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: SAP Final Version: 23- April-2019

STATISTICAL ANALYSIS PLAN

Study protocol code	BP40822
Biotrial code	1RO119
Study 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
Study investigational medicinal product	RO7017773
Development phase	Phase I
Sponsor	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 BASEL SWITZERLAND
Version of the statistical analysis plan	Final version
Date of the statistical analysis plan	18 April 2019

SIGNATURE PAGE

RESPONSIBILITY	NAME & OFFICE	SIGNATURE	DATE
Biostatistics Project Leader	[redacted] BIOTRIAL BIOMETRICS 7-9 rue Jean-Louis Bertrand CS 34246 35042 Rennes Cedex FRANCE	[redacted]	18APR2019.
Pharmacokineticist	[redacted] BIOTRIAL 7-9 rue Jean-Louis Bertrand CS 34246 35042 Rennes Cedex FRANCE	[redacted]	18 APR 2019
Sponsor's statistician	[redacted] F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 BASEL SWITZERLAND	[redacted]	23 APR 2019
[redacted]	[redacted] Roche Products Ltd 6 Falcon Way Welwyn Garden City AL7 1TW UNITED KINGDOM	[redacted]	23Apr 2019

REVISION HISTORY

Date	Version number	Reason for change	Authored by
27FEB2019	Draft 01	Initial version	[redacted]
01APR2019	Draft 02	Integration of comments from ROCHE	[redacted]
18APR2019	Final version	Integration of comments from ROCHE after the data review meeting	[redacted]

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	DEFINITION
ADPP	ADaM Pharmacokinetic Parameters
AE	Adverse Event
ANOVA	ANalysis Of VAriance
AUC	Area Under the Curve
AUC_{0-24}	Area Under the Curve from time zero to 24 hours
AUC_{0-72}	Area Under the Curve from time zero to 72 hours
AUC_{0-last}	Area Under the Curve from time zero to last measurable plasma concentration
AUC_{0-inf}	Area Under the Curve from time zero to infinity
BID	*Bis in die* (Twice a day)
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
C_{last}	Last observed plasma concentration
C_{max}	Maximum observed plasma concentration
C_{trough}	Concentration at the end of a dosing interval before the next dose administration
C-SSRS	Columbia-Suicide Severity Rating Scale
CI	Confidence Interval
CL/F	Apparent total body clearance
CV	Coefficient of Variation
e.g.	*exempli gratia*
eCRF	electronic Case Report Form
ECG	ElectroCardioGram
GMR	Geometric mean ratio
HR	Heart Rate
i.e.	id est
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product (synonymous with "study drug")
IS	Included Set
λ_z	Apparent terminal elimination rate constant
MedDRA	Medical Dictionary for Regulatory Activities
ND	Not Determined
PK	PharmacoKinetics

ABBREVIATION	DEFINITION
PKS	PharmacoKinetic Set
PR	PR interval
PT	Preferred Term
QD	Once daily
QRS	QRS interval duration
QT	Time interval for ventricular depolarisation and repolarisation
QTc	Corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
R_{Cmax}	C_{max} ratio calculated as RO7017773 C_{max} Period 2 over RO7017773 C_{max} Period 1
$R_{AUC0\text{-}inf}$	AUC ratios calculated as RO7017773 $AUC_{0\text{-}inf}$ Period 2 over RO7017773 $AUC_{0\text{-}inf}$ Period 1
RR	RR interval
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System®
SD	Standard Deviation
SEM	Standard Error of the Mean
SOC	System Organ Class
SS	Safety Set
$T_{1/2}$	Apparent terminal elimination half-life
T_{last}	Time to reach last observed plasma concentration
T_{max}	Time to reach maximum observed plasma concentration
TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organisation

1. Introduction

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analysing study data and outlines the statistical programming specifications, tables, figures and listings. It describes the safety and pharmacokinetics variables and populations, anticipated data transformations and manipulations, and other details of the analyses not provided in the study protocol.

The analyses described are based upon the final clinical study protocol V3.0 dated 14 November 2018 including amendments (#1 and #2) and will be prepared in accordance with the International Conference on Harmonisation (ICH) E9.

The statistical analyses will be performed by the Biostatistics unit of BIOTRIAL BIOMETRICS in agreement with the sponsor.

The SAP will be validated and signed before the study database is locked.

2. Study objectives

2.1. Primary objective

The primary objective is to investigate the effect of multiple oral doses of itraconazole on the pharmacokinetics (PK) of a single oral dose of RO7017773 in healthy participants.

2.2. Secondary objectives

The secondary objectives are:

- 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.
- 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.

2.3. Exploratory objectives

The exploratory objectives are:

- To screen for the presence of RO7017773-derived metabolites.
- To assess the relative abundance and PK parameters of any metabolite as 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.

3. Study methodology

This is a 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, 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] The

dose for Itraconazole will be 200 mg BID (12 hours apart) on Day 1 and 200 mg QD from Day 2 to Day 9.

[redacted]

As individual discontinuation criteria were not met, and the safety and tolerability profile was considered acceptable during the review of safety, tolerability and PK data of Cohort A, the subjects of Cohort B will be dosed with the same dose like Cohort A (RO7017773 [redacted]).

The flow chart and the schedule of assessments are available in section 14.1.

4. *Sample Size*

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]

5. Changes to the planned analysis from protocol

Not Applicable

6. Statistical considerations

Demography and safety data will be analysed using SAS® software version 9.4 or higher (SAS institute Inc. Cary NC USA).

Pharmacokinetic data will be analysed using Phoenix® WinNonlin® version 8.1 or higher (Certara USA, Inc., Princeton, NJ) and SAS® software version 9.4 or higher (SAS Institute Inc. Cary NC USA).

Descriptive statistics will be supplied according to the nature of the criteria:

- Quantitative variable: sample size, arithmetic mean, standard deviation (SD), standard error of the mean (SEM), minimum, median and maximum, and quartiles if necessary [with geometric mean, arithmetic and geometric coefficients of variation (CV), and quartiles for PK parameters].
- Qualitative variable: sample size, absolute and relative frequencies per class. Percentages will be provided with one decimal place.

Unless specified otherwise, the calculation of percentages will be based on the number of observed values. Therefore, counts of missing values will be included in the denominator and displayed as a separate category if any.

For the values measured outside of the treatment periods, data will be organised overall.

For the values obtained during the treatment periods, data will be organised by treatment group:

- For analyses of adverse events:
  - RO7017773 alone,
  - Itraconazole alone,
  - RO7017773 + itraconazole.
- For the other safety and PK analyses:
  - RO7017773 alone,
  - RO7017773 + itraconazole.

All safety listings will be sorted by subject and measurement time if applicable.

All pharmacokinetics listings will be sorted by treatment group, subject and measurement time.

All listings containing an evaluation date will display the study day defined as the day relative to the first administration of study drug:

- Study day 1 will be defined as the day of the first administration date.
- Study day -1 will be defined as the day prior to the first administration date.
- There will be no study day 0.

Handling of missing and retest values

No management of missing values or values below/above a limit of detection/quantification will be performed, except for pharmacokinetic values (see section 9.1).

For all parameters and for subjects with retest values, the last reliable value will be used for the measurement time before the first investigational medicinal product (IMP) administration in each period (provided it was measured before IMP administration in each period) and the first reliable value will be used for the measurement time after the first IMP administration in each period.

Handling of incomplete dates

No management of incomplete dates will be performed. The incomplete dates will be labelled as such in the listings.

Baseline definition

For all parameters, baseline will be defined as the last available measurement prior to the first IMP administration in each period.

Duration

Duration (in days, hh:mm) will be calculated by the difference between the start and stop date and time (e.g. duration of adverse event (AE) (days, hh:mm) = end of AE date and time – AE onset date and time).

Duration (in days) will be calculated by the difference between the start and stop date + 1 (e.g. duration of a medication (days) = end of medication date – onset of medication date + 1).

Type I error rate

Unless stated otherwise, statistical tests will be two-sided and will be carried out at the 5% level of significance.

7. Description of study subjects

7.1. Definition of analysis sets

The following analysis sets will be defined:

Included set (IS): all of the subjects included in the study.

Safety set (SS): 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 set (PKS): 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.

The analysis sets will be precisely defined and validated during the data review meeting.

The safety and pharmacokinetic sets will be analysed using subjects as treated.

7.2. Subject disposition

A summary table with the description of the number of included subjects, the number of subjects who completed the study and the number of subjects who discontinued the study, classified by main reason of withdrawal, will be prepared overall for the subjects in the included set. Corresponding individual listings will be provided.

A summary table with the description of the number and percentage of subjects in each analysis set (Safety set and Pharmacokinetic Set) will be prepared overall. A specific listing of subjects excluded from safety and pharmacokinetic analyses will be provided with the reason(s) for exclusion.

Listings with end of study status and study visit dates will also be generated.

7.3. Protocol deviations

A summary table with the number and percentage of subjects presenting deviations relating to inclusion/exclusion criteria will be prepared overall for the subjects in the included set. A summary table with the number and percentage of subjects presenting other protocol deviations (all deviations judged relevant during the data review meeting) will also be

prepared overall by status of the deviations (minor/major). The corresponding listings will be provided with the status of the deviations.

8. Demographic data and baseline characteristics

The analyses of the demographic and baseline characteristics will be performed on the safety set.

8.1. Demographic data

The subjects' demographic characteristics (age, sex, ethnicity, height, weight and body mass index (BMI) recorded at screening) will be summarised overall, and listed.

8.2. Other baseline characteristics

Abnormal or positive results as well as all individual data for coagulation, immunology, serum/urine pregnancy tests (for females only) will be listed.

Childbearing potential (for females only) and birth control method (for males only) as well as results for hormonology (for post-menopausal women only) and clinical genotyping will only be listed.

8.3. Medical and surgical history and procedures

Information on medical and surgical history recorded at the screening visit and procedures will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1.

A table with the number and percentage of subjects having at least one previous/ongoing medical history or one surgical history will be generated overall. Previous/ongoing medical history will be listed as well as prior surgeries and concomitant surgeries.

8.4. Previous and concomitant medications

Information on previous and concomitant medications will be coded according to the GNE Drug Thesaurus.

A previous medication will be defined as a medication stopped prior to the date and time of the first administration of IMP. A concomitant medication will be defined as a medication that is taken by subjects any time during the treatment period (on or after the date and time of first IMP administration for each subject). If the date value does not allow allocation of a medication to the previous or concomitant category (missing or incomplete start or end date), this medication will be considered concomitant.

A table with the number and percentage of subjects having taken at least one previous medication and a table with the number and percentage of subjects having taken at least one concomitant medication will be generated overall (overall and by medication class and medication drug name). Previous and concomitant medications will be listed separately.

8.5. Compliance

A listing with IMP administration dates and times will be generated. Time of meals intake will also be listed.

9. Pharmacokinetic data

The pharmacokinetic analysis will be performed on the PKS.

9.1. Generalities

The following rules for **PK parameter calculation** after each administration will be used:

- Actual sampling times will be used for deriving PK parameters.
- If an entire concentration-time profile is below the limit of quantification (BLQ), BLQ values will not be replaced and the profile will be excluded from the PK analysis.
- For plasma concentrations, all BLQ values occurring prior to the first detectable concentration for each administration and negative values will be replaced by "0".
- All BLQ values occurring after the first detectable concentration for each administration and embedded BLQ values (BLQ values between two measurable concentrations) will be treated as missing.
- If a result is BLQ for the pre-dose PK sample, then the result is set to 0, as well as for all other samples being BLQ before the first detectable concentration and occurring before T_{max}. For subsequent time points, the result must be set to missing. Of note, BLQ values that occur between the first detectable concentration and the T_{max} shall be set to missing.
- If the pre-dose concentration is $\leq$ 5% of the C_{max} value of the corresponding period for a particular subject, that subject's data, without any adjustments, may be included in all pharmacokinetic and statistical analysis. For each period, if the pre-dose value is > 5% of C_{max}, two analyses will be performed: one with the pre-dose value and the other one with the pre-dose value replaced by 0. [redacted]
- If there are late positive concentration values following 2 BLQ concentration values in the apparent terminal phase, these values will be evaluated. If these values are considered to be anomalous, they will be set to missing.
- Some conditions for PK parameters have to be fulfilled:

  1) the percentage of the extrapolated AUC should not exceed 20% of the $AUC_{0\text{-}inf}$ of each individual profile,
  2) the elimination rate constant should be determined over a time interval equal to at least 2 x $T_{1/2}$,
  3) the determination of λ_z should use only those data points judged to describe the terminal log-linear decline resulting in an adjusted coefficient of determination value $R^2 > 0.7$, and a minimum of 3 data points will be used in calculating λ_z excluding C_{max}.

  If these conditions are not fulfilled, the following unreliable PK parameters will not be calculated, will be considered not determined (ND) in the listings and will be excluded from the analysis:

  1) if extrapolated AUC > 20%: AUC_{ext}, $AUC_{0\text{-}inf}$ and CL/F.
  2) if the time interval used for the determination of the elimination rate constant is inferior to 2 x $T_{1/2}$ or if the adjusted $R^2 < 0.7$: λ_z, $T_{1/2}$, AUC_{ext}, $AUC_{0\text{-}inf}$, R^2 and CL/F.

The following rules for **plasma concentration versus time graphic representation** will be used:

- No graphic representation will be done if all values are BLQ.
- BLQ values occurring prior to the first detectable concentration will be replaced by "0".
- All BLQ values occurring after the first detectable concentration will be treated as missing.

The following rules for **mean plasma concentration calculation** will be used:

For BLQ concentrations before the first detectable concentration:

- If more than (or equal to) half of the values are either BLQ values replaceable by zero and/or numeric values: statistics will be calculated with the replaceable and numeric values.
- If more than half of the values are BLQ values not replaceable by zero (i.e., subjects for whom all values are BLQ): only the maximum will be presented and the other statistics will be considered BLQ.

For BLQ concentrations after the first detectable concentration:

- If more than (or equal to) half of the values are not BLQ: statistics will be calculated with BLQ values considered missing data.
- If more than half of the values are BLQ: only the maximum will be presented and the other statistics will be considered BLQ.

For **summary statistics for PK parameters**:

- If more than (or equal to) half of the values are not ND and not missing: statistics will be calculated with the available values.
- If more than half of the values are ND or missing: only the minimum, median and maximum of the available numeric values will be presented. All other statistics will not be calculated and will be presented as ND.

All BLQ concentrations and missing data will be labelled as such in the concentration data listings.

9.2. Plasma concentrations and pharmacokinetic parameters

9.2.1. Plasma parameters

[redacted]

- [redacted]
- [redacted]

[redacted]

- [redacted]

- [redacted]

Relevant plasma pharmacokinetic (PK) parameters will be calculated for RO7017773, and Itraconazole and its metabolite (hydroxy-itraconazole) by standard non-compartmental methods for the subjects with sufficient plasma concentration data. The rules defined in the previous section (9.1) will be used.

The different areas under the concentration-time curve (AUC) will be calculated using the linear-log trapezoidal method.

[redacted]

Parameters (unit)	Definition
C_{max} (unit)	Maximum observed plasma concentration
T_{max} (h)	Time to reach maximum observed plasma concentration
C_{last} (unit)	Last observed plasma concentration
T_{last} (h)	Time to reach last observed plasma concentration
$AUC_{0\text{-}24}$ (unit.h)	Area under the plasma concentration-time curve from time zero to 24 hours (only for Itraconazole)
$AUC_{0\text{-}72}$ (unit.h)	Area under the plasma concentration-time curve from time zero to 24 hours (only for RO7017773)
$AUC_{0\text{-}last}$ (unit.h)	Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration
$AUC_{0\text{-}inf}$ (unit.h)	Area under the plasma concentration-time curve from time zero to infinity, calculated as follows: $AUC_{0\text{-}inf} = AUC_{0\text{-}last} + C_{last}/\lambda_z$, where C_{last} is the last quantifiable concentration
$T_{1/2}$ (h)	Apparent terminal elimination half-life, calculated as follows: $T_{1/2} = Ln(2)/\lambda_z$
λ_z (h^{-1})	Apparent terminal elimination rate constant

[redacted]

Parameters (unit)	Definition
CL/F (L/h)	Apparent total body clearance, calculated as follows: $CL/F = Dose / AUC_{0\text{-}inf}$

[redacted]

Parameters (unit)	Definition

Parameters (unit)	Definition
R_{Cmax} (no unit)	Ratio for C_{max}, calculated as follows: $R_{Cmax} = C_{max\ Period\ 2} / C_{max\ Period\ 1}$
$R_{AUC0\text{-}inf}$ (no unit)	Ratio for $AUC_{0\text{-}inf}$, calculated as follows: $R_{AUC0\text{-}inf} = AUC_{0\text{-}inf\ Period\ 2} / AUC_{0\text{-}inf\ Period\ 1}$

[redacted]

Parameters (unit)	Definition
C_{trough} (unit)	Concentration at the end of a dosing interval before the next dose administration

9.2.2. Plasma pharmacokinetic analysis

Listings with plasma concentrations (including PK blood sampling dates and times) and PK parameters will be provided by treatment group and subject. These listings will be generated for all subjects with an available PK profile (complete or incomplete), including those who are excluded from the PKS.

Plasma concentrations and PK parameters of RO7017773, and Itraconazole and its metabolite (hydroxy-itraconazole) including descriptive statistics will be presented in tables separately for each treatment group.

Individual plasma concentration versus time profiles of RO7017773, and Itraconazole (and metabolite) will be presented graphically on linear and log/linear coordinates for each subject with all treatment groups received by the subject on the same graph.

The graph of arithmetic mean ± SD over time will be provided for plasma concentration of RO7017773, and Itraconazole (and metabolite) on linear and log/linear coordinates with all treatment groups on the same graph as well as with all analytes on the same graph only for Itraconazole.

The graph of trough concentrations (mean ± SD) of Itraconazole (and metabolite) on linear coordinates will also be provided.

Scatter plots and box whisker plots will be generated for the comparison of the C_{max} and AUC ($AUC_{0\text{-}inf}$ if it can be derived, otherwise truncated as appropriate ($AUC_{0\text{-}72}$)) parameters of RO7017773 between the treatment groups.

For the evaluation of the effect of RO7017773 + itraconazole versus RO7017773 alone, the following linear statistical model will be applied to the log-transformed PK variables AUC ($AUC_{0\text{-}inf}$ if it can be derived, otherwise truncated as appropriate ($AUC_{0\text{-}72}$)) and C_{max} of RO7017773:

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

where μ denotes the general mean of the transformed variables, τ_j is the effect of the treatment (RO7017773 + itraconazole versus RO7017773 alone), 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 (90% CIs) will be derived to compare the relative bioavailability of the different treatments.

Under this model the geometric mean ratios (GMRs) $\frac{AUC_{(RO7017773 + itraconazole)}}{AUC_{(RO7017773\ alone)}}$ and $\frac{C_{max(RO7017773 + itraconazole)}}{C_{max(RO7017773\ alone)}}$ 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.

The following SAS code will be used:

```
proc mixed data=ADPP method=REML;
        by PARAMCD;
        class TRTAN USUBJID;
        model ln(AVAL) = TRTAN / solution cl alpha=0.10 ddfm=kr;
        random USUBJID;
        lsmeans TRTAN / cl alpha=0.10;
        estimate 'Test versus Reference' TRTAN -1 1 / cl alpha=0.10 e;
run;
```

10. Pharmacodynamics data

As specified in the section 8.2, the genotyping data will be listed only.

[redacted]

11. Safety data

The safety analyses will be performed on the safety set.

11.1. Adverse events

Adverse events, including pre-treatment serious events only, will be recorded from the time of consent through 15 to 20 days after the end of treatment period.

Adverse events will be coded according to MedDRA Version 21.1.

A treatment-emergent adverse event (TEAE) is an adverse event that occurs on or after the first IMP administration of each period or that was present prior to dosing but was exacerbated on or after the first IMP administration of each period.

Adverse events will be summarised in tables as follows [overall and by System Organ Class (SOC) and Preferred Term (PT)]:

- Number and percentage of subjects with at least one adverse event and number of occurrences of an adverse event by treatment group (before any treatment and after first intake of each treatment) and overall,
- Number and percentage of subjects with at least one TEAE and number of occurrences of a TEAE by treatment group,

- By intensity, with the number and percentage of subjects with at least one TEAE and number of occurrences of a TEAE by treatment group,
- By causality (to RO7017773 alone, to itraconazole alone and to both RO7017773 and itraconazole), with the number and percentage of subjects with at least one TEAE and number of occurrences of a TEAE by treatment group.

If there are only a few adverse events (≤10), only a listing will be generated.

All adverse events reported in the electronic Case Report Form (eCRF) will be listed with the SOC, the PT and the investigator's verbatim. All TEAEs will also be listed with the SOC and the PT. An additional listing will be provided for AEs leading to death and other serious and significant AEs (SAEs or AEs leading to study withdrawal).

Note:

i. In the descriptive tables, the number of subjects with at least one adverse event/TEAE for a given PT will also correspond to the number of adverse events/TEAEs whatever the number of occurrences during the studied period.
ii. In case of a change of intensity or causality for an event during the same treatment period, the intensity will be the highest recorded intensity and the causality will be the highest likelihood recorded.
iii. A treatment-emergent AE will be associated with the treatment group of the current period if this AE starts between the first IMP administration of the current period and the first IMP administration of the next period.

11.2. Clinical laboratory data

The following clinical laboratory parameters will be measured (see section 14.1):

- at screening visit,
- in Period 1: on Day -1, Day 3 and Day 8,
- in Period 2: on Day -1, Day 4, Day 7, Day 10 and Day 16,
- at follow-up visit.

Haematology parameters will be listed and grouped as follows:

- Red blood cells: erythrocytes (10^12/L), hematocrit (ratio) and hemoglobin (g/L).

- White blood cells: basophils (10^9/L), eosinophils (10^9/L), leukocytes (10^9/L), lymphocytes (10^9/L), monocytes (10^9/L) and neutrophils (10^9/L).

- Other parameters: platelets (10^9/L).

Blood chemistry parameters will be listed and grouped as follows:

- Liver function: alanine aminotransferase (IU/L), alkaline phosphatase (IU/L), aspartate aminotransferase (IU/L), bilirubin (µmol/L), direct bilirubin (µmol/L).

- Renal chemistry: creatinine (µmol/L) and urea (mmol/L).

- Electrolytes: bicarbonate (mmol/L), calcium (mmol/L), chloride (mmol/L), phosphate (mmol/L), potassium (mmol/L) and sodium (mmol/L).

- Metabolism parameters: cholesterol (mmol/L), glucose (mmol/L), lactate dehydrogenase (IU/L), triglycerides (mmol/L) and urate (µmol/L).

- Other proteins: albumin (g/L) and protein (g/L).

Urinalysis parameters will be listed and grouped as follows:

- Planned urinalysis parameters: dipstick determination of erythrocytes, glucose, leukocytes, nitrite and protein, pH and specific gravity.

- Direct microscopy (in case of abnormal urinalysis parameters and in the listing only): cytology (erythrocytes, leukocytes, epithelial cells, granular casts and hyaline casts), bacteria (/uL) and crystals (calcium phosphate crystals, calcium oxalate crystals and monosodium urate crystals).

For haematology and blood chemistry, raw data and changes from baseline will be described by treatment group and measurement time.

For urinalysis, raw data (planned parameters) will be described by summary statistics or frequency tables by treatment group and measurement time.

For haematology, blood chemistry and urinalysis, values higher or lower than the laboratory reference range (H, L) will be listed.

Values (raw data and changes from baseline) will be listed and data out of normal ranges will be flagged with clinical significance information.

Urinalysis values will be listed, including direct microscopy, if any.

11.3. Other safety parameters

11.3.1. Vital signs data

Supine systolic and diastolic blood pressure (mmHg) and heart rate (HR) (beats/min) will be measured (see section 14.1):

- at screening visit,
- in Period 1: on Day -1, Day 1 at pre-dose, H1, H2, H5, H6 and H8, Day 2, Day 3, Day 4, Day 5 and Day 8,
- in Period 2: on Day -1, Day 1, Day 4 at pre-dose, H1, H2, H5, H6, H8, Day 5, Day 6, Day 8, Day 9, Day 12 and Day 16,
- at follow-up visit.

Body temperature (C°) will be measured (see section 14.1):

- at screening visit,
- in Period 1: on Day -1, Day 1 at pre-dose, H1 and H6, and Day 2,
- in Period 2: on Day -1, Day 1, Day 4 at pre-dose, H1 and H6, and Day 5,
- at follow-up visit.

Raw data and changes from baseline will be described by treatment group and measurement time.

Values higher or lower than the normal range will be listed. The normal ranges are the following:

PARAMETER	LOWER NORMAL VALUE	UPPER NORMAL VALUE
Supine HR	≤ 40 beats/min	≥ 100 beats/min
Supine SBP	≤ 90 mmHg	≥ 140 mmHg
Supine DBP	≤ 50 mmHg	≥ 90 mmHg

Values (raw data and changes from baseline) will be listed and data out of normal ranges will be flagged with clinical significance information.

11.3.2. Electrocardiogram data

Standard 12-lead electrocardiogram (ECG) parameters (including heart rate (beats/min), PR interval (msec), RR interval (msec), QRS duration (msec), QT interval (msec) and Fridericia QTc interval (msec)) and ECG abnormalities will be recorded in triplicate (see section 14.1):

- at screening visit,
- in Period 1: on Day -1, Day 1 at pre-dose, H1, H2, H5, H6 and H8, Day 2, Day 3, Day 4, Day 5 and Day 8,
- in Period 2: on Day -1, Day 1, Day 4 at pre-dose, H1, H2, H5, H6, H8, Day 5, Day 6, Day 8, Day 9, Day 12 and Day 16,
- at follow-up visit.

The mean of the triplicate ECGs will serve as analysable data.

Only interpretable ECGs will be analysed.

Raw data and changes from baseline (except for ECG abnormalities) will be described by treatment group and measurement time.

Values [raw data/ECG abnormalities and changes from baseline)] will be listed.

11.3.3. Physical examination

A complete physical examination will be measured (see section 14.1):

- at screening visit,
- in Period 1: on Day -1,
- in Period 2: on Day -1 and Day 12,
- at follow-up visit.

Weight will be measured at screening and follow-up visits.

Abnormal results as well as all individual data of physical examination will be listed.

Raw data of weight and BMI will be described overall and listed.

11.3.4. Alcohol breath test and urine drug of abuse

Alcohol breath test and urine drug of abuse will be measured (see section 14.1):

- at screening visit,
- in Period 1: on Day -1,
- in Period 2: on Day -1.

Positive results as well as all individual data of alcohol breath test and urine drug of abuse will be listed.

11.3.5. Columbia-suicide severity rating scale

The Columbia-suicide severity rating scale (C-SSRS) will be measured (see section 14.1):

- at screening visit,
- in Period 1: on Day -1 and Day 4,
- in Period 2: on Day -1, Day 3 and Day 11.

The items of suicidal ideation, intensity of ideation and suicidal behavior will only be listed.

11.3.6. Subjects' habits

The subject' habits (tobacco, caffeine, alcohol and grapefruit consumptions) will be measured (see section 14.1):

- at screening visit (for tobacco consumption only),
- in Period 1: on Day -1, Day 5, Day 6 and Day 8,
- in Period 2: on Day -1, Day 13, Day 14, Day 15 and Day 16,
- at follow-up visit.

The subject' habits will be summarised by treatment group and measurement time, and listed.

12. Reporting conventions

All tables, figures and listings are detailed in section 14.3. They will be prepared using SAS® software as rtf files and the rtf files will be compiled as PDF files (one PDF file by main section).

The footers will be presented as follows: --- STUDY BP40822 / <name of the program>.SAS / <name of the output>.RTF / DDMMMYYYY HH:MM ---.

Table and Listing Page Set Up Requirements:

- Font Type = Courier New
- Font Size = 8 pt (at a minimum)
- Page Margins: Top=2 cm; Bottom=2 cm; Left=2 cm; Right=2 cm
- Paper Size = A4 (21 cm x 29.7 cm)
- Page Orientation: Landscape
- Graphs: Portable Network Graphics (PNG) format

Summary statistics will be presented as follows.

Parameter (unit)	**Statistics / Category**	**Group X (N=xx)**
Quantitative variable (unit)*	n	xx
	Mean ± SD	xx.xx ± xx.xx
	SEM	xx.xx
	Median	xx.xx
	Min ; Max	xx.x ; xx.x
Qualitative variable	Class 1 n (%)	xx (xx.x)
	Class 2 n (%)	xx (xx.x)
	…	…

* All statistics, except the minimum and the maximum, will be provided with an additional decimal place compared to the variable itself. PK parameter coefficients of variation will be provided with one decimal place.

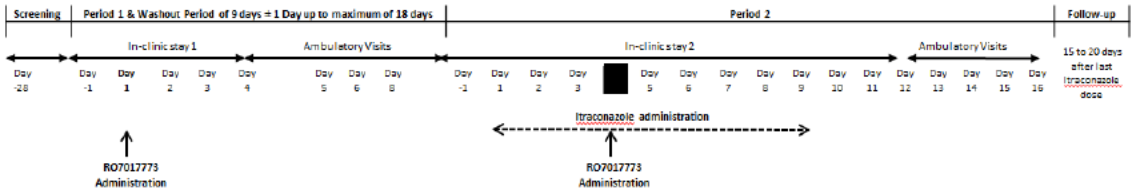
13. References

Not Applicable

14. Appendices

14.1. Appendix 1 - Flow chart and schedule of assessments of the study

Flow chart



Schedule of assessments

- 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]			[redacted]											[redacted]													
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

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.

- Detailed Table Period 1

Day	[redacted]	Vital Signs [a]	ECG-12 lead [c]	Safety Laboratory Tests	RO7017773 Administration	Standard Meal	PK Sample (RO7017773)	Clinical Genotyping
Day 1		x [b]	x			x [e]		x
					[redacted]			
		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				

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.

[redacted]

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

- 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

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.

14.2. Appendix 2 - List of tables, listings and figures included in the clinical study report

NUMBER	TITLE
14	**TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT**
14.1	**Demographic data**
14.1.1	**Description of study subjects**
14.1.1.1	Subject disposition - Included set
14.1.1.2	Analysis sets - Included set
14.1.2	**Protocol deviations**
14.1.2.1	Deviations relating to inclusion/exclusion criteria - Included set
14.1.2.2	Other deviations - Included set
14.1.3	**Demographic data and baseline characteristics**
14.1.3.1	**Demographic data - Safety set**
14.1.3.2	**Other baseline characteristics**
14.1.3.2.1	Listing of abnormal coagulation results - Safety set
14.1.3.2.2	Listing of positive immunology results - Safety set
14.1.3.2.3	Listing of positive serum pregnancy test (for females only) - Safety set
14.1.3.2.4	Listing of positive urinary pregnancy test (for females only) - Safety set
14.1.3.3	**Medical and surgical history - Safety set**
14.1.4	**Previous and concomitant medications**
14.1.4.1	Previous medications - Safety set
14.1.4.2	Concomitant medications - Safety set
14.2	**Pharmacokinetic and Pharmacodynamics data**
14.2.1	**Pharmacokinetic data**
14.2.1.1	**Plasma concentrations and pharmacokinetic parameters**
14.2.1.1.1	**Plasma concentrations**
14.2.1.1.1.1	**RO7017773**
14.2.1.1.1.1.1	Plasma concentrations for RO7017773 - Pharmacokinetic set
14.2.1.1.1.1.2	Graphs of plasma concentration means (±SD) over time for RO7017773 - Pharmacokinetic set
14.2.1.1.1.2	**Itraconazole**
14.2.1.1.1.2.1	Plasma concentrations for Itraconazole (and metabolite) - Pharmacokinetic set
14.2.1.1.1.2.2	Graphs of plasma concentration means (±SD) over time for Itraconazole (and metabolite) - Pharmacokinetic set
14.2.1.1.1.2.3	Graphs of plasma concentration means (±SD) over time for Itraconazole and metabolite on the same graph - Pharmacokinetic set
14.2.1.1.1.2.4	Graphs of trough concentration means (±SD) over time for Itraconazole (and

NUMBER	TITLE
	metabolite) - Pharmacokinetic set
14.2.1.1.2	**PK parameters in plasma**
14.2.1.1.2.1	**RO7017773**
14.2.1.1.2.1.1	PK parameters in plasma for RO7017773 - Pharmacokinetic set
14.2.1.1.2.1.2	Scatter plots of C_{max} and AUC (AUC_{0-inf} or AUC_{0-72}) for RO7017773 - Pharmacokinetic set
14.2.1.1.2.1.3	Box whisker plots of C_{max} and AUC (AUC_{0-inf} or AUC_{0-72}) for RO7017773 - Pharmacokinetic set
14.2.1.1.2.1.4	Analysis of drug interaction for C_{max} and AUC (AUC_{0-inf} or AUC_{0-72}) for RO7017773 - Pharmacokinetic set
14.2.1.1.2.2	**PK parameters in plasma for Itraconazole (and metabolite) - Pharmacokinetic set**
14.2.2	**Pharmacodynamics data**
14.2.2.1	Graph of individual RO7017773 exposure (C_{max} and AUC_{0-inf} for RO7017773) versus functional status of CYP3A4 and CYP3A5 genotypes after administration on Day 1 in Period 1 - Pharmacokinetic set
14.2.2.2	Graph of individual RO7017773 exposure (C_{max} and AUC_{0-inf} for RO7017773) versus functional status of CYP3A4 and CYP3A5 genotypes after administration on [redacted] - Pharmacokinetic set
14.3	**Safety data**
14.3.1	**Adverse events**
14.3.1.1	**Adverse events - Safety set**
14.3.1.2	**Treatment-emergent adverse events**
14.3.1.2.1	Treatment-emergent adverse events - Safety set
14.3.1.2.2	Treatment-emergent adverse events by intensity - Safety set
14.3.1.2.3	Treatment-emergent adverse events by causality - Safety set
14.3.2	**Listing of deaths, other serious and significant adverse events - Safety set**
14.3.3	**Clinical laboratory data**
14.3.3.1	**Haematology**
14.3.3.1.1	Summary statistics - Safety set
14.3.3.1.2	Listing of subjects presenting abnormal values - Safety set
14.3.3.2	**Blood chemistry**
14.3.3.2.1	Summary statistics - Safety set
14.3.3.2.2	Listing of subjects presenting abnormal values - Safety set
14.3.3.3	**Urinalysis**
14.3.3.3.1	Summary statistics - Safety set
14.3.3.3.2	Listing of subjects presenting abnormal values - Safety set
14.3.4	**Other safety parameters**

NUMBER	TITLE
14.3.4.1	**Vital signs data**
14.3.4.1.1	Summary statistics - Safety set
14.3.4.1.2	Listing of subjects presenting abnormal values - Safety set
14.3.4.2	**Electrocardiogram data - Summary statistics - Safety set**
14.3.4.3	**Physical examination**
14.3.4.3.1	Listing of abnormal physical examination results - Safety set
14.3.4.3.2	Summary statistics (Weight and BMI) - Safety set
14.3.4.4	**Alcohol breath test and urine drug of abuse**
14.3.4.4.1	Listing of positive alcohol breath test results - Safety set
14.3.4.4.2	Listing of positive urine drug of abuse results - Safety set
14.3.4.5	**Subjects' habits - Summary statistics - Safety set**
16.1	**STUDY INFORMATION**
16.1.9	**Documentation of statistical methods**
16.1.9.1	*Statistical analysis plan (integrated by the medical writer during the creation of the appendices of the clinical study report)*
16.1.9.2	ANOVA: Analysis of drug interaction for C_{max} and AUC (AUC_{0-inf} or AUC_{0-72}) for RO7017773 - Pharmacokinetic set
16.2	**SUBJECT DATA LISTINGS**
16.2.1	**Subject disposition**
16.2.1.1	Discontinued subjects - Included set
16.2.1.2	Subject disposition and analysis sets - Included set
16.2.1.3	End of study status - Included set
16.2.1.4	Subject visit dates - Included set
16.2.2	**Protocol deviations**
16.2.2.1	Deviations relating to inclusion/exclusion criteria - Included set
16.2.2.2	Other deviations - Included set
16.2.3	**Subjects excluded from analysis sets - Included set**
16.2.4	**Demographic data and baseline characteristics**
16.2.4.1	**Demographic data - Included set**
16.2.4.2	**Other baseline characteristics**
16.2.4.2.1	Coagulation - Included set
16.2.4.2.2	Immunology - Included set
16.2.4.2.3	Serum pregnancy tests (for females only) - Included set
16.2.4.2.4	Urine pregnancy tests (for females only) - Included set
16.2.4.2.5	Childbearing potential (for females only) - Included set

NUMBER	TITLE
16.2.4.2.6	Birth control method (for males only) - Included set
16.2.4.2.7	Hormonology - Included set
16.2.4.2.8	Clinical genotyping - Included set
16.2.4.3	**Medical and surgical history and procedures**
16.2.4.3.1	Medical history - Included set
16.2.4.3.2	Surgical history - Included set
16.2.4.3.3	Concomitant procedures - Included set
16.2.4.4	**Previous and concomitant medications**
16.2.4.4.1	Previous medications - Included set
16.2.4.4.2	Concomitant medications - Included set
16.2.5	**Compliance and/or drug concentration data**
16.2.5.1	**Compliance and dosing data**
16.2.5.1.1	IMP administration - Included Set
16.2.5.1.2	Meals intake - Included Set
16.2.5.2	**Pharmacokinetic data**
16.2.5.2.1	**Plasma concentrations and pharmacokinetic parameters**
16.2.5.2.1.1	Plasma concentrations - Included set
16.2.5.2.1.2	Individual plasma concentration-time curves - RO7017773 - Pharmacokinetic set
16.2.5.2.1.3	Individual plasma concentration-time curves - Itraconazole (and metabolite) - Pharmacokinetic set
16.2.5.2.1.4	PK parameters in plasma - Included set
16.2.7	**Adverse event listings**
16.2.7.1	Treatment-emergent adverse events - Included set
16.2.7.2	All adverse events - Included set
16.2.8	**Clinical laboratory data**
16.2.8.1	**Haematology**
16.2.8.1.1	Normal ranges for SI units and local units
16.2.8.1.2	All haematology values (SI unit) - Included set
16.2.8.2	**Blood chemistry**
16.2.8.2.1	Normal ranges for SI units and local units
16.2.8.2.2	All blood chemistry values (SI unit) - Included set
16.2.8.3	**Urinalysis**
16.2.8.3.1	Normal ranges for SI units and local units
16.2.8.3.2	All urinary values (SI unit) - Included set

NUMBER	TITLE
16.2.9	**Other safety parameters**
16.2.9.1	**Vital signs data - Included set**
16.2.9.2	**Electrocardiogram data - Standard 12-lead ECG parameters - Included set**
16.2.9.3	**Physical examination**
16.2.9.3.1	Physical examination - Included set
16.2.9.3.2	Height, weight and BMI - Included set
16.2.9.4	**Alcohol breath test and urine drug of abuse**
16.2.9.4.1	Alcohol breath test - Included set
16.2.9.4.2	Urine drug of abuse - Included set
16.2.9.5	**Columbia-suicide severity rating scale - Included set**
16.2.9.6	**Subjects' habits - Included set**