants who regularly smoke more than 5 cigarettes daily or equivalent and unable or unwilling not to smoke during the in-house period (see Section 5.3.2).
23. Participants who have donated over 500 mL of blood or blood products or had significant blood loss within 3 months prior to screening.
24. Participants under judicial supervision, guardianship or curatorship.
25. Presence of a cardiac pacemaker or other electronic device; ferromagnetic metal foreign bodies in vulnerable positions; presence of certain tattoos that might make it unsafe for an MRI; participant working as a machinist, welder or metal worker; claustrophobia; as assessed by a standard pre MRI questionnaire.
26. *Occupational radiation exposure or radiation* ~~Exposure~~ *exposure from medical diagnostic or treatments* ~~to ionising radiation in medical research~~ over the past 12 months, *that would result in a dose in excess of 10 mSv* ~~which~~ *when* combined with *the planned exposure from* this study ~~would result in an effective dose in excess of 10 mSv~~.
27. Contraindication for arterial cannulation; Allen's test indicating potential risk in placement of the arterial cannula.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and Dietary Restrictions

Participants will have to be fasted for at least 4 hours prior to laboratory safety tests at screening.

[redacted]

5.3.2 Caffeine, Alcohol, and Tobacco

The consumption of food and beverages containing caffeine or other methylxanthine-containing products (e.g., tea, coffee, caffeinated soft drinks, cola, chocolate) will not be permitted from 48 hours before dosing until the end of the residential period. During the period from screening to the follow-up visit when participants are not resident in the unit, participants will be asked to limit coffee or tea consumption to no more than 3 cups per day, and methylxanthine-containing products (e.g. cola and chocolate) must be limited to a maximum of 1 liter per day.

Consumption of alcohol will not be allowed from 48 hours before dosing until the end of the residential period and participants will be asked to limit alcohol to a maximum of 2 units/day (1 unit equates to approximately 330 mL beer, 125 mL of wine or 25 mL of spirits) during the out-clinic period until follow-up. The use of tobacco will not be permitted from 48 hours before dosing until the end of the residential period and participants will be asked to limit tobacco use to a maximum of 5 cigarettes a day or equivalent amount of tobacco during the out-clinic period until follow-up.

5.3.3 Activity

Light ambulatory activities will be permitted, with the level of activities kept as similar as possible on all days in the clinical research unit.

After the participants leave the unit they will be asked to refrain from strenuous physical activity until the end of their participation in the study.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized to study treatment/entered in the study.

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

Individuals who do not meet the criteria for participation in this study (screen failure) will not be re-screened unless agreed with the Sponsor. A repeat of a screening laboratory test because of a borderline result is not considered a re-screening.

5.5 RECRUITMENT PROCEDURES

Participants will be identified for potential recruitment using pre-screening enrollment logs, clinical database and IEC/IRB approved newspaper/radio/social-media advertisements prior to consenting to take place on this study.

6. TREATMENTS

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

All IMPs required for completion of this study (RO7017773) will be provided by the Sponsor. All study drug administration will be administered at the study center under supervision of site staff. The radiolabeled PET tracer [^{11}C]Ro15-4513 is considered as non-IMP.

At the start of each PET/CT scan, participants will receive an IV dose of [^{11}C]Ro15-4513.

6.1 TREATMENTS ADMINISTERED

Table 6 summarizes the treatments administered in the study.

Table 6 Summary of Treatment Administered and PET Ligand

Study Treatment Name:	**RO7017773**	**[^{11}C]Ro15-4513**
Dosage Formulation:	Capsule	Sterile solution for IV injection
Unit Dose Strength(s)/Dosage Level(s):	[redacted]	Not applicable.
Dose:	[redacted]	Will not exceed 10 µg for each PET/CT scan (maximum activity 370 MBq).
Route of Administration:	Oral	Intravenous
Dosing Instructions:	[redacted]	An appropriate aliquot of [^{11}C]Ro15-4513 concentrate for injection is to be diluted with up to 20 mL Sodium chloride for injection immediately prior to the IV administration. The injection with [^{11}C]Ro15-4513 occurs simultaneously with the start of the PET/CT scan.
Packaging and Labeling:	Study treatment will be provided in bottles. Each bottle will be labeled according to the country requirements.	Radiolabeled [^{11}C]Ro15-4513 solution for injection packaging will be overseen locally according to GMP and site SOPs.
Storage Conditions	[redacted]	[^{11}C]Ro15-4513 solution for injection is prepared immediately prior to administration.
Manufacturer	F. Hoffmann-La Roche Ltd	[redacted]

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 6.6 or Section 7, respectively. See Section 5.3.1 for study food restrictions. Details on the synthesis of [^{11}C]Ro15-4513 and the preparation of the concentrate for injection are given in the "Quality documentation for the PET tracer [^{11}C]Ro15-4513" (see the Pharmacy Manual).

Please see the RO7017773 Investigator's Brochure and Pharmacy Manual for more details.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Study drug RO7017773 packaging will be overseen by the Roche clinical trial supplies department and bear a label with the identification required by local law, the protocol number, drug identification and dosage.

The packaging and labeling of the study medication will be in accordance with Roche 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 IMP (RO7017773) for damage.
- Verify proper identity, quantity, integrity of seals and temperature conditions.
- Report any deviations or product complaints to the Monitor upon discovery.

The qualified individual responsible for dispensing the study treatment will prepare the correct dose according to the randomization schedule and Pharmacy Manual.

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

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

The Investigator, Institution, or the Head of the Medical Institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation and final disposition records).

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

Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual.

6.2.1 PET Tracer [^{11}C]Ro15-4513

The radiolabeled PET tracer [^{11}C]Ro15-4513 will be synthesized from the precursor by a qualified person. The preparation of the concentrate for injection will be performed according to the "Quality documentation for the PET tracer [^{11}C]Ro15-4513" (see Pharmacy Manual) immediately prior to the administration. Radiolabeled [^{11}C]Ro15-4513 solution for injection packaging will be overseen locally according to GMP and site SOPs.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.3.1 Method of Treatment Assignment

The study is open-label. Up to 15 healthy participants will be enrolled in this study. The participant numbers will be allocated sequentially in the order in which the participants are enrolled. The randomization numbers will be generated by the Sponsor or its designee and it will be sent to the Investigator.

6.3.2 Blinding

This is an open label study, blinding procedures are not applicable.

6.4 TREATMENT COMPLIANCE

The qualified individual responsible for dispensing the study treatment will prepare the correct dose according to the randomization schedule. This individual will write the date dispensed and participant number on the study treatment vial label and on the Drug Accountability Record. This individual will also record the study treatment number received by each participant during the study.

6.5 CONCOMITANT THERAPY

6.5.1 Permitted Therapy

Any medication or vaccine (including over-the-counter [OTC] or prescription medicines, 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 4 weeks prior to screening until the follow-up visit must be recorded along with reason for use, dates of administration (including start and end dates) and dosage information (including dose and frequency).

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

All concomitant medications should be reported to the Investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF).

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

Use of the following therapies is permitted, as specified below:

- [redacted]
- Acetaminophen/paracetamol is allowed up to a maximum dose of 2 g/day up to 48 hours prior to dosing and after the in-house period, but should not exceed 4 g total during the week prior to dosing.

6.5.2 Prohibited Therapy

All medications (prescription and OTC) taken within 30 days of study screening will be recorded on the appropriate eCRF.

As a general rule, no concomitant medication will be permitted, with the exception of medications to treat AEs, unless the rationale for exception is discussed and clearly documented between the Investigator and the Sponsor.

Use of the following therapies is prohibited during the study and for at least 30 days or at least 5 half-lives of the medication prior to initiation of study treatment (whichever is longer), unless otherwise specified below:

- Any prescribed or over-the-counter medication (including herbal products, vitamin, mineral, energy drinks and dietary supplements), unless specified in Section 6.5.1.
- [redacted]
- [redacted]
- [redacted]
- Acetylsalicylic acid and other anti-platelet and anti-coagulation medication, e.g., adenosine diphosphate (ADP) receptor inhibitors, heparin, warfarin and non-vitamin K antagonist oral anticoagulants (NOACs).

6.6 DOSAGE MODIFICATION

The study is adaptive in nature to adequately evaluate the exposure versus RO relationship. The subsequent dose levels will be selected based on the evaluation of the

PK-RO relationship and safety and tolerability data. The maximum daily dose will not exceed the highest tolerable and safe dose in the SAD part of study [redacted] (Section 4.3).

6.7 TREATMENT AFTER THE END OF THE STUDY

The Sponsor does not intend to provide RO7017773 or other study interventions to participants after conclusion of the study.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

An excessive rate of withdrawals (either participants discontinuing study treatment or withdrawing from the study) can render the study non-interpretable. Therefore, unnecessary withdrawal of participants should be avoided and efforts should be taken to motivate participants to comply with all the study specific procedures as outlined in this protocol.

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

7.1 DISCONTINUATION OF STUDY TREATMENT

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 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 for safety reasons will not be replaced. Participants who withdraw from the study for other reasons may be replaced to ensure adequate numbers of evaluable participants. Replacement of participants for other reasons will be discussed between the Investigator and the Sponsor, based on existing data.

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

7.3 LOST TO FOLLOW-UP

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

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their time-points are summarized in the Schedules of Activities (SoA; Section 1.3). Protocol waivers or exemptions are not allowed.

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

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the Informed Consent Form (ICF) may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time-frame defined in the SoA.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 EFFICACY ASSESSMENTS

Efficacy parameters will not be evaluated in this study.

8.2 SAFETY ASSESSMENTS

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

8.2.1 Physical Examinations

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

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

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

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

8.2.2 Vital Signs

Vital signs will include temperature (tympanic), systolic and diastolic blood pressure and pulse rate. They will be taken before blood collection and will be measured in a supine position after at least 5 minutes rest at the time point specified in the SoA tables (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

Triplicate 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

At each time point at which triplicate ECGs are required, three individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 5 minutes.

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.

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. If considered appropriate by Roche, ECGs may be analyzed retrospectively at a central laboratory.

ECG characteristics, including heart rate, QRS duration, and PR, and QT intervals, will be recorded on the eCRF or loaded electronically. QTcF (Fridericia's correction) and RR will be calculated automatically and recorded on the eCRF or loaded electronically. Changes in T-wave and U-wave morphology and overall ECG interpretation will be documented on the eCRF or loaded electronically. T-wave information will be captured as normal or abnormal, U-wave information will be captured in two categories: absent/normal or abnormal.

8.2.4 Clinical Safety Laboratory Assessments

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

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which 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.
- If laboratory values from non-protocol specified laboratory assessments performed at the local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose-modification) then, the results must be recorded in the CRF.

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

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

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

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

8.2.5 Medical History and Demographic Data

Medical history includes clinically significant diseases and all medications (e.g., prescription drugs, OTC drugs, herbal or homeopathic remedies, nutritional supplements) used by the participant within 30 days prior to the screening visit.

Demographic data will include age, sex, and self−reported race/ethnicity.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The definitions of an AE or serious adverse event (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 Section 8.3.6.

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

Procedures used for recording adverse events are provided in Appendix 3.

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

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

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

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

After initiation of study treatment, all adverse events, regardless of relationship to study treatment, will be reported until 14 days after the last dose of study treatment.

Post-study adverse events and serious adverse events: The Investigator is not required to actively monitor participants for adverse events after the end of the adverse event reporting period {14 days after the last dose of study treatment}.

However, if the Investigator learns of any SAE (including a death) or other adverse events of concern that are believed to be related to prior treatment with study treatment, 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 treatment 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 is the preferred method to inquire about AE occurrence.

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

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

8.3.3.1 Investigator Follow-Up

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

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

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

8.3.3.2 Sponsor Follow-Up

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

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

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

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

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

An investigator who receives an investigator safety report describing a 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 monitors is available 24 hours a day 7 days a week. Medical monitors contact details will be available on a separate list generated by the study management team.

8.3.5 Pregnancy

[redacted]

Male participants will be instructed through the Informed Consent Form to immediately inform the Investigator if their partner becomes pregnant during the study or within 90 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 treatment, as defined below:

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

8.3.7 Management of Specific Adverse Events

Treatment of specific AEs will be considered on a case-by-case basis according to local standard of care.

8.4 TREATMENT OF OVERDOSE

Study treatment overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not an adverse event unless it results in untoward medical effects (see Section 7 of Appendix 3 for further details).

8.5 PHARMACOKINETICS

Plasma concentrations of RO7017773 will be measured by a specific and validated LC-MS/MS method.

The PK samples will be taken as outlined in the Schedules of Activities tables (see Section 1.3). If required, remaining PK samples may also be used for assay development/validation experiments.

The blood samples will be destroyed within 6 months after the date of final CSR. Details on sampling procedures, sample storage and shipment are given in the Sample Handling Manual.

[redacted]

8.8 IMAGING

8.8.1 PET/CT Scans

Dynamic PET/CT scans will be performed at [redacted] using a PET/CT scanner.

A venous cannula will be inserted into the forearm or antecubital vein for injecting the PET tracer. Participants will be placed in the PET/CT scanner and appropriate devices (e.g., foam padding) will be used to decrease movement during the scan and to standardize the orientation of the head.

[redacted]

Motion tracking software and hardware (e.g. lightweight goggles) may be used for accurate monitoring of any residual head movement. The participant will be monitored continuously by a qualified PET technician.

A low-dose CT scan will be performed before each injection of the radioligand to correct for the attenuation of emitted radiation. After the low-dose CT scan, participants will then receive an intravenous bolus injection of up to 370 MBq of the [^{11}C]Ro15-4513 radioligand. Dynamic emission data will be recorded for up to about 90 min after injection of the radioligand.

8.8.2 Magnetic Resonance Imaging (MRI) Scans

Structural MRI acquisition will be performed at [redacted] using a 3 Tesla [redacted] clinical MRI system ([redacted], Germany), and will consist of a structural scanning protocol. MRI scans will be evaluated by a radiologist to exclude any participants with major pathology or abnormalities. A radiologist will provide a report of each MRI scan to the investigator.

For each participant, a MRI scan will be acquired after initial screening, but prior to the PET/CT scan.

The MRI scan will be used as an eligibility criterion and also co-registered with the subsequent PET/CT scans and used for anatomical localization.

Only participant eligibility following the MRI will be captured on the eCRF where date, time, and categorization in normal/abnormal will be recorded. Any additional data will not be required and will remain at the site.

8.9 BIOMARKERS

Biomarkers are not evaluated in this study.

8.10 HEALTH ECONOMICS/MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

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 Pre-treatment Assessments

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

All screening and pre-treatment 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.

An Eligibility Screening Form (ESF) documenting the Investigator's assessment of each screened participant with regard to the protocol's inclusion and exclusion criteria is to be completed by the Investigator and kept at the investigational site.

Screening and pre-treatment assessments will be performed at the time-points indicated in the SoA (see Section 1.3), unless otherwise specified.

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 must be performed as per SoA (see Section 1.3). Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment, unless otherwise noted in the schedule of assessments.

8.11.3 Assessments at Study Completion/Early Termination Visit

Participants who complete the study (defined as) or discontinue from the study early will be asked to return to the clinic days after the last dose of study drug for a follow-up visit. The visit at which response assessment shows progressive disease may be used as the study completion/early termination visit.

8.11.4 Follow-Up Assessments

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

9. STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The study is an exploratory one, and there are no null hypotheses to be tested.

9.2 SAMPLE SIZE DETERMINATION

It is anticipated that a maximum of 15 participants will be enrolled in the study. At each anticipated dose level, up to 2 to 3 participants may be enrolled with 2 participants per cohort.

The sample size is chosen for practical and feasibility reasons and is within the range generally accepted for PET studies. It is considered adequate to allow modelling of the relationship between RO7017773 plasma concentrations and the occupancy of α5-containing $GABA_A$ receptors.

9.3 POPULATIONS FOR ANALYSES

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

Table 7 Analysis Populations

Population	Description
Safety	All participants randomized to study treatment and who received at least one dose of the study treatment, whether prematurely withdrawn from the study or not, will be included in the safety analysis.
PK	All participants who have received at least one dose of study treatment and who have data from at least one post-dose sample will be included in the PK analysis population. Participants will be excluded from the PK analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete which may influence the PK analysis. Excluded cases will be documented together with the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.
PK/PD	All participants who received at least one on-treatment PET/CT scan. Participants will be excluded from the PK/PD analysis population if they significantly violate the inclusion or exclusion criteria or deviate significantly from the protocol. Participants will also be excluded if unavailable or incomplete data significantly affect the PK/PD analysis. Excluded cases will be documented together with the reason for exclusion. All decisions on exclusions from the analysis will be made before database lock.

9.4 STATISTICAL ANALYSES

9.4.1 Demographics and Baseline Characteristics

Demographic and other baseline characteristics of the safety analysis population will be listed.

9.4.2 Safety Analyses

All safety analyses will be based on the safety analysis population.

Table 8 Safety Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Adverse events	The original terms recorded on the eCRF by the Investigator for adverse events will be coded by the Sponsor. Adverse events will be summarized by mapped term and appropriate thesaurus level.
Clinical laboratory tests	All clinical laboratory data will be stored on the database in the units in which they were reported. Laboratory test values will be presented in International System of Units (SI units; Système International d'Unités) by individual listings with flagging of abnormal results.
Vital signs	Vital signs data will be presented by individual listings with flagging of values outside the normal ranges and flagging of abnormalities. In addition, tabular summaries will be used, as appropriate.
ECG data analysis	ECG data will be presented by individual listings. In addition, tabular summaries will be used, as appropriate.
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.

9.4.3 Pharmacokinetic Analyses

PK concentration data will be summarized using the PK Population, see Table 7.

Individual plasma concentrations of RO7017773 will be listed and summarized. Formal PK analysis will not be done.

9.4.4 Pharmacodynamic Analyses

Pharmacodynamic analysis will be done using the PK/PD Analysis Population, see Table 7.

Occupancy of α5-containing $GABA_A$ receptors by RO7017773 will be calculated for target ROIs. ROIs will be regions with strong [^{11}C]Ro15-4513 signal (i.e. regions with relatively high density of $GABA_A\alpha5$ and appreciable size) and including, but not limited to the amygdala, hippocampus, insular cortex, anterior cingulate, and ventral striatum.

Structural MRI image will be co-registered to a standard reference space. A template brain image and associated atlas will be nonlinearly warped to each participant's MRI to enable automated definition of ROIs. Dynamic PET images will be registered to each participant's MRI scan and corrected for motion using a frame-to-frame registration process with a normalized mutual information cost function. ROIs defined on the MRI images will be applied to the dynamic PET data to derive regional time-activity curves (TACs) for ROIs. The total volume of distribution (V_T) for each ROI will be derived and used to calculate RO by RO7017773:

RO and regional V_T data will be presented by listings and no formal statistical analysis will be performed.

Additional PD analyses will be conducted as appropriate.

9.4.5 Pharmacokinetic/pharmacodynamic Relationship

[redacted]

9.5 SUMMARIES OF CONDUCT OF STUDY

All protocol deviations will be listed. Data for study drug administration and concomitant medication will be listed. The number of participants who were randomized, discontinued and completed the study will be summarized and listed.

10. REFERENCES

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Positron emission tomography (PET) study in baboon to investigate brain GABAA α5 receptor occupancy of RO7017773 using [^{11}C]RO0154513. Roche Report (RDR) 1080714; in preparation.

WHO (World Health Organization). Autism spectrum disorders and other developmental disorders: From raising awareness to building capacity. Meeting Report 16-18 September 2013, Geneva, Switzerland.

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), and Appendix 5 (contraceptive guidance and collection of pregnancy information). Additional study-related appendices are listed in order of appearance in the protocol.

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. FDA regulations and applicable local, state, and federal laws. Studies conducted in the EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC).

1.2. INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

1.3. INFORMED CONSENT

The Sponsor's Master Informed Consent Form (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 will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center. The Sponsor

or its designee must review and approve any proposed deviations from the Sponsor's sample ICFs or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes according to local requirements. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study. A copy of the ICF(s) signed by all parties must be provided to the participant or the participant's legally authorized representative.

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

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

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.

1.4. CONFIDENTIALITY

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

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

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

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

1.5. FINANCIAL DISCLOSURE

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

2. DATA HANDLING AND RECORD

2.1. DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

2.1.1. Data Quality Assurance

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

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

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

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

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

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

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

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

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

2.1.4. Use of Computerized Systems

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

2.2. RETENTION OF RECORDS

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for at least 15 years after study completion 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 participants 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. 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.

2.4 STUDY AND SITE CLOSURE

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

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

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

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

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

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

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

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

1. DEFINITION OF ADVERSE EVENTS

According to the E2A ICH guideline for Good Clinical Practice, an **adverse event** is any untoward medical occurrence in a participant or clinical investigation participant 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, or urinalysis) or other clinical test (e.g., ECG, X−ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment.
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

Events NOT Meeting the AE Definition:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting 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 preexisting condition that did not worsen from baseline is not considered an AE.
- **Results in persistent or significant disability/incapacity**

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

  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**.
- **Other significant events**:

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

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or

convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

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

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

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

There may be instances when copies of medical records for certain cases are requested by 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 predefined 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 treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

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

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

4. FOLLOW-UP OF AES AND SAES

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

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

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

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

5. IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

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

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

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

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

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

Events that Occur prior to Study Treatment Initiation

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

Events that Occur after Study Treatment Initiation

For reports of serious adverse events and non-serious adverse events of special interest (Section 8.3.6) that occur after initiation of study treatment (Section 8.3.1), investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the appropriate Adverse Event of Special Interest/ Serious

Adverse Event eCRF form and submit the report via the 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 immediately (i.e., no more than 24 hours after learning of the event).

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

Reporting of Post-Study Adverse Events and Serious Adverse Events

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

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}:

- RO7017773 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.

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

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

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

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

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

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

5. ABNORMAL VITAL SIGN VALUES

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

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

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

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high 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 most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Appendix 2, 5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 8.3.6).

7. OVERDOSE

Any study treatment overdose or incorrect administration of study treatment should be noted on the Study treatment Administration eCRF.

All adverse events associated with an overdose or incorrect administration of study treatment should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious 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, 5.1).

8. DEATHS

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").

9. 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”).

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).

The following hospitalization scenarios are not considered to be serious adverse events:

- Planned hospitalization required by the protocol {(e.g., for study drug administration or insertion of access device for study drug administration)}.
- Hospitalization for a pre-existing 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 healthy volunteer has not suffered an adverse event.

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

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

Appendix 4
Clinical Laboratory Tests

The tests detailed in Table 1 will be performed by the local or central laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and Section 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

Laboratory Assessments	Parameters
Hematology	• Leucocytes, erythrocytes, hemoglobin, hematocrit, platelets, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes).
Clinical Chemistry	• Sodium, potassium, chloride, bicarbonate, glucose (fasting), urea, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, gamma-glutamyl-transferase (g-GT), creatine phosphokinase (CPK), LDH.
Coagulation	• Prothrombin time (INR) and activated thromboplastin time (aPTT).
Viral Serology	• HIV (specific tests HIV1 antibody, HIV-1/2 antibody, HIV-2 antibody), hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody.
Hormone	• For post-menopausal female only to confirm post-menopausal status: follicle stimulating hormone (FSH) and estradiol.
Pregnancy Test	• Serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed [redacted]
Urinalysis	• Specific gravity • Dipstick: pH, glucose, protein, blood, nitrite, leukocyte If there is a positive result (confirmed by a positive repeated sample), urine will be sent to the laboratory for microscopy and if necessary a urine 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 (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria), if blood or protein is abnormal.
Other Screening Tests	• Urine drug screen (to include at minimum: amphetamines, methamphetamines, barbiturates, cocaine, opiates, methadone, cannabinoids and benzodiazepines) • Alcohol breath test.

The results of each test will be provided electronically or captured in the eCRF. Investigators must document their review of each laboratory safety report.

Additional Statistical Considerations for Clinical Laboratory Data

- Standard Reference Ranges and Transformation of Data

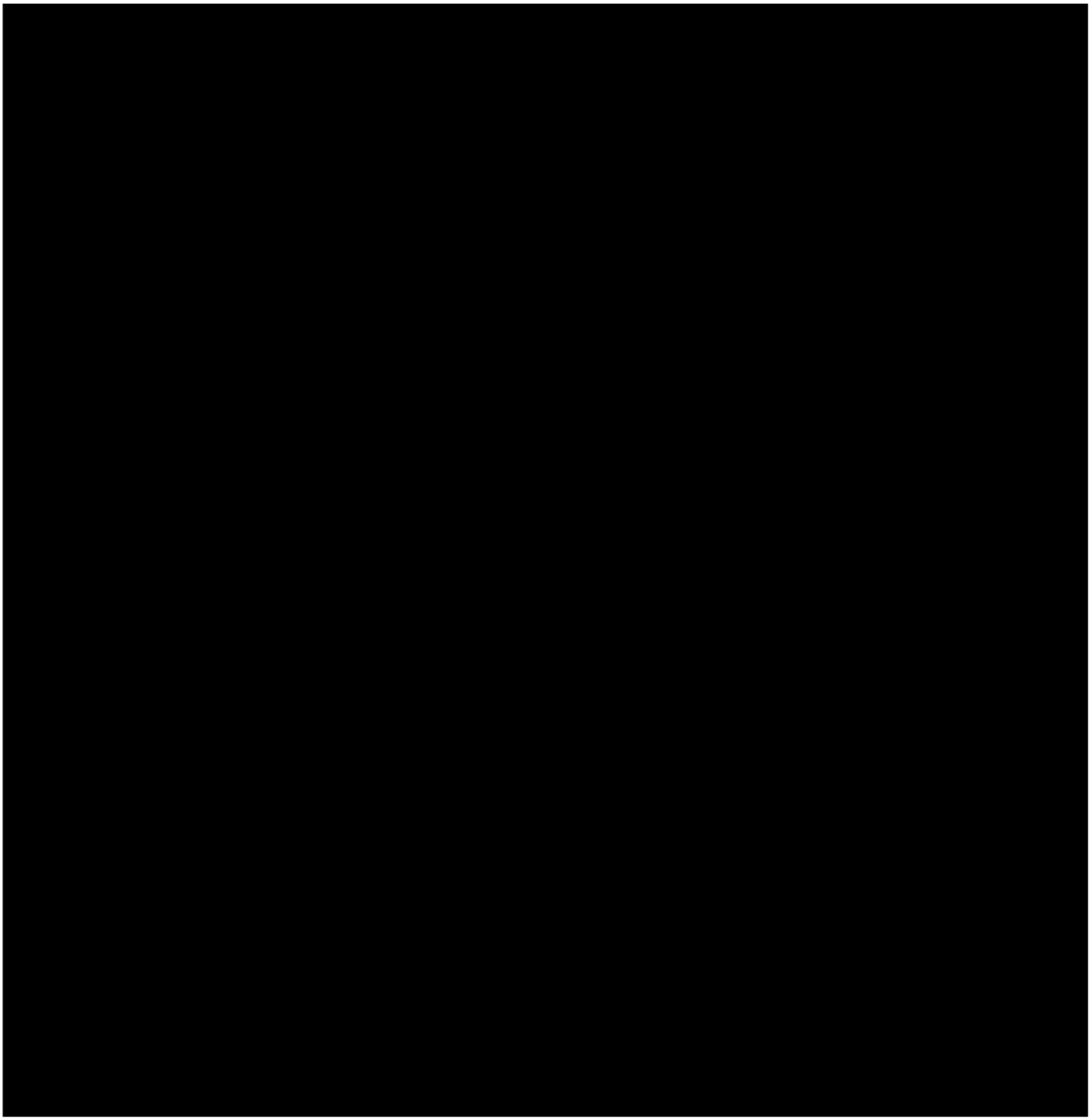
Roche standard reference ranges, rather than the reference ranges of the Investigator, will be used for all parameters. For most parameters, the measured laboratory test result will be assessed directly using the Roche standard reference range. Certain laboratory parameters will be transformed to Roche's 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.



[redacted]

3. PREGNANCY TESTING

For WO*N*CBP 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

- **Male participants with partners who become pregnant**

The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study (see Section 8.3.5 Pregnancy). This applies only to male participants who receive RO7017773.

Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant exposed to study treatment. The Investigator will record pregnancy information on the Clinical Trial Pregnancy Reporting Form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the Investigator should update the Clinical Trial Pregnancy Reporting Form with additional information on the course and outcome of the pregnancy when available. An Investigator who is contacted by the male participant or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician. The female partner will be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Monitoring of the participant's partner should continue until conclusion of the pregnancy. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

[redacted]

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 or~~ female partner of a male participant exposed to study treatment should be classified as a 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.