Official Title: **A Non-Randomized, Open-Label, One Sequence, Two Period Cross-Over Study to Investigate the Effect of CYP3A Inhibition on the Pharmacokinetics of RO7017773 in Healthy Participants**

NCT Number: NCT03774576

Document Date: Protocol Version 3: 14-November-2018

PROTOCOL

TITLE:	**A NON-RANDOMIZED, OPEN-LABEL, ONE SEQUENCE, TWO-PERIOD CROSS-OVER STUDY TO INVESTIGATE THE EFFECT OF CYP3A INHIBITION ON THE PHARMACOKINETICS OF RO7017773 IN HEALTHY PARTICIPANTS**
PROTOCOL NUMBER:	BP40822
VERSION:	3
EUDRACT NUMBER:	2018-002889-40
TEST PRODUCT:	RO7017773
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 15 August 2018
DATE AMENDED:	Version 2: 6 September 2018 Version 3: See electronic date stamp below

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	14-Nov-2018 15:11:36

PROTOCOL ACCEPTANCE FORM

TITLE:	**A NON-RANDOMIZED, OPEN-LABEL, ONE SEQUENCE, TWO-PERIOD CROSS-OVER STUDY TO INVESTIGATE THE EFFECT OF CYP3A INHIBITION ON THE PHARMACOKINETICS OF RO7017773 IN HEALTHY PARTICIPANTS**
PROTOCOL NUMBER:	BP40822
VERSION NUMBER:	3
EUDRACT NUMBER:	2018-002889-40
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 3: RATIONALE

Protocol BP40822 has been amended to incorporate the following changes based on health authority feedback:

- The dose regimen and duration of itraconazole dosing was modified. Itraconazole will now be dosed 200 mg BID on Day 1 and 200 mg QD on Days 2 to 9.
- Physiologically based pharmacokinetic (PBPK) predictions were updated to reflect the change in study design.
- Exclusion criterion 10 was updated to remove text regarding inclusion of individuals with isolated bilirubin $>$ 1.5 $\times$ ULN if bilirubin is fractionated and direct bilirubin $<$ 35%.
- A sentinel cohort was added and rationale to support dosing and potential dose adjustment based on review of safety, tolerability and pharmacokinetics was also added.
- Study and individual stopping criteria were added to the protocol.

Additional minor changes and corrections have been made to improve clarity and consistency. Substantial new information appears in italics.

PROTOCOL AMENDMENT, VERSION 3: SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

1.3 Schedule of Activities

Table 1 Schedule of Activities – Main Table

Table 1 has been updated to reflect the changes to the protocol

Footnotes

g) ~~The~~ *An* oral dose of itraconazole will be given twice daily (2 x 200 mg) with 12 hours between the two doses and under fed conditions, i.e., 30 minutes after starting a meal in the morning and the evening *on Day 1 only. On Days 2 to 9, an oral dose of itraconazole will be given once daily (1 x 200 mg) under fed conditions, i.e., 30 minutes after starting a meal in the morning.*

Table 3 Schedule of Activities – Detailed Table Period 2

Table 3 has been updated to reflect the changes to the protocol

e) ~~The~~ *An* oral dose of itraconazole will be given twice daily (2 x 200 mg) with 12 hours between the two doses and under fed conditions, i.e., 30 minutes after starting a meal in the morning and the evening *on Day 1 only. On Days 2 to Day 9, an oral dose of itraconazole will be given once daily (1 x 200 mg) under fed conditions, i.e., 30 minutes after starting a meal in the morning.*

2.3 Benefit/Risk Assessment

[redacted]

[redacted]

Itraconazole is generally well tolerated. The itraconazole dosing regimen in this study is consistent with the prescribing recommendations for itraconazole (SmPC). Approved dosing regimens for the treatment of fungal infections include doses up to 200 mg BID for periods of up to one year. Itraconazole doses of 200 mg QD or BID are also commonly used in DDI studies to ensure adequate CYP3A inhibition (Ke et al 2014; Liu et al 2015).

4.1 Overall Design

In Period 1, participants will be administered a single oral dose of RO7017773 alone in fed state. In Period 2, after a wash-out period of 10 days, participants will receive multiple doses of itraconazole in fed state for ~~8~~ *9* days and be administered [redacted] RO7017773 [redacted] in combination with itraconazole [redacted]

[redacted]

[redacted]

Healthy participants will be admitted to the clinical unit on Day -1 of Period 1. An oral dose of [redacted] RO7017773 will be administered alone, 30 minutes after starting a standardized breakfast on the morning of Day 1 of Period 1. Participants will be discharged on the morning of Day 4 after all assessments have been completed. They will return to the clinical unit for 3 ambulatory visits at Day 5, Day 6, and Day 8 for PK sampling and safety monitoring.

After a wash-out period of 10 days, participants will be admitted to the clinical unit on Day -1 of Period 2 and will remain in-house until the morning of Day ~~10~~*12*. They will be administered 200 mg of itraconazole BID (12 hours apart) ~~from~~ *on* Day 1 *and 200 mg of itraconazole QD from Day 2* to Day ~~8~~ *9* in Period 2. Itraconazole will be administered as oral capsules containing 200 mg every 12 hours (BID), 30 minutes after starting a standardized breakfast in the morning and after a standardized dinner in the evening *on Day 1 only and on Days 2 to 9 oral capsules containing 200 mg once a day (QD), 30 minutes after starting a standardized breakfast in the morning*. [redacted] RO7017773 will be administered to each participant in combination with the morning dose of itraconazole. Participants will be discharged on the morning of Day ~~11~~ *12* after all assessments have been completed. They will return to the clinical unit for ~~3~~ *4* ambulatory visits at Day 13, Day 14, *Day 15,* and Day ~~15~~ *16* for PK sampling and safety monitoring.

Participants will visit the clinical research unit for a safety follow-up visit 15 to 20 days after the last dose of itraconazole.

[redacted] Similarly, safety data will be collected in Period 1 and Period 2 in order to assess the effect of itraconazole on the safety profile of RO7017773.

4.1.1 Length of the Study

The total duration of the study for each participant will be up to 10 weeks, divided as follows (see also Section 1.3, Figure 1):

- **Screening:** Up to 4 weeks
- **In-clinic and dosing Period 1:** Day -1 to Day 4 with a single oral dose of [redacted] RO7017773 administered on Day 1.

- **Ambulatory visit Period 1:** Day 5, 6 and 8 (PK sampling and safety monitoring)
- **Washout Period:** Approximately 9 days *to a maximum of 18 days* (± 1 Day) (i.e., between Day 1 of Period 1 and Day -1 of Period 2).
- **In-clinic and dosing Period 2:** Day -1 to Day ~~11~~ *12* with multiple oral dose administrations of itraconazole (200 mg BID *Day 1 and 200 mg QD Days 2 to Day 9*) from Day 1 to Day ~~8~~ *9* and [redacted] RO7017773 with itraconazole [redacted]
- **Ambulatory visit Period 2:** Day 13, Day 14, *Day 15,* and Day ~~15~~ *16* (PK sampling and safety monitoring).
- **Follow-up visit:** 15 to 20 days after the last dose of itraconazole.

4.2 Stopping Rules Criteria

4.2.1 Study Stopping Criteria

Dosing will be stopped at any time during the study if one of the following circumstances occurs in the participants, unless it is determined by the Investigator that the occurrence is not related to the administration of study drug:

- *One serious adverse event*
- *Severe non-serious adverse events (i.e., considered at least related to RO7017773 administration) in two or more participants.*

[redacted]

4.2.2 Individual Stopping Criteria

Dosing will be stopped at any time during the study in a given individual participant if compared to baseline one of the following circumstances occurs, unless it is determined by the Investigator that the occurrence is not related to the administration of the study drug:

- *a serious adverse event*
- *one (or more) severe adverse events (see Section 3.1 of Appendix 2 for definition of severity)*
- *clinically significant changes in vital signs or ECG, such as a QTcF > 480 ms (if confirmed by repeated measurement within 30 minutes) or QTcF change-from-baseline > 60 ms (if confirmed by repeated measurement within 30 minutes)*
- *an elevation of ALT > 3 x ULN, with an associated increase in bilirubin > 2 x ULN and with ALP > 2 ULN, in the absence of an alternative explanation*

- *other findings, that at the joint discretion of the Sponsor Clinical Pharmacologist, the Sponsor Safety Science leader and the Investigator, indicate that dosing in this individual should be stopped.*
- [redacted]

[redacted]

[redacted]

~~4.3~~4.4 Dose Justification

For this DDI study, the dose of [redacted] RO7017773 has been chosen, ensuring that no individual participant exceeds the geometric mean RO7017773 exposure observed at 375 mg, the highest dose tested in the [redacted] The dose of [redacted] is recommended to minimize the risk of observing a similar AE profile (mainly somnolence) [redacted]. Based on preliminary PBPK simulation, a geometric mean exposure of [redacted] ng/mL for C_{max} and [redacted] h.ng/mL for $AUC_{0\text{-}inf}$ is anticipated in Period 1 in which RO7017773 is administered alone in the fed state. In Period 2, based on PBPK simulations with the assumption of [redacted] the expected geometric mean plasma exposure of RO7017773 in combination with itraconazole will be [redacted] ng/mL for C_{max} and [redacted] h.ng/mL for $AUC_{0\text{-}inf}$, accounting for the FE, i.e., [redacted] Additionally, taking into consideration the worst case

scenario for C_{max} [redacted]

[redacted]

Doses of 200 mg QD or 200 mg BID of itraconazole are commonly used for DDI studies in healthy participants (CHMP, 2012). The itraconazole dosing regimen selected in this study (200 mg BID *on Day 1 and QD on Days 2 to 9*) reflects the higher therapeutic regimen for the treatment of itraconazole-sensitive fungal infections. Itraconazole will be administered with food to ensure maximum bioavailability.

Multiple doses of 200 mg itraconazole BID *on Day 1 and QD on Days 2 to 9* will be administered to maintain itraconazole exposure over the PK profile of the substrate RO7017773. To ensure that a close to maximal inhibition potential of itraconazole is reached as shown by PBPK simulations, [redacted] While 3 days is not sufficient for attainment of steady-state with itraconazole, [redacted] allows for some accumulation, with higher itraconazole and hydroxy-itraconazole exposure and therefore potentially greater degree of CYP3A inhibition, with consideration for safety concerns associated with a longer itraconazole run-in period. This strategy has been demonstrated in multiple drug-drug interaction studies to provide adequate CYP3A inhibition (Ke et al 2014; Liu et al 2015). [redacted]

[redacted]

5.2 Exclusion Criteria

10. Alanine aminotransferase (ALT) and/or bilirubin > 1.5 × the upper limit of normal (ULN). ~~(isolated bilirubin > 1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%).~~

5.3.1 Meals and Dietary Restrictions

On Day 1 of Period 1, study drug administration (RO7017773) will be performed 30 minutes after starting a standardized breakfast. This breakfast should be consumed within 30 min or less.

~~From~~ *On* Day 1 ~~to Day 8~~ of Period 2, itraconazole will be administered at a dose of 200 mg every 12 hours (BID), 30 min after starting a standardized breakfast and after a standardized dinner in the evening. *From Days 2 to Day 9 of Period 2, itraconazole will be administered at a dose of 200 mg once a day (QD), 30 min after starting a standardized breakfast.* [redacted] RO7017773 will be administered to each participant in combination with the morning dose of itraconazole [redacted]

On the days of RO7017773 administration [redacted] a standard lunch will be provided 4 hours after dosing. On all other days of the in-house period, standard breakfast, lunch, dinner and snack will be provided at the times deemed convenient by the site, unless required for study drug administration.

6.1 Treatments Administered

Table 5 Summary of Treatments Administered

Study Treatment Name:	RO7017773	Itraconazole (Sporanox®)
Dosage Formulation:	Capsule	Capsule
Unit Dose Strength(s)/Dosage Level(s):	25 mg	100 mg
Dose:	[redacted]	200 mg BID *and QD*
Route of Administration:	Oral	Oral
Dosing Instructions:	RO7017773 will be administered with water in the morning 30 minutes after starting a standardized breakfast. Breakfast should be consumed within 30 minutes or less.	Itraconazole will be administered with water in the morning and in the evening (12 hours apart), 30 minutes after starting a standardized breakfast and a standardized dinner *on Day 1 only. On Days 2 to 9 itraconazole will be administered with water in the morning, 30 minutes after starting a standardized breakfast.* Breakfast and dinner should be consumed within 30 minutes or less.
Packaging and Labeling:	Study treatment will be provided in bottles. The IMP will be labeled as required per country requirements.	Marketed oral capsule(s) (100 mg) of itraconazole will be used during the study. Sporanox® will be sourced by the clinical site.
Storage Conditions	Store at 2°C to 8°C, protect from light and moisture	Sporanox® capsules will be stored according to the SmPC.
Manufacturer	F. Hoffmann-La Roche Ltd.	Janssen-Cilag Ltd

6.3.1 Method of Treatment Assignment

The study is open-label. Up to ~~14~~ *18* healthy participants will be enrolled in this study. The participant numbers will be allocated sequentially in the order in which the participants are included. The subject numbers will be generated by the Sponsor or its designee and it will be sent to the Investigator.

6.6 Dosage Modification

RO7017773 will be administered as a single dose of [redacted] on Day 1 in Period 1 and [redacted] Period 2. Doses of 200 mg BID *and QD* of itraconazole are used at therapeutic doses. See Section 4.4 for dose justification.

9.2 Sample Size Determination

Fourteen *to eighteen* participants will be enrolled in order to obtain at least 12 evaluable participants. This sample size has been chosen to ensure that the ratios of the treatment geometric means can be estimated with sufficient precision. [redacted]

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ANOVA	Analysis of variance
ASD	Autism spectrum disorder
AST	Aspartate aminotransferase
AUC	Area under the curve
BID	bis in die (twice daily)
$AUC_{0\text{-}inf}$	Area under the plasma concentration-time curve extrapolated to infinity
$AUC_{0\text{-}last}$	Area under the plasma concentration-time curve up to the last measurable concentration
$AUC_{0\text{-}t}$	Area under the plasma concentration-time curve from time 0 up to time t
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve from time 0 up to 24 hours
BMI	Body mass index
CDC	Center for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence intervals
C_{max}	Maximum plasma concentration
CL/F	Apparent oral clearance
CNS	Central nervous system
CRO	Contract research organization
CSR	Clinical study report
C-SSRS	Columbia Suicide-Severity Rating Scale
CTCAE	Common terminology criteria for adverse events
C_{trough}	Trough (pre-dose) plasma concentration for itraconazole and its metabolites, e.g. hydroxy-itraconazole
CYP3A	Cytochrome P450 (CYP) 3A
fmCYP3A4	Fraction metabolized CYP3A4
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECG	Electrocardiogram

eCRF	Electronic case report form
EDC	Electronic data capture
EEA	European Economic Area
EFD	Embryo fetal development
Emax	Maximum effect
ESF	Eligibility screening form
EU	European Union
FDA	Food and Drug Administration
FE	Food effect
FSH	Follicle-stimulating hormone
GABA	Gamma-aminobutyric acid
GLP	Good Laboratory Practice
$GABA_A$	Gamma-aminobutyric acid type A
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HR	Heart rate
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IRB	Institutional Review Board
IUD	Intrauterine device
LDH	Lactate dehydrogenase
LPLO	Last participant, last observation
MAD	Multiple ascending doses
NCI	National Cancer Institute
NOAEL	No-observed-adverse-effect level
NSAESI	Non-serious adverse event of special interest
OTC	Over-the-counter
PAM	Positive allosteric modulator
PBPK	Physiologically based pharmacokinetic
PET	Positron emission tomography
PK	Pharmacokinetic
PQ	PQ interval
PR	PR interval

PT	Prothrombin time
QRS	QRS interval
QT	QT interval
QTc	QT corrected for heart rate
QTcF	QT corrected for heart rate using the Fridericia's correction factor
$R_{AUCo-inf}$	AUC ratios calculated as RO7017773 AUC_{0-inf} Period 2 over RO7017773 AUC_{o-inf} Period 1
RBC	Red blood cell
R_{Cmax}	C_{max} ratio calculated as RO7017773 C_{max} Period 2 over RO7017773 C_{max} Period 1
RR	RR interval
SAD	Single-ascending dose
SAE	Serious adverse event
SBP	Systolic blood pressure
SE	Standard error
SmPC	Summary of Product Characteristics
SoA	Schedule of activities
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reactions
T_{max}	Time to reach maximum plasma concentration
$T_{1/2}$	Apparent terminal half-life
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of non-childbearing potential

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**A NON-RANDOMIZED, OPEN-LABEL, ONE SEQUENCE, TWO-PERIOD CROSS-OVER STUDY TO INVESTIGATE THE EFFECT OF CYP3A INHIBITION ON THE PHARMACOKINETICS OF RO7017773 IN HEALTHY PARTICIPANTS**
SHORT TITLE	**OPEN-LABEL, ONE SEQUENCE, TWO-PERIOD CROSS-OVER DDI STUDY BETWEEN RO7017773 AND ITRACONAZOLE**
PROTOCOL NUMBER:	BP40822
VERSION:	3
TEST PRODUCT:	RO7017773
PHASE:	I

RATIONALE

The aim of the study is to investigate the effect of multiple oral doses of itraconazole on the pharmacokinetics of RO7017773. Since CYP3A is one of the major metabolizing enzymes of RO7017773, CYP3A inhibitors are likely to increase the plasma exposure of RO7017773. Itraconazole is a strong CYP3A inhibitor and is commonly used as a prototypical CYP3A4 inhibitor in drug-drug interaction (DDI) studies.

This study will allow assessing the magnitude of increase in systemic exposure of RO7017773 when co-administered with CYP3A inhibitors like itraconazole.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To investigate the effect of multiple oral doses of itraconazole on the pharmacokinetics (PK) of a single oral dose of RO7017773 in healthy participants.	• RO7017773 concentrations and RO7017773 pharmacokinetic parameters.
• **Secondary**	
• To assess the safety and tolerability of a single oral dose of RO7017773 alone and in combination with multiple doses of itraconazole in healthy participants.	• Incidence and severity of AEs. • Changes in vital signs, physical findings, ECG parameters, and clinical laboratory results during and after RO7017773 administration alone and in combination with itraconazole. • Change in suicide risk (using the Columbia Suicide Severity Rating Scale [C-SSRS]).
• To assess the PK of itraconazole following multiple oral doses of itraconazole alone and in combination with a single oral dose of RO7017773 to ensure adequate CYP3A4 inhibition.	• Concentrations and PK parameters for itraconazole and its metabolites.

OVERALL DESIGN

Study Design

Single-center, non-randomized, open-label, one-sequence, two-period crossover study in healthy male and female participants. In Period 1, participants will be administered a single oral dose of RO7017773 alone in fed state. In Period 2, participants will be administered [redacted] RO7017773 [redacted] after repeated administration of itraconazole [redacted].

[redacted]

Treatment Groups and Duration

The total duration of the study for each participant will be up to 10 weeks, divided as follows:

- **Screening:** Up to 4 weeks
- **In-clinic and dosing Period 1:** Day -1 to Day 4 with a single oral dose of [redacted] RO7017773 administered on Day 1.
- **Ambulatory visit Period 1:** Day 5, 6, and 8 (PK sampling and safety monitoring)
- **Washout Period:** approximately 9 days *to a maximum of 18 days* (± 1 Day) (i.e., between Day 1 of Period 1 and Day -1 of Period 2).
- **In-clinic and dosing Period 2:** Day -1 to Day *12* with multiple oral dose administrations of itraconazole (200 mg twice a day [BID] *on Day 1 and 200 mg once a day [QD] on Days 2-9*) from Day 1 to Day *9* and co-administration of [redacted] RO7017773 with itraconazole on the morning [redacted]
- **Ambulatory visit Period 2:** Day 13, Day 14, *Day 15* and Day *16* (PK sampling and safety monitoring).

- **Follow-up visit:** 15 to 20 days after the last dose of itraconazole.

The investigational medicinal product is: RO7017773, 25 mg capsules for oral administration.

Length of Study

The total duration of the study for each participant will be up to 10 weeks.

End of Study

The end of the study is defined as the date when the last participant last observation (LPLO) occurs. LPLO is expected to occur approximately 2 weeks after the last participant's last dose of itraconazole.

PARTICIPANT POPULATION

The participants of this study are healthy volunteers between 18 and 55 years of age, inclusive, who fulfill all the inclusion criteria and for whom none of the exclusion criteria apply.

Inclusion Criteria

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

1. Able and willing to provide written informed consent and to comply with the study protocol according to International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines and local regulations.
2. Participants must be 18 to 55 years of age inclusive, at the time of signing the informed consent.
3. Participants who are healthy as judged by the Investigator. Healthy status will be defined as the absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination, vital signs, 12-lead ECG, hematology, blood chemistry, serology and urinalysis.
4. Body mass index (BMI) within the range 18 to 30 kg/m^2 (inclusive).
5. Male and female participants.

   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.

   a) Female participants:

      Women of non-childbearing potential (WONCBP).

   b) Male participants:

      During the treatment period and for at least 28 days after the last dose of the study treatment, 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), or pregnant female partners, to avoid exposing the embryo to study treatment.

      Refrain from donating sperm for at least 28 days after the last dose of the study drug.

Exclusion Criteria

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

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 participant's ability 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 convulsions (other than benign febrile convulsions of childhood) including epilepsy, or personal history of significant cerebral trauma or central nervous system (CNS) infections (e.g., meningitis).
4. History of clinically significant hypersensitivity (e.g., drugs, excipients) or allergic reactions.
5. 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.
6. Abnormal blood pressure, i.e., systolic blood pressure (SBP) greater than 140 mmHg or less than 90 mmHg, and diastolic blood pressure (DBP) greater than 90 mmHg or less than 50 mmHg.
7. Abnormal pulse rate, resting pulse rate greater than 100 beats per minute (bpm) or less than 40 bpm.
8. History or presence of clinically significant ECG abnormalities before study drug administration (e.g., PQ/PR interval $>$ 220 ms, QT interval corrected for heart rate using the Fridericia's correction factor [QTcF] $>$ 450 ms) 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).
9. 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 at any time during screening or on Day -1 to confirm eligibility.
10. Alanine aminotransferase (ALT) and/or bilirubin $>$ 1.5 $\times$ the upper limit of normal (ULN).
11. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's Syndrome or asymptomatic gallstones).
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 (results from the C-SSRS assessment should be taken into account).
13. Participants likely to need concomitant medication during the study period (including medication for dental conditions).
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. Positive test for drugs of abuse or alcohol.
16. For women of non-childbearing potential (WONCBP), a positive pregnancy test.
17. Evidence of human immunodeficiency virus (HIV) infection and/or positive human HIV antibodies.
18. Positive result for hepatitis B virus (HBV) or hepatitis C virus (HCV), presence of hepatitis B surface antigen (HBsAg) or positive HCV antibody test result at screening or within 3 months prior to starting study treatment.
19. Dietary restrictions that would prohibit the consumption of standardized meals.
20. Use of any prohibited medications and/or food before study start and during the study.
21. Any suspicion or history of alcohol abuse and/or any suspicion of regular consumption of drugs of abuse or previous history of or treatment for a dependence disorder.
22. Sensitivity to any of the study treatments, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates the participation in the study.
23. Participants who regularly smoke more than 5 cigarettes daily or equivalent and unable or unwilling not to smoke during the in-house period.
24. Participants who have donated over 500 mL of blood or blood products or had significant blood loss within 3 months prior to screening.
25. Participants under judicial supervision, guardianship, or curatorship.

26. Hypersensitivity to itraconazole, to any of the other excipients, or to any other triazole antifungal.
27. Any other known contraindications to itraconazole as stated in the Summary of Product Characteristics (SmPC).

NUMBER OF PARTICIPANTS

Fourteen *to eighteen* participants will be enrolled in order to obtain at least 12 evaluable participants.

CONCOMITANT MEDICATIONS

Permitted Therapies

- Continuation of hormone-replacement therapy or other maintenance therapy is permitted throughout the study for participants who already use them.
- 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

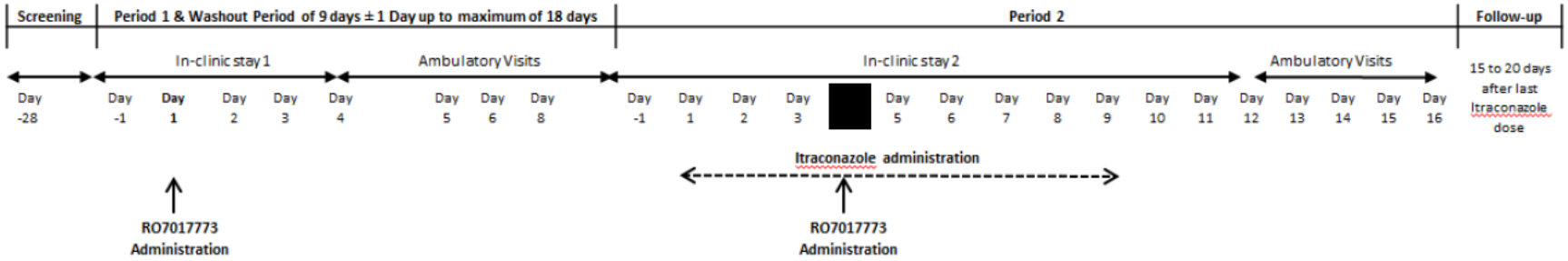
Use of the following therapies is prohibited during the study and for at least 30 days, or at least 5 half-lives of the medication, prior to initiation of study treatment (whichever is longer), unless otherwise specified below:

- Any prescribed or OTC medication (including herbal products, vitamins, minerals, energy drinks and dietary supplements).
- Any known inhibitor of CYP3A4 or P-glycoprotein taken within 2 weeks prior to the start of administration of the study drug (Period 1, Day 1) or within 5 times the elimination half-life of the medication prior to the start of study drug intake (whichever is longer) including but not limited to the following drugs: ketoconazole, fluconazole, erythromycin, clarithromycin, mifebradil, nefazodone, diltiazem, verapamil and cimetidine.
- Any known inducer of CYP3A4 or P-glycoprotein taken within 4 weeks prior to start of administration of study drug (Period 1 Day 1), including but not limited to the following drugs: rifampicin, rifabutin, glucocorticoids, carbamazepine, oxcarbazepine, phenytoin, phenobarbital, and St. John's Wort.

1.2 SCHEMATIC OF STUDY DESIGN

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

Figure 1 Overview of Study Design



1.3 SCHEDULE OF ACTIVITIES

The schedule of the activities is provided in Table 1 to Table 3.

Table 1 Schedule of Activities – Main Table

		Treatment Period 1 & Washout period of 9 Days ± 1 Day up maximum of 18 Days								Treatment Period 2																	Follow-up Visit (15 to 20 days after last itraconazole
Day	Screening up to Day-28	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 8	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	
Assessments																											
Informed Consent	x																										
Demography	x																										
Medical History	x																										
Physical Examination[a]	x	x								x												x					x
In house Period		x	x	x	x					x	x	x	x	x	x	x	x	x	x	x	x						
Discharge from the unit						x																x					
Ambulatory Visit							x	x	x														x	x	x	x	
Vital Signs [b]	x	x	x	x	x	x	x		x	x	x			x	x	x		x	x			x				x	x
12-Lead ECG [c]	x	x	x	x	x	x	x		x	x	x			x	x	x		x	x			x				x	x
Serology	x																										
Pregnancy Test[d]	x	x																									
Hormone Panel [e]	x	x																									
Alcohol Breath Test	x	x								x																	
Urine Drugs of Abuse	x	x								x																	
Urinalysis	x	x			x				x	x				x			x			x						x	x
Blood Chemistry	x	x			x				x	x				x			x			x						x	x
Hematology	x	x			x				x	x				x			x			x						x	x
Coagulation	x	x																									
RO7017773 Administration[f]			■											▮													
Itraconazole Administration[g]											x	x	x	x	x	x	x	x	x								
Standard Meal [h]		x	x [i]							x	x	x	x	x [i]	x	x	x	x	x								
[redacted]			[redacted]																								
Itraconazole and metabolites PK sample											x			x	x	x	x	x	x	x	x	x	x	x	x	x	
Clinical Genotyping			x																								
C-SSRS	x	x				x				x			x								x						
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

PK = Pharmacokinetic

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

a) Physical examination will include body weight at screening and follow-up, and height at screening when body mass index (BMI) will be derived.

b) Vital signs will include blood pressure, pulse rate, and (at selected time points) body temperature. Vital sign measurements will be taken after the participant has rested in a supine position for at least 5 minutes.

c) Triplicate 12-lead ECG will be recorded after the participant has rested in a supine position for at least 10 minutes.

d) Serum test at screening, urine test at Day -1.

e) Hormonal panel for postmenopausal women only.

f) The oral dose of RO7017773 will be given in the morning, 30 min after starting a standardized breakfast.

g) *An* oral dose of itraconazole will be given twice daily (2 x 200 mg) with 12 hours between the two doses and under fed conditions, i.e., 30 minutes after starting a meal in the morning and the evening *on Day 1 only. On Days 2 to 9, an oral dose of itraconazole will be given once daily (1 x 200 mg) under fed conditions, i.e., 30 minutes after starting a meal in the morning.*

h) On the morning of study drug treatment, breakfast should be consumed within 30 min or less. On itraconazole administration days, the evening meal should be consumed within 30 min or less.

i) The same food conditions (in terms of meal constitution and time of administration) will apply on RO7017773 administration days.

Table 2 Schedule of Activities – Detailed Table Period 1

Day	[redacted]	Vital Signs [a]	ECG-12 lead [c]	Safety Laboratory Tests	RO7017773 Administration	Standard Meal	[redacted]	Clinical Genotyping
Day 1		x [b]	x			x [e]		x
					x [d]			
		x [b]	x					
		x	x					
						x		
		x	x					
		x [b]	x					
		x	x					
						x		
Day 2		x [b]	x					
Day 3		x	x	x				
Day 4		x	x					
Day 5		x	x					
Day 6								
Day 8		x	x	x				

PK = Pharmacokinetic

Table 2 Schedule of Activities – Detailed Table Period 1 (cont.)

a) Blood pressure and pulse rate will be measured after the participant has rested in a supine position for at least 5 minutes.

b) Body temperature to be measured.

c) Triplicate 12-lead ECG will be recorded after the participant has rested in a supine position for at least 10 minutes.

d) The oral dose of RO7017773 will be given in the morning, 30 min after starting a standardized breakfast.

e) On the morning of study drug administration, breakfast should be consumed within 30 min or less.

Table 3 Schedule of Activities – Detailed Table Period 2

Day	[redacted]	Vital Signs [a]	ECG-12 lead [d]	Safety Laboratory Tests	Itraconazole Administration [e]	RO7017773 Administration	Standard Meal [g]	[redacted]	Itraconazole & Metabolites PK Sample
Day 1		x [b]	x						x
					x		x		
									x
					x		x		
Day 2					x		x		x
Day 3					x		x		
Day 4		x [b,c]	x[c]	x	x	[redacted]	x		x[c]
		x [b]	x						x
		x	x						x
									x
							x		x
		x	x						x
		x [b]	x						x
		x	x						x
									x
							x		x
Day 5		x [b]	x		x		x		x
							x		x
Day 6		x	x		x		x		x
Day 7				x	x		x		x
Day 8		x	x		x		x		x
Day 9		x	x		x		x		x
Day 10				x					x
Day 11									x
Day 12		x	x						x
Day 13									x
Day 14									x
Day 15									x
Day 16		x	x	x					x

PK = Pharmacokinetic

Table 3 Schedule of Activities – Detailed Table Period 2 (cont.)

a) Blood pressure and pulse rate will be measured after the participant has rested in a supine position for at least 5 minutes.

b) Body temperature to be measured.

[redacted]

d) Triplicate 12-lead ECG will be recorded after the participant has rested in a supine position for at least 10 minutes.

e) *An* oral dose of itraconazole will be given twice daily (2 x 200 mg) with 12 hours between the two doses and under fed conditions, i.e., 30 minutes after starting a meal in the morning and the evening *on Day 1 only. On Days 2 to Day 9, an oral dose of itraconazole will be given once daily (1 x 200 mg) under fed conditions, i.e., 30 minutes after starting a meal in the morning.*

[redacted]

g) On the morning of study drug administration, breakfast should be consumed within 30 min or less. On itraconazole administration days, the evening meal should be consumed within 30 min or less.

2. INTRODUCTION

2.1 STUDY RATIONALE

RO7017773 is being developed for the treatment of the 2 core domains of Autism Spectrum Disorder (ASD): social communication deficits and repetitive and restrictive behaviors. RO7017773 has the potential to normalize GABAergic signaling in key brain regions implicated in ASD without the side effects of non-specific $GABA_A$ modulators (e.g., benzodiazepines).

The aim of the study is to investigate the effect of multiple oral doses of itraconazole on the pharmacokinetics (PK) of RO7017773. [redacted] CYP3A inhibitors are likely to increase the plasma exposure of RO7017773. Itraconazole, a potent and widely used triazole antifungal agent, is a strong CYP3A inhibitor and is a commonly used as a prototypical CYP3A inhibitor in drug-drug interaction (DDI) studies.

This study will allow assessing the magnitude of increase in systemic exposure of RO7017773 when co-administered with CYP3A inhibitors like itraconazole.

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

2.2 BACKGROUND

ASD is a complex, heterogeneous neurodevelopmental disorder characterized by impairments in social communication and interaction, as well as by repetitive behaviors and restricted interests (Diagnostic and Statistical Manual of Mental Disorders [DSM 5]). The estimated prevalence of ASD in the United States is 1 in 68 children (CDC, 2014), and it is estimated that 1% of the world's population have ASD (WHO, 2013).

No approved pharmacological treatment exists for the core social communication and social interaction deficits and repetitive behavior of ASD, and this disorder continues to be an area of high unmet medical need. Current treatments for associated symptoms of ASD may include antipsychotics (risperidone and aripiprazole) used for the treatment of irritability associated with ASD symptoms. Multiple lines of evidence suggest that an imbalance between excitatory/inhibitory neurotransmission in favor of excitation may arise from a dysfunction of the GABAergic signaling system (the main inhibitory neurotransmitter system in the brain) early in development; this imbalance represents a central characteristic of the neurobiology of autism, leading to some of the impairments observed in individuals with ASD.

2.2.1 Background on RO7017773

RO7017773 is a selective $GABA_A$ $\alpha 5$ subunit containing receptor positive allosteric modulator.

[redacted]

[redacted]

2.2.1.2 Previous and ongoing clinical studies

At the time of writing, RO7017773 has been investigated in 2 healthy adult participant studies, one ongoing Entry-into-Human study (BP40091) with single ascending doses (SAD) and multiple ascending doses (MAD) and one completed positron emission tomography (PET) study (BP40257).

[redacted]

[redacted]

[redacted].

[redacted]

[redacted]

2.2.2 Background on Itraconazole

Itraconazole is a potent and widely used triazole antifungal agent and a prototypic competitive inhibitor of CYP3A ([FDA, 1999; CHMP, 2012; Bjornsson et al 2003). It reduces the metabolism and increases exposure of drugs metabolized by the CYP3A4 pathway. Itraconazole is available as oral capsules and the recommended doses in adults are 100 or 200 mg once daily (QD) or twice daily (BID) administered with food.

Itraconazole is generally well tolerated. Gastrointestinal disturbances are the most frequently reported AEs following the oral use of itraconazole. Nausea, vomiting, diarrhea, and abdominal pain have been commonly reported in patients undergoing treatment of systemic fungal infections. These AEs are dose-related and may be minimized by giving itraconazole with food. Rash was also observed in patients; however, rash tends to occur more frequently in immunocompromised patients receiving immunosuppressive medications. Itraconazole has been associated with rare cases of serious hepatotoxicity. Some of these cases had neither pre-existing liver disease nor a serious underlying medical condition and some of these cases developed within the first week of treatment. If clinical signs or symptoms develop that are consistent with liver disease, treatment should be discontinued and liver function testing performed. Other AEs include pruritus and angioedema, and rare cases of anaphylaxis have been reported. Fatigue, headache, dizziness, hypertension, decreased libido, impotence, visual disturbances and somnolence may also occur (SmPC).

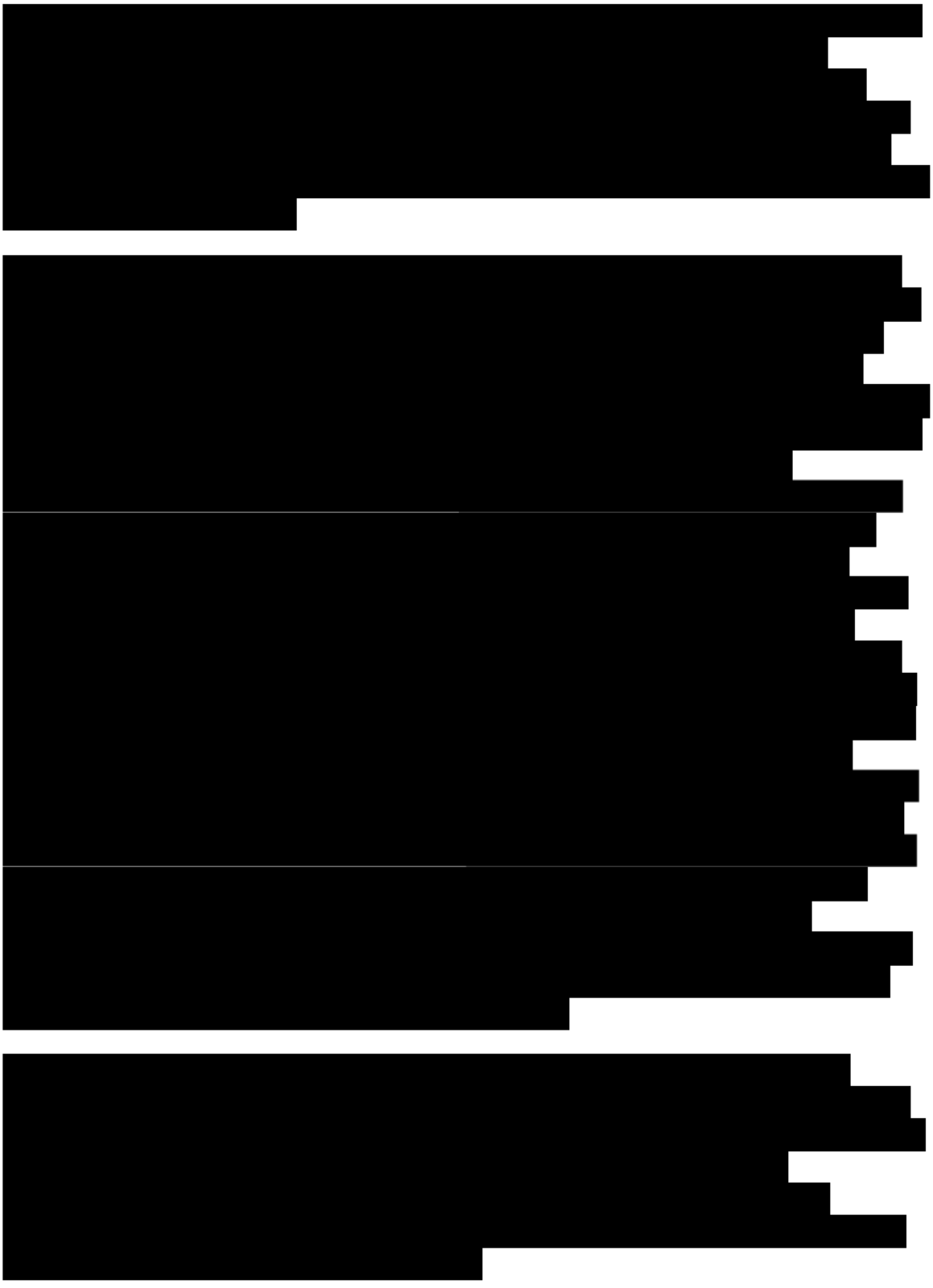
A detailed description of the chemistry, pharmacology, efficacy and safety of itraconazole is provided in the Summary of Product Characteristics (SmPC).

2.3 BENEFIT/RISK ASSESSMENT

This study is being conducted to evaluate the PK of RO7017773 with and without concomitant administration of itraconazole to investigate the effects of inhibition of CYP3A on RO7017773 exposure.

In order to minimize the number of participants required in the study, a within-subject study design has been chosen and an open-label, one-sequence design was selected.

[redacted]



Itraconazole is generally well tolerated. The itraconazole dosing regimen in this study is consistent with the prescribing recommendations for itraconazole (SmPC). Approved dosing regimens for the treatment of fungal infections include doses up to 200 mg BID

for periods of up to one year. Itraconazole doses of 200 mg QD or BID are also commonly used in DDI studies to ensure adequate CYP3A inhibition (Ke et al 2014; Liu et al 2015).

There is extensive clinical experience of the use of itraconazole and the potential clinical risks are well characterized. While some side effects occur frequently (e.g., headache, abdominal pain, and nausea), these generally do not require any medical intervention and side effects requiring treatment tend to occur rarely. There are a number of contraindications and precautions within the approved itraconazole prescribing information, but potential risks will be minimized by enrolling only healthy participants and specifically excluding people for whom the drug is contraindicated (e.g. history of heart failure).

Itraconazole PK will be measured when given alone and concomitantly with RO7017773 to ascertain that the PK concentrations of itraconazole ensure maximal CYP3A4 inhibition. Participants will be kept in the clinical unit under continuous medical supervision and monitoring for 3 days after single administration of RO7017773 alone and one week after RO7017773 administration in combination with itraconazole. They will remain in the clinical unit up to 3 days after the administration of the last dose of itraconazole.

More detailed information about the known and expected benefits in the context of potential risks and reasonably expected AEs of RO7017773 and itraconazole are provided in the Investigator's Brochure and in the SmPC, respectively.

3. OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints are provided in Table 4.

Table 4 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To investigate the effect of multiple oral doses of itraconazole on the pharmacokinetics (PK) of a single oral dose of RO7017773 in healthy participants.	• RO7017773 concentrations and RO7017773 PK parameters.
Secondary	
• To assess the safety and tolerability of a single oral dose of RO7017773 alone and in combination with multiple doses of itraconazole in healthy participants.	• Incidence and severity of AEs. • Changes in vital signs, physical findings, ECG parameters, and clinical laboratory results during and after RO7017773 administration alone and in combination with itraconazole. • Change in suicide risk (using the Columbia Suicide Severity Rating Scale [C-SSRS]).
• To assess the PK of itraconazole following multiple oral doses of itraconazole alone and in combination with a single oral dose of RO7017773 to ensure adequate CYP3A4 inhibition.	• Concentrations and PK parameters for itraconazole and its metabolites.
Exploratory	
• To screen for the presence of RO7017773-derived metabolites.	• PK concentrations of RO7017773-derived metabolites, if appropriate.
• To assess the relative abundance and PK parameters of any metabolite as appropriate.	• PK parameters of RO7017773-derived metabolites, if appropriate.
• To investigate whether genetic variants of drug-metabolizing enzymes (e.g. CYP3A4) can be related to the pharmacokinetic behavior or observations on the safety of RO7017773 in combination with itraconazole.	• Clinical genotyping.

4. STUDY DESIGN

4.1 OVERALL DESIGN

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

This is a single-center, non-randomized, open-label, one-sequence, two-period crossover study in healthy male and female participants to investigate the effect of CYP3A inhibition on the PK of RO7017773 using concomitant administration of itraconazole as CYP3A inhibitor.

In Period 1, participants will be administered a single oral dose of RO7017773 alone in fed state. In Period 2, after a wash-out period of 10 days, participants will receive multiple doses of itraconazole in fed state for 9 days and be administered [redacted] RO7017773 [redacted] in combination with itraconazole [redacted].

[redacted]

Healthy participants will be admitted to the clinical unit on Day -1 of Period 1. An oral dose of [redacted] RO7017773 will be administered alone, 30 minutes after starting a standardized breakfast on the morning of Day 1 of Period 1. Participants will be discharged on the morning of Day 4 after all assessments have been completed. They will return to the clinical unit for 3 ambulatory visits at Day 5, Day 6, and Day 8 for PK sampling and safety monitoring.

After a wash-out period of 10 days, participants will be admitted to the clinical unit on Day -1 of Period 2 and will remain in-house until the morning of Day *12*. They will be administered 200 mg of itraconazole BID (12 hours apart) *on* Day 1 *and 200 mg of itraconazole QD from Day 2* to Day *9* in Period 2. Itraconazole will be administered as oral capsules containing 200 mg every 12 hours (BID), 30 minutes after starting a standardized breakfast in the morning and after a standardized dinner in the evening *on Day 1 only and on Days 2 to 9 oral capsules containing 200 mg once a day (QD), 30 minutes after starting a standardized breakfast in the morning*. On the morning [redacted] RO7017773 will be administered to each participant in combination with the morning dose of itraconazole. Participants will be discharged on the morning of Day *12* after all assessments have been completed. They will return to the clinical unit for *4* ambulatory visits at Day 13, Day 14, *Day 15,* and Day *16* for PK sampling and safety monitoring.

Participants will visit the clinical research unit for a safety follow-up visit 15 to 20 days after the last dose of itraconazole.

[redacted] Similarly, safety data will be collected in Period 1 and Period 2 in order to assess the effect of itraconazole on the safety profile of RO7017773.

4.1.1 Length of the Study

The total duration of the study for each participant will be up to 10 weeks, divided as follows (see also Section 1.3, Figure 1):

- **Screening:** Up to 4 weeks
- **In-clinic and dosing Period 1:** Day -1 to Day 4 with a single oral dose of [redacted] RO7017773 administered on Day 1.
- **Ambulatory visit Period 1:** Day 5, 6 and 8 (PK sampling and safety monitoring)
- **Washout Period:** Approximately 9 days *to a maximum of 18 days* (± 1 Day) (i.e., between Day 1 of Period 1 and Day -1 of Period 2).
- **In-clinic and dosing Period 2:** Day -1 to Day *12* with multiple oral dose administrations of itraconazole (200 mg BID *Day 1 and 200 mg QD Days 2 to Day 9*) from Day 1 to Day *9* and co-administration of [redacted] RO7017773 with itraconazole on the morning [redacted].
- **Ambulatory visit Period 2:** Day 13, Day 14, *Day 15,* and Day *16* (PK sampling and safety monitoring).
- **Follow-up visit:** 15 to 20 days after the last dose of itraconazole.

4.2 *STOPPING RULES CRITERIA*

4.2.1 *Study Stopping Criteria*

Dosing will be stopped at any time during the study if one of the following circumstances occurs in the participants, unless it is determined by the Investigator that the occurrence is not related to the administration of study drug:

- *One serious adverse event*
- *Severe non-serious adverse events (i.e., considered at least related to RO7017773 administration) in two or more participants*

[redacted]

4.2.2 *Individual Stopping Criteria*

Dosing will be stopped at any time during the study in a given individual participant if compared to baseline one of the following circumstances occurs, unless it is determined by the Investigator that the occurrence is not related to the administration of the study drug:

- *a serious adverse event*
- *one (or more) severe adverse events (see section 3.1 of Appendix 2 for definition of severity)*
- *clinically significant changes in vital signs or ECG, such as a QTcF > 480 ms (if confirmed by repeated measurement within 30 minutes) or QTcF change-from-baseline > 60 ms (if confirmed by repeated measurement within 30 minutes)*
- *an elevation of ALT > 3 x ULN, with an associated increase in bilirubin > 2 x ULN and with ALP > 2 ULN, in the absence of an alternative explanation*
- *other findings, that at the joint discretion of the Sponsor Clinical Pharmacologist, the Sponsor Safety Science leader and the Investigator, indicate that dosing in this individual should be stopped*
- [redacted]

4.3 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study rationale is provided in Section 2.1.

Based on preclinical experiments, it is expected that there will be an effect of itraconazole, due to its inhibitory effect on the metabolism of RO7017773. To minimize the number of participants required, a two period crossover design has been selected. As the elimination of RO7017773 may be prolonged by itraconazole, an open-label, one-sequence design has been selected.

4.3.1 Rationale for Study Population

The participants of this study, healthy men and women of non-childbearing potential (WONCBP) aged 18 to 55 years (inclusive), have been chosen because of the absence of confounding diseases, which will permit a clearer and more consistent assessment of drug disposition and safety profile. In addition, healthy participants are unlikely to require concomitant medications which could interfere with the study drug or its PK.

4.3.2 Rationale for Pharmacokinetic Assessments

The investigation of the effect of multiple oral doses of itraconazole on the PK of a single oral dose of RO7017773 in healthy participants is the primary objective of the study. Pharmacokinetic assessments of RO7017773 will be performed in plasma. The timings of PK sample collection are based on PK modeling and on observed PK data collected in study BP40091 and are considered adequate to allow for a characterization of the absorption, distribution and elimination phases following a single oral dose administration of RO7017773. [redacted]

Plasma PK samples for itraconazole and its metabolite (hydroxy-itraconazole) will be collected to ensure that adequate exposure to itraconazole and its metabolites (e.g., hydroxy-itraconazole) is achieved.

Plasma PK samples may also be screened for exploratory RO7017773 metabolite identification with the use of non-validated methods to allow for an early identification of the metabolite(s) formed in vivo, and in particular to determine if any human-specific metabolite(s) are produced. In such circumstances, metabolite concentrations may be measured in residual pharmacokinetic plasma samples retrospectively, as appropriate.

[redacted]

[redacted]

4.4 DOSE JUSTIFICATION

For this DDI study, the dose of [redacted] RO7017773 has been chosen, ensuring that no individual participant exceeds the geometric mean RO7017773 exposure observed at [redacted], the highest dose tested in the [redacted] The dose of [redacted] is recommended to minimize the risk of observing a similar AE profile (mainly somnolence) [redacted]. Based on preliminary PBPK simulation, a geometric mean exposure of [redacted] for C_{max} and [redacted] for $AUC_{0\text{-}inf}$ is anticipated in Period 1 in which RO7017773 is administered alone in the fed state. In Period 2, based on PBPK simulations with the assumption of [redacted] the expected geometric mean plasma exposure of RO7017773 in combination with itraconazole will be [redacted] ng/mL for C_{max} and [redacted] h.ng/mL for $AUC_{0\text{-}inf}$, accounting for the FE, i.e., [redacted]. Additionally, taking into consideration the worst case scenario for C_{max}, [redacted]

[redacted]

[redacted]

Doses of 200 mg QD or 200 mg BID of itraconazole are commonly used for DDI studies in healthy participants (CHMP, 2012). The itraconazole dosing regimen selected in this study (200 mg BID *on Day 1 and QD on Days 2 to 9*) reflects the higher therapeutic regimen for the treatment of itraconazole-sensitive fungal infections. Itraconazole will be administered with food to ensure maximum bioavailability.

Multiple doses of 200 mg itraconazole BID *on Day 1 and QD on Days 2 to 9* will be administered to maintain itraconazole exposure over the PK profile of the substrate RO7017773. To ensure that a close to maximal inhibition potential of itraconazole is reached as shown by PBPK simulations, [redacted] While 3 days is not sufficient for attainment of steady-state with itraconazole, [redacted] allows for some accumulation, with higher itraconazole and hydroxy-itraconazole exposure and therefore potentially greater degree of CYP3A inhibition, with consideration for safety concerns associated with a longer itraconazole run-in period. This strategy has been demonstrated in multiple drug-drug interaction studies to provide adequate CYP3A inhibition (Ke et al 2014; Liu et al 2015). [redacted] This duration of inhibition of CYP3A4 is considered sufficient to get a good overall estimate of the interaction between itraconazole and RO7017773.

4.5 END OF STUDY DEFINITION

The end of the study is defined as the date when the last participant last observation (LPLO) occurs. LPLO is expected to occur approximately 2 weeks after the last participant's last dose of itraconazole.

5. STUDY POPULATION

The study population rationale is provided in Section 4.3.1.

The participants of this study are healthy volunteers between 18 and 55 years of age, inclusive, who fulfill all the inclusion criteria listed in Section 5.1 and for whom none of the exclusion criteria listed in Section 5.2 apply.

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

5.1 INCLUSION CRITERIA

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

Informed Consent

1. Able and willing to provide written informed consent and to comply with the study protocol according to International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines and local regulations.

Age

2. Participants must be 18 to 55 years of age inclusive, at the time of signing the informed consent.

Type of Participants and Disease Characteristics

3. Participants who are healthy as judged by the Investigator. Healthy status will be defined as the absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination, vital signs, 12-lead ECG, hematology, blood chemistry, serology and urinalysis.

Weight

4. Body mass index (BMI) within the range 18 to 30 kg/m^2 (inclusive).

Sex

5. Male and female participants.

   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.

   a) Female participants

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

   b) Male participants:

   During the treatment period and for at least 28 days after the last dose of the study treatment, agree 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 at least 28 days after the last dose of the study drug.

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 participant's ability 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 convulsions (other than benign febrile convulsions of childhood) including epilepsy, or personal history of significant cerebral trauma or central nervous system (CNS) infections (e.g., meningitis).
4. History of clinically significant hypersensitivity (e.g., drugs, excipients) or allergic reactions.
5. 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.
6. Abnormal blood pressure, i.e., systolic blood pressure (SBP) greater than 140 or less than 90 mmHg, and diastolic blood pressure (DBP) greater than 90 or less than 50 mmHg.
7. Abnormal pulse rate, resting pulse rate greater than 100 beats per minute (bpm) or less than 40 bpm.
8. History or presence of clinically significant ECG abnormalities before study drug administration (e.g., PQ/PR interval $>$ 220 ms, QT interval corrected for heart rate using the Fridericia's correction factor [QTcF] $>$ 450 ms) 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).
9. 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 at any time during screening or on Day -1 to confirm eligibility.
10. Alanine aminotransferase (ALT) and/or bilirubin $>$ 1.5 $\times$ the upper limit of normal (ULN).
11. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's Syndrome or asymptomatic gallstones).
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 (results from the C-SSRS assessment should be taken into account).

13. Participants likely to need concomitant medication during the study period (including medication 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.

Diagnostic Assessments

15. Positive test for drugs of abuse or alcohol.
16. For women of non-childbearing potential (WONCBP), a positive pregnancy test.
17. Evidence of human immunodeficiency virus (HIV) infection and/or positive human HIV antibodies.
18. Positive result for hepatitis B virus (HBV) or hepatitis C virus (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

19. Dietary restrictions that would prohibit the consumption of standardized meals.
20. Use of any prohibited medications and/or food before study start and during the study (see Section 6.5.2 and Section 5.3.1).
21. Any suspicion or history of alcohol abuse and/or any suspicion of regular consumption of drug of abuse or previous history of or treatment for a dependence disorder.
22. Sensitivity to any of the study treatments, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates the participation in the study.
23. Participants who regularly smoke more than 5 cigarettes daily or equivalent and unable or unwilling not to smoke during the in-house period.
24. Participants who have donated over 500 mL of blood or blood products or had significant blood loss within 3 months prior to screening.
25. Participants under judicial supervision, guardianship or curatorship.
26. Hypersensitivity to itraconazole, to any of the other excipients, or to any other triazole antifungal.
27. Any other known contraindications to itraconazole as stated in the SmPC.

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 and for at least 8 hours prior to laboratory safety tests performed between Day-1 of Period 1 and the follow-up visit.

On Day 1 of Period 1, study drug administration (RO7017773) will be performed 30 minutes after starting a standardized breakfast. This breakfast should be consumed within 30 min or less.

On Day 1 of Period 2, itraconazole will be administered at a dose of 200 mg every 12 hours (BID), 30 min after starting a standardized breakfast and after a standardized dinner in the evening. *From Days 2 to Day 9 of Period 2, itraconazole will be administered at a dose of 200 mg once a day (QD), 30 min after starting a standardized breakfast.* On the morning [redacted], an oral dose [redacted] RO7017773 will be administered to each participant in combination with the morning dose of itraconazole 30 minutes after starting a standardized breakfast. This breakfast should be consumed within 30 minutes or less.

On the days of RO7017773 administration [redacted] a standard lunch will be provided 4 hours after dosing. On all other days of the in-house period, standard breakfast, lunch, dinner and snack will be provided at the times deemed convenient by the site, unless required for study drug administration.

Consumption of nutrients known to modulate CYP3A activity (e.g., grapefruit or grapefruit juice, Seville orange) will not be permitted within 2 weeks prior to first dosing until the safety follow up visit.

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 in-clinic period. During the participants' ambulatory periods between screening and the follow-up visit, participants will be asked to limit their coffee or tea consumption to no more than 3 cups per day, and their consumption of methylxanthine-containing products (e.g. cola) 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 participants' in-clinic stays and participants will be asked to limit their alcohol consumption 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 2 ambulatory periods until follow-up. The use of tobacco will not be permitted from 48 hours before dosing until the end of the in-clinic stay and participants will be asked to limit their tobacco use to a maximum of 5 cigarettes a day or an equivalent amount of tobacco during the 2 ambulatory periods until follow-up.

5.3.3 Activity

Participants should refrain from strenuous exercise from 7 days prior to first admission until the follow-up visit. The level of activities should be kept as similar as possible on all study days until the follow-up visit.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently 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 uncertain or questionable results during screening is not considered a re-screening.

5.5 RECRUITMENT PROCEDURES

Participants will be identified for potential recruitment using e.g., pre-screening enrollment logs, clinical database, and any Independent Ethics Committee/Institutional Review Board (IEC/IRB) approved materials.

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 investigational medicinal products (IMPs) required for completion of this study (RO7017773) will be provided by the Sponsor. Marketed oral capsules of itraconazole (Sporanox®) will be sourced by the clinical site.

All study drug administration will be at the study center under supervision of site staff.

6.1 TREATMENTS ADMINISTERED

Table 5 summarizes the treatments administered.

Table 5 Summary of Treatments Administered

Study Treatment Name:	RO7017773	Itraconazole (Sporanox®)
Dosage Formulation:	Capsule	Capsule
Unit Dose Strength(s)/Dosage Level(s):	25 mg	100 mg
Dose:	[redacted]	200 mg BID *and QD*
Route of Administration:	Oral	Oral
Dosing Instructions:	RO7017773 will be administered with water in the morning 30 minutes after starting a standardized breakfast. Breakfast should be consumed within 30 minutes or less.	Itraconazole will be administered with water in the morning and in the evening (12 hours apart), 30 minutes after starting a standardized breakfast and a standardized dinner *on Day 1 only. On Days 2 to 9 itraconazole will be administered with water in the morning, 30 minutes after starting a standardized breakfast.* Breakfast and dinner should be consumed within 30 minutes or less.
Packaging and Labeling:	Study treatment will be provided in bottles. The IMP will be labeled as required per country requirements.	Marketed oral capsule(s) (100 mg) of itraconazole will be used during the study. Sporanox® will be sourced by the clinical site.
Storage Conditions	Store at 2°C to 8°C, protect from light and moisture	Sporanox® capsules will be stored according to the SmPC.
Manufacturer	F. Hoffmann-La Roche Ltd.	Janssen-Cilag Ltd

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 6.6 or Section 7, respectively.

For itraconazole (Sporanox®), see the SmPC for more details.

For RO7077713, see the Investigator's Brochure and Pharmacy Manual (if available) for more details.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Study drug 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, the site pharmacy personnel will complete the following:

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

The qualified individual responsible for dispensing the study treatment will prepare the correct dose according to the treatment assignment schedule and e.g., IMP user guidelines.

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

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 or delegate 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.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.3.1 Method of Treatment Assignment

The study is open-label. Up to *18* healthy participants will be enrolled in this study. The participant numbers will be allocated sequentially in the order in which the participants are included. The subject numbers will be generated by the Sponsor or its designee and it will be sent to the Investigator.

6.4 TREATMENT COMPLIANCE

The qualified individual responsible for dispensing the study treatment will prepare the correct dose according to the treatment assignment. This individual will write the date dispensed and subject number on the study treatment 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 Therapies

Any medication or vaccine (including over-the-counter [OTC] or prescription medicines, approved dietary and herbal supplements, nutritional supplements) used by a participant from 4 weeks prior to screening until the follow-up visit must be recorded along with the reason for use, dates of administration (including start and end dates) and dosing 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).

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

- Continuation of hormone-replacement therapy or other maintenance therapy is permitted throughout the study for participants who already use them.
- 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 Therapies

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 prior to study drug administration until follow-up, with the exception of medications to treat AEs and medications listed in Section 6.5.1, 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 OTC medication (including herbal products, vitamins, minerals, energy drinks and dietary supplements).
- Any known inhibitor of CYP3A4 or P-glycoprotein taken within 2 weeks prior to the start of the administration of study drug (Period 1 Day 1) or within 5 times the elimination half-life of the medication prior to the start of study drug intake (whichever is longer) including but not limited to the following drugs: ketoconazole, fluconazole, erythromycin, clarithromycin, mifebradil, nefazodone, diltiazem, verapamil and cimetidine.
- Any known inducer of CYP3A4 or P-glycoprotein taken within 4 weeks prior to start of administration of study drug (Period 1 Day 1), including but not limited to the following drugs: rifampicin, rifabutin, glucocorticoids, carbamazepine, oxcarbazepine, phenytoin, phenobarbital, and St. John's Wort.

[redacted]

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 or any earlier participant withdrawal.

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.

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

Participants who discontinue study treatment prematurely will be asked to return to the clinic for a study completion/early termination visit (see Section 8.10.3) and may undergo follow-up assessments (see Section 8.10.4). The primary reason for premature study treatment discontinuation should be documented on the appropriate eCRF.

Participants who discontinue study treatment prematurely may be replaced in order to ensure obtaining 12 evaluable participants.

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.

See SoA (Section 1.3 for data to be collected at the time of study discontinuation and at the follow-up visit, 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 (Section 1.3).

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, neurological, and musculoskeletal systems in addition to head, eyes, ears, nose, throat, neck and lymph nodes. Height and weight will also be measured and recorded. The physical examination will NOT include pelvic, rectal or breast examinations.

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

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

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

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

8.2.2 Vital Signs

Vital signs will include temperature (tympanic), SBP and DBP, 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 QRS complex, PR, 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 ≥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.

ECGs should be performed prior to meals and blood draws as appropriate.

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 and RR interval will be calculated automatically and recorded on the eCRF or loaded automatically. 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., serious adverse event [SAE] or AE or dose-modification), the results must be recorded in the eCRF.

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 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 Suicidal Risk Monitoring

RO7017773 is considered to be a CNS-active study treatment. There has been some concern that some CNS-active study treatments may be associated with an increased risk of suicidal ideation or behavior when given to some participants. Although this study treatment or other similar drugs in this class have not been shown to be associated with an increased risk of suicidal thinking or behavior when given to healthy participants, the Sponsor considers it important to monitor for such events before or during this clinical study.

Baseline assessment of suicidal ideation and behavior AND/OR treatment-emergent suicidal ideation and behavior will be monitored during the study using the C-SSRS. C-SSRS assessments will be completed by the clinician.

8.2.6 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, if acceptable by local regulations.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The definitions of an AE or SAE can be found in Appendix 2. The non-serious adverse events of special interest (NSAESI) and disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs are discussed in Sections 8.3.6 and Section 8.3.7.

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

Procedures used for recording AEs are provided in Appendix 3.

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

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

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

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

After initiation of study treatment, all AEs, 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 AEs after the end of the AE reporting period (14 days after the last dose of study treatment).

However, if the Investigator learns of any SAE (including a death) or other AEs of concern that are believed to be related to prior treatment with study 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 procedures 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 AE information at all participant evaluation time−points.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

8.3.3.1 Investigator Follow-Up

The Investigator should follow each 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 SAEs considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the 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 SAEs, NSAESIs, 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, IRB, 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

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 28 days after the last dose of study drug.

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

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

8.3.6 Non-Serious Adverse Events of Special Interest

NSAESIs 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).

NSAESIs for this study include the following:

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

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a

patient exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.

8.3.7 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 AE unless it results in untoward medical effects (see Section 5 and 5.2 of Appendix 2 for further details).

Decisions regarding dose-interruptions or modifications of itraconazole will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

In the event of an overdose, the Investigator should:

1. Contact the Sponsor's Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until resolved.
3. Document the quantity of the excess dose, as well as the duration of the overdose (for itraconazole only), in the eCRF.

PK samples collected per protocol may be used to further evaluate overdose or incorrect administration of itraconazole.

8.5 PHARMACOKINETICS

Blood samples for the determination of plasma concentrations of RO7017773 will be collected as outlined in the SoA (see Section 1.3). Plasma RO7017773 concentrations will be measured by a specific and validated LC-MS/MS method. Plasma concentrations of RO7017773 metabolites may also be measured as appropriate using a specific assay.

Blood samples for the determination of plasma concentrations of itraconazole and its metabolite (hydroxy-itraconazole) will be also collected as detailed in the SoA (see Section 1.3). Plasma concentrations of itraconazole and its metabolite (hydroxy-itraconazole) will be measured by a specific and validated LC-MS/MS method.

PK parameters for RO7017773 and itraconazole and its metabolite will be read directly from the plasma concentration-time profiles or estimated using standard non-compartmental methods where appropriate.

If required, remaining PK samples may also be used for assay development/validation, e.g., metabolites and measurement of exploratory biomarkers.

The blood samples will be destroyed up to 6 months after the date of final clinical study report (CSR). Details on sampling procedures, sample storage and shipment are given in the Sample Handling Manual.

8.6 PHARMACODYNAMICS

Pharmacodynamic parameters are not evaluated in this study.

8.7 GENETICS

8.7.1 Clinical Genotyping

A blood sample will be collected for deoxyribonucleic acid (DNA) extraction according to the SoA (Section 1.3). If, however, the genetic blood sample is not collected during the scheduled visit, it may be collected at any time during the conduct of the clinical study.

The DNA may be used to determine if alleles (e.g., at metabolic enzymes, transporters, receptors) affect the PK and/or safety of RO7017773.

Any remaining blood after the specified analyses may also be used for additional (assay) validation experiments.

Data arising from this study will be subject to the same confidentiality as the rest of the study.

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

8.8 BIOMARKERS

Biomarkers are not evaluated in this study.

8.9 MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

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

8.10 TIMING OF STUDY ASSESSMENTS

8.10.1 Screening and Pre-treatment Assessments

Written informed consent for participation in the study must be obtained before performing any study‑specific screening tests or evaluations. Informed Consent Forms 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 time-points indicated in the SoA (see Section 1.3), unless otherwise specified.

If possible and if the Sponsor agrees, any assessments identical to those planned in the protocol for the participants' screening that have already been performed within the time frames stipulated by the protocol for the screening exams may be used for the protocol in order to minimize the burden for the participants.

8.10.2 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 Subject 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.

8.10.3 Assessments at Study Completion/Early Termination Visit

Participants who complete the study or discontinue from the study early will be asked to return to the clinic 15 to 20 days after the last dose of study treatment for a follow-up visit.

8.10.4 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 formal null hypotheses to be tested.

9.2 SAMPLE SIZE DETERMINATION

Fourteen *to eighteen* participants will be enrolled in order to obtain at least 12 evaluable participants. This sample size has been chosen to ensure that the ratios of the treatment geometric means can be estimated with sufficient precision. [redacted]

9.3 POPULATIONS FOR ANALYSES

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

Table 6 Analysis Populations

Population	Description
Safety	All participants who have been administered 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.
Pharmacokinetic	All participants who have received at least one dose of study treatment and who have data from at least one post-dose sample will be included in the PK analysis population. Participants will be excluded from the PK analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete which may influence the PK analysis. Excluded cases will be documented together with the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.

9.4 STATISTICAL ANALYSES

9.4.1 Demographics and Baseline Characteristics

Demographic and other baseline characteristics of the safety analysis population will be listed and summarized using descriptive statistics.

9.4.2 Safety Analyses

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

Table 7 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.
Columbia Suicide-Severity Rating Scale (C-SSRS)	Individual data at will be presented in listings.

9.4.3 Pharmacokinetic Analyses

Analyses will be carried out on the PK analysis population.

9.4.3.1 Pharmacokinetic Parameters

The primary RO7017773 PK study variable will be the AUC ($AUC_{0\text{-}inf}$ if it can be derived, otherwise truncated as appropriate) and C_{max}. All other PK parameters will be regarded as secondary.

The following PK parameters of RO7017773 and of itraconazole and its metabolites (e.g., hydroxy-itraconazole) will be read from the concentration versus time profiles or estimated using non-compartmental methods where appropriate:

- T_{max} : Time to maximum plasma concentration
- C_{max} : maximum observed plasma concentration
- $AUC_{0\text{-}t}$: area under the plasma concentration-time curve up to time t
- $AUC_{0\text{-}last}$: area under the plasma concentration-time curve up to the last measurable concentration
- $AUC_{0\text{-}inf}$: area under the plasma concentration-time curve extrapolated to infinity

- $T_{1/2}$: apparent terminal half-life, computed as $\ln(2)/\lambda_z$
- CL/F: apparent oral clearance, calculated as Dose/$AUC_{0\text{-inf}}$
- $R_{AUCo\text{-inf}}$: AUC ratios calculated as RO7017773 $AUC_{0\text{-inf Period 2}}$ over RO7017773 $AUC_{o\text{-inf Period 1}}$
- R_{Cmax}: C_{max} ratio calculated as RO7017773 $C_{max\ Period\ 2}$ over RO7017773 $C_{maxPeriod\ 1}$
- C_{trough}: trough (pre-dose) plasma concentration for itraconazole and its metabolites hydroxy-itraconazole.

Additional PK parameters may be reported as appropriate.

All pharmacokinetic concentration and calculated PK parameters for RO7017773, itraconazole and its metabolite will be presented in individual listings and summary tables (including descriptive summary statistics: mean, standard deviation, coefficient of variation, median, minimum, and maximum), and graphs (including concentration vs. time plots on linear and semi-logarithmic scales) as appropriate.

9.4.3.2 Statistical Analysis

The following linear statistical model will be applied to the log-transformed, dose-normalized PK variables AUC ($AUC_{0\text{-}\infty}$ if it can be derived, otherwise truncated as appropriate) and C_{max}:

$$y_{ij} = \mu + \tau_j + s_i + \varepsilon_{ij} \quad (i = 1, 2, \dots, 12; j = 1,2)$$

where μ denotes the general mean of the transformed variables, τ_j is the effect of the treatment (RO7017773 alone vs. RO7017773 together with Itraconazole), s_i is the random subject effect and ε_{ij} is the random error (within subject variability). The random subject effect and the random error are assumed to be independent and normally distributed with zero means and variances σ_s^2 and σ_ε^2 respectively.

Least square means with corresponding 90% confidence intervals (CI) will be derived to compare the relative bioavailability of the different treatments.

Under this model the (geometric means) ratios $\frac{AUC(\text{RO7017773+IT})}{AUC(\text{RO7017773})}$ and $\frac{C_{max}(\text{RO7017773+IT})}{C_{max}(\text{RO7017773})}$ are obtained as $\frac{\mu_{\lambda 1}}{\mu_{\lambda 2}} = e^{\lambda_1 - \lambda_2}$, i.e. by exponentiation of the corresponding estimated differences in the analysis of variance (ANOVA) model.

9.5 INTERIM ANALYSES

No interim analyses are planned for this study.

9.6 SUMMARIES OF CONDUCT OF STUDY

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

10. REFERENCES

Bjornsson TD, Callaghan JT, Einolf HJ, et al. Pharmaceutical Research and Manufacturers of America Drug Metabolism/Clinical Pharmacology Technical Working Group; FDA Center for Drug Evaluation and Research (CDER). The conduct of in vitro and in vivo drug-drug interaction studies: a Pharmaceutical Research and Manufacturers of America (PhRMA) perspective. Drug Metab Dispos. 2003; 31(7):815-32.

Columbia-Suicide Severity Rating Scale. Available at http://www.cssrs.columbia.edu/.

Committee for Human Medicinal Products (CHMP). Guideline on the investigation of drug interactions. June 2012.

Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators, Centers for Disease Control and Prevention (CDC). Prevalence of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2010. MMWR Surveill Summ 2014;63:1-21.

Investigator's Brochure for RO7017773.

Ke AB, Zamek-Gliszczynski MJ, Higgins JW, et al. Itraconazole and clarithromycin as ketoconazole alternatives for clinical CYP3A inhibition studies. Clin Pharmacol Ther. 2014 May;95(5):473-6.

Liu L, Bello A, Dresser MJ, Heald D, et al. Best practices for the use of itraconazole as a replacement for ketoconazole in drug-drug interaction studies. J Clin Pharmacol. 2015 Jun 4.

Sporanox® (Itraconazole) SmPC, Janssen Cilag Ltd, July 2017.

U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for Industry. In Vivo Drug Metabolism/Drug Interaction Studies – Study Design, Data Analysis, and Recommendations for Dosing and Labeling. November 1999.

World Health Organization. Meeting report: autism spectrum disorders and other developmental disorders: from raising awareness to building capacity; World Health Organization, Geneva, Switzerland 16-18 September 2013.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

The following section includes standard appendices such as Appendix 1 (for regulatory, ethical and study oversight considerations), Appendix 2 (for AE definitions, reporting) and Appendix 3 (procedures of recording), Appendix 5 (contraceptive guidance and collection of pregnancy information). Additional study-related appendices are 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.

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.

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., LPLO).

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.

A contract research organization (CRO) will be responsible for data management of this study, including quality checking of the data. Sites will be responsible for data entry into the electronic data capture (EDC) system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will produce a Data Management Plan or equivalent document that describes the quality checking to be performed on the data. Central laboratory data and/or other electronic data will be sent directly to the CRO, using the CRO's standard procedures to handle and process the electronic transfer of these 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.

2.1.3. Source Data Records

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

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

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

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

2.1.4. Use of Computerized Systems

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

2.2. RETENTION OF RECORDS

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

3. ADMINISTRATIVE STRUCTURE

The Sponsor of the trial is F. Hoffmann-La Roche Ltd. The Sponsor has contracted with CRO(s) who will be delegated responsibility for various aspects of this clinical trial.

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 patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event can therefore be:

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

Events Meeting the AE Definition:

- Any deterioration in a laboratory value (hematology, clinical chemistry, 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 pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

Events NOT Meeting the AE Definition:

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

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

2. DEFINITION OF SERIOUS ADVERSE EVENTS

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

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

- **Results in death.**
- **Is life-threatening.**
- The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization (see *Appendix 3*).**
- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- **Results in persistent or significant disability/incapacity**

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

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

- **Is a congenital anomaly/birth defect**.

- **Other significant events**:

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

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

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

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

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

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

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

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

3.1. ASSESSMENT OF SEVERITY

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

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe, or according to a pre-defined grading criteria [e.g., National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] criteria); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

Table 1 Adverse Event Severity Grading Scale

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

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

3.2. ASSESSMENT OF CAUSALITY

Investigators should use their knowledge of the participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study 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 (where applicable).
- 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.

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)

Accidental overdoses or medication errors (see Appendix 2, Section 5.2 for details on reporting requirements).

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

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

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

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

Events that Occur prior to Study 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 on the paper Serious Adverse Event/Adverse Event of Special Interest Reporting Form and forward this form to the SAE Responsible within 24 hours after learning of the event.

Reporting of Post-Study Adverse Events and Serious Adverse Events

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

5.2 REPORTING REQUIREMENTS FOR CASES OF ACCIDENTAL OVERDOSE OR MEDICATION ERROR

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. All special situations associated with RO7017773, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

For RO7017773 and itraconazole, each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Appendix 2, Section 5.1). RO7017773, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

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

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

The Sponsor will promptly evaluate all serious adverse events and NSAESI against cumulative product experience to identify and expeditiously communicate possible new

safety findings to Investigators, IRBs, ECs, and applicable Health Authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- RO7017773 Investigator's Brochure
- Itraconazole Summary of Product Characteristics

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Appendix 2, Section 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. 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").

8. PREEXISTING MEDICAL CONDITIONS

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

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

9. HOSPITALIZATION OR PROLONGED HOSPITALIZATION

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

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or insertion of access device for study treatment administration)

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
    - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.
    - The participant has not suffered an adverse event.

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

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

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 5.2, respectively, of the protocol.

Additional repeat or unscheduled tests may be performed at any time during the study as determined for necessary safety reasons or technical issues with the samples.

Table 1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	• Leucocytes, erythrocytes, hemoglobin, hematocrit, platelets, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).
Clinical Chemistry	• Sodium, potassium, chloride, bicarbonate, glucose (fasting), urea, creatinine, protein, albumin, phosphate, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, urate, LDH.
Coagulation	• Prothrombin time (INR) and activated thromboplastin time (aPTT).
Viral Serology	• HIV (specific tests HIV-1 antibody, HIV-1/2 antibody, HIV-2 antibody), hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody.
Lipids	• Cholesterol, triglycerides.
Hormone	• For post-menopausal women only to confirm post-menopausal status: Estradiol and follicle-stimulating hormone (FSH).
Pregnancy Test	• Serum or urine human chorionic gonadotropin (hCG) pregnancy test.
Urinalysis	• Specific gravity • Dipstick: pH, glucose, protein, blood, nitrite, leukocyte If there is a clinically significant positive result (confirmed by a positive repeated sample), urine will be sent to the laboratory for microscopy and/or 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.
Other Screening Tests	• Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines). • Alcohol Breath test.

The results of each test will be provided electronically or captured in the CRF.

Investigators must document their review of each laboratory safety report.

Additional Statistical Considerations for Clinical Laboratory Data

- Standard Reference Ranges and Transformation of Data

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

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

- Definition of Laboratory Abnormalities

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

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

Appendix 5
Contraceptive Guidance and Collection of Pregnancy Information

1. DEFINITIONS

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

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile.

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

a) Pre-menarchal

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

– Documented hysterectomy.

– Documented bilateral salpingectomy.

– Documented bilateral oophorectomy.

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

c) Post-menopausal female

– A post-menopausal state is defined as no menses for ≥ 12 months without an alternative medical cause other than menopause. A high follicle-stimulating hormone (FSH) level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

– Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status before study enrollment.

2. CONTRACEPTION GUIDANCE

- **Female Participants**

Table 1 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User-Dependent[a] (Failure rate of < 1% per year when used consistently and correctly)
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User-Independent[a]
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

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

3. PREGNANCY TESTING

For WONCBP enrolled in the study, blood sample and urine pregnancy tests will be performed according to Schedule of Activity tables (see Section 1.3 and Appendix 4). If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test.

Pregnancy testing may also be performed 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 study treatment.

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.

- **Female participants who become pregnant**

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

While pregnancy itself is not considered to be an AE or SAE, and should not be recorded on the AE eCRF, any pregnancy complication will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study treatment by the Investigator, will be reported to the Sponsor as described in Appendix 2.

While the Investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.

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

5 ABORTIONS

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

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

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

6 CONGENITAL ANOMALIES/BIRTH DEFECTS

Any congenital anomaly/birth defect in a child born to a female 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*).