Statistical Analysis Plan

A multicentric, open-label, non-randomized study to evaluate the pharmacokinetic, safety and tolerability of ITF2357 given as an oral single 50 mg dose in participants with chronic hepatic impairment relative to matched participants with normal hepatic function.

NCT number: NCT06736223

Unique protocol ID: ITF/2357/60

Version Date: 20 May 2025

STATISTICAL ANALYSIS PLAN

Study protocol code	ITF/2357/60
Biotrial code	1ITAL3
Study title	A multicentric, open-label, non-randomized study to evaluate the pharmacokinetic, safety and tolerability of ITF2357 given as an oral single 50 mg dose in participants with chronic hepatic impairment relative to matched participants with normal hepatic function.
Study investigational medicinal product	ITF2357
Development phase	Phase I
Sponsor	ITALFARMACO SpA Via dei Lavoratori 54 20092 Cinisello Balsamo, Milano, ITALY
Version of the statistical analysis plan	V1.0
Date of the statistical analysis plan	20MAY2025

This document contains confidential information that should only be disclosed to those persons responsible for the study. This information must not be disclosed to any third party without prior written authorization from the Sponsor.

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	
Pharmacokineticist	[redacted] BIOTRIAL 7-9 rue Jean-Louis Bertrand CS 34246 35042 Rennes Cedex FRANCE	
Sponsor's Clinical R&D Director	[redacted] ITALFARMACO S.p.A. Via dei Lavoratori 54 20092 Cinisello Balsamo, Milano, ITALY	
Sponsor's Biometrics and Data Sciences Director	[redacted] ITALFARMACO S.p.A. Via dei Lavoratori 54 20092 Cinisello Balsamo, Milano, ITALY	
Sponsor's statistician	[redacted] (consultant statistician for Italfarmaco S.p.A.) ITALFARMACO S.p.A. Via dei Lavoratori 54 20092 Cinisello Balsamo, Milano, ITALY	

REVISION HISTORY

Date	Version number	Reason for change	Authored by
31JAN2025	D0.1	Not Applicable - Initial Version	[redacted]
18APR2025	D0.2	Implementation of Sponsor's comments	[redacted]
12MAY2025	D0.3	Implementation of Sponsor's comments	[redacted]
20MAY2025	V1.0	Implementation of Sponsor's comments	[redacted]

TABLE OF CONTENTS

1. Introduction ***8***

2. Study objectives ***8***

2.1. Primary objective 8

2.2. Secondary objectives 8

3. Study methodology ***9***

3.1. Protocol overview 9

3.2. Planned analyses 9

4. Sample Size ***9***

5. Changes to the planned analysis from protocol ***9***

6. Statistical considerations ***10***

6.1. Handling of missing and retest values 10

6.2. Handling of missing and incomplete dates 11

6.3. Baseline definition 11

6.4. Duration 11

6.5. Type I error rate 12

7. Description of study participants ***12***

7.1. Definition of analysis sets 12

7.2. Participant disposition 12

7.3. Protocol deviations 13

8. Demographic data and baseline characteristics ***13***

8.1. Demographic data 13

8.2. Other baseline characteristics 13

8.3. Medical and surgical histories and concomitant procedures 14

8.4. Previous and concomitant medications 14

8.5. Compliance 14

9. Pharmacokinetic data ***14***

9.1. Generalities 15

9.2. Plasma concentrations and pharmacokinetic parameters 16

9.2.1. Plasma parameters 16

9.2.2. Plasma pharmacokinetic analysis 18

9.2.3. Hepatic impairment effect 18

9.2.3.1. Primary analysis 18

9.2.3.2. Secondary analysis 19
10. Pharmacodynamics data 19
11. Safety data 19
11.1. Adverse events 19
11.2. Clinical laboratory data 20
11.2.1. Pregnancy test (for females only) 21
11.3. Other safety parameters 21
11.3.1. Vital signs data 21
11.3.2. Electrocardiogram data 22
11.3.3. Physical examination 23
12. Procedures and data formats 23
13. Reporting conventions 23
14. References 24
15. Appendices 25
15.1. Appendix 1 - Schedule of Activities of the study 25
15.1.1. Overall Study - Schedule of Activities (SOA) 25
15.1.2. Period - Schedule of Activities (SOA) 27
15.2. Appendix 2 - Criteria for Potentially Clinically Significant Abnormalities (PCSA) 28

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	DEFINITION
AE	Adverse Event
AIC	Akaike's Information Criterion
ALT	ALanine aminoTransferase
aPTT	activated Partial Thromboplastin Time
ATC	Anatomic Therapeutic Chemical
AST	ASpartate aminoTransferase
AUC	Area Under the Curve
$AUC_{0\text{-last}}$	Area under the plasma concentration-time curve from time zero to the last quantifiable concentration
$AUC_{0\text{-inf}}$	Area Under the Curve from time zero to infinity
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
C_{last}	Last quantifiable plasma concentration
C_{max}	Maximum plasma concentration
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
CV	Coefficient of Variation
D	Day
eCRF	electronic Case Report Form
ECG	ElectroCardioGram
EOS	End-Of-Study
FDA	Food Drug Administration
FSH	Follicle-Stimulating Hormone
GGT	Gamma Glutamyl Transferase
HGB	Hemoglobin
HI	Hepatic Impairment
i.e.	id est
ICH	International Council on Harmonization
IMP	Investigational Medicinal Product (synonymous with "study drug")
INR	Intl. Normalized Ratio
λ_z	First order terminal elimination rate constant

ABBREVIATION	DEFINITION
LLN	Lower Limit of Normal range
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Event
ND	Not Determined
PCSA	Potentially Clinically Significant Abnormalities
PK	PharmacoKinetics
PT	Preferred Term
QRS	QRS interval duration
QT	Time interval for ventricular depolarisation and repolarisation
QTc	Corrected QT interval
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System®
SD	Standard Deviation
SEM	Standard Error of the Mean
SOA	Schedule Of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
$t_{1/2}$	Terminal elimination half-life
t_{max}	time to reach maximum plasma concentration
TEAE	Treatment-Emergent Adverse Event
ULN	Upper Limit of Normal range
ULQ	Upper Limit of Quantification
WHO	World Health Organization

1. Introduction

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

The table, listing and figure shells are supplied in a separate document.

The analyses described are based upon the final clinical study protocol V2.0 dated 24 March 2025 and will be prepared in accordance with the International Council on Harmonization (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 first participant inclusion since this is an open label study.

2. Study objectives

2.1. Primary objective

The primary objective is to evaluate the effect of mild and moderate hepatic impairment (HI) on the pharmacokinetics (PK) of ITF2357 (C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$) in comparison with matched participants with normal hepatic function, after a single oral dose of 50 mg ITF2357 (dose is expressed as givinostat hydrochloride monohydrate).

2.2. Secondary objectives

The secondary objectives are:

- To evaluate the effect of mild and moderate HI on additional PK parameters of ITF2357 in comparison with matched participants with normal hepatic function, after a single oral dose of 50 mg ITF2357.
- To evaluate the effect of mild and moderate HI on the pharmacokinetic of the 2 metabolites of ITF2357: ITF2374 and ITF2375 in comparison with matched participants with normal hepatic function after a single oral dose of 50 mg ITF2357.
- To assess the effect of mild and moderate HI on the free fraction of ITF2357, and its metabolites with high protein binding ITF2374 and ITF2375 in comparison with matched participants with normal hepatic function.
- To assess the safety and tolerability of ITF2357 given as a single oral dose of 50 mg in participants with mild and moderate HI and in matched participants with normal hepatic function.

3. Study methodology

3.1. Protocol overview

This is a phase I, open-label non-randomized, single-period single dose study, conducted in 3 groups:

- Participants with mild HI (Child-Pugh class A)
- Participants with moderate HI (Child-Pugh class B)
- Participants with normal hepatic function, matched to participants with moderate HI based on weight (1:1). For this, each matched participant with normal hepatic function should weigh within 10% of the average weight of participants with moderate HI.

It is planned that the participants with HI (both mild and moderate) will be recruited first, then the matched participants with normal hepatic function (healthy participant) will be recruited.

The duration of study participation will be 38 days maximum, including:

- A screening period from Day (D)-28 to D-2
- One 6-day/5-night inpatient period (from D-1 morning to D5 morning)
    - Baseline assessments will be conducted on D-1 and D1 pre-dose
    - A single dose administration of ITF2357 will be administered on D1
    - Discharge on D5 morning
- An end-of-study (EOS) evaluation to be done on D10 (±1 day), or to be organized as soon as possible in case of early withdrawal.

The Schedule of Activities is added in section 15.1.

3.2. Planned analyses

Final analyses will be performed when all participants complete the study and after the database lock.

4. Sample Size

Sample size for this study was based upon empirical considerations and no sample size calculation was performed. Eight participants with mild HI, eight participants with moderate HI and eight control participants with normal hepatic function, who will be matched with the moderate HI patients based on the weight. This sample size is consistent with the sample size recommended in the Food Drug Administration (FDA) Guidance on pharmacokinetics in patients with impaired hepatic function, for study design including more than one group of participants with hepatic impairment (May 2003) [2].

If feasible and to be able to compare the groups, at least 3 males and 3 females should be included in each group (mild HI, moderate HI and healthy participants).

5. Changes to the planned analysis from protocol

The standard error of the mean (SEM) was planned to be reported in the descriptive statistics for all sections as per the protocol, but it will be reported for PK data only.

The definition of postural hypotension from the European Society of Cardiology and the American Autonomic Society—symptomatic regardless of blood pressure change, or asymptomatic with a

decrease in SBP ≥ 20 mmHg and/or DBP ≥ 10 mmHg within 3 minutes of standing—differs from the protocol definitions, which use only SBP thresholds (≥ 30 mmHg for HI participants and ≥ 20 mmHg for participants with normal hepatic function).

6. Statistical considerations

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

Pharmacokinetic parameters will be derived from PK concentrations using Phoenix® WinNonlin® version 8.4 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), minimum, median and maximum, and quartiles if necessary [with geometric mean, arithmetic and geometric coefficients of variation (CV), quartiles and standard error of the mean (SEM) for PK analyses].
- Qualitative variable: sample size, absolute and relative frequencies per class. Percentages will be provided with one decimal place.

If the sample size of one population group is less than or equal to 1, only the number of observed values will be presented for quantitative variables.

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

Data will be organized by population group:

- Normal hepatic function,
- Mild hepatic impairment,
- Moderate hepatic impairment.

All listings will be sorted by population group, participant and visit/measurement timepoint if applicable.

In the core of the Clinical Study Report (CSR), overall and by population group results will be presented for baseline description.

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

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

6.1. 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 PK values (see section 9.1).

For all parameters and for participants with retest values, the last reliable value will be used for the measurement timepoint/visit before the investigational medicinal product (IMP) administration (provided it was measured before IMP administration) and the first reliable value will be used for the measurement timepoint/visit after the IMP administration.

6.2. Handling of missing and incomplete dates

The imputed dates will be identified in the listings.

AE, concomitant medications date imputation

Unless the event or medication is ongoing, the end/resolution date will be imputed as follows:

- In case "End Date" is completely missing, no imputation is performed.
- Otherwise:
    - If "End Date" is clearly before EOS date (defined as: maximum possible value < EOS date), then impute as <maximum possible date>
    - Otherwise, impute as: min(<maximum possible date>, <EOS date>)

The start date will be imputed as follows:

- In case "Start Date" is completely missing, no imputation is performed.
- Otherwise:
    - If "Start Date" is clearly before treatment start date (defined as: maximum possible value < treatment start date), then impute as:
        - For AE Start Date: max(<minimum possible date>, <ICF signature date>)
            - An event is only considered an AE if it starts during the study period.
        - For CM Start Date: <minimum possible date>
    - If "Start Date" is clearly on or after treatment start date (defined as: minimum possible date >= treatment start date), then impute as: <minimum possible date>
    - Otherwise, if the "Start Date" is not clearly before or after the treatment start date, impute as following:
        - If the "End Date" is clearly before treatment start date (defined as: maximum possible value < treatment start date), then impute as: <minimum possible date>
        - Otherwise, impute as: <treatment start date>

Minimum possible date defined as:

- Only day missing: impute day=1
- Both day and month missing: impute as 01-JAN

Maximum possible date defined as:

- Only day missing: impute day=last day of the month
- Both day and month missing: impute as 31-DEC

6.3. Baseline definition

For all parameters, baseline will be defined as the last non-missing measurement prior to the IMP administration (including unscheduled assessments).

6.4. Duration

Duration (in days, hh:mm) will be calculated by the difference between the start and stop date and time (e.g. duration of 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 - start of medication date + 1).

In case either the start or end time is missing, the duration will be calculated in days only.

6.5. Type I error rate

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

7. Description of study participants

7.1. Definition of analysis sets

The following analysis sets will be defined:

Enrolled set: all participants having signed their informed consent.

All Treated Analysis set: all included participants having taken at least one dose of IMP.

PK Analysis set: all treated participants with available PK plasma time-concentration data.

PK-evaluable Analysis set: subset of the PK population who have adequate dosing and plasma concentration-time data for estimation of PK parameters.

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

The All Treated, PK and PK-evaluable Analysis sets will be analyzed using participants as treated.

7.2. Participant disposition

A table summarizing the pre-treatment participant disposition, with the description of the number and percentage of participants in the Enrolled set and participants in the All Treated Analysis set will be prepared by population group and overall, for the participants in the enrolled set.

The number and percentage of participants in the Enrolled set will also be described by country and site.

A table summarizing the participant disposition, with the description of the number and percentage of participants in the All Treated Analysis set, participants in the PK Analysis set, participants in the PK-evaluable Analysis set, participants who completed the study and participants who prematurely discontinued the study (classified by main reason of withdrawal) will be prepared by population group and overall, for the participants in the All Treated Analysis set.

Study duration (days) will also be summarized by population group and overall, for the All Treated Analysis Set. The study duration will be derived as:

$$Study\ duration(days) = \begin{pmatrix} study\ completion\ date\ or\ date \\ of\ early\ study\ withdrawal \end{pmatrix} - \begin{pmatrix} Informed\ consent \\ date \end{pmatrix} + 1$$

Where this data is analyzed prior to study completion, the study duration will be calculated as follows for participants who have not yet completed the study:

$$Study\ duration\ (days) = (date\ of\ data\ cut\ for\ analysis) - \begin{pmatrix} Informed\ consent \\ date \end{pmatrix} + 1$$

Corresponding individual listings will be provided. Eligibility for each of the analysis sets (Enrolled set, All Treated Analysis set, PK Analysis set, PK-evaluable Analysis set) along with reasons for exclusion will be listed.

Listings with end of study status, study visit dates and study duration (days) will also be generated.

7.3. Protocol deviations

Prior to database lock, Italfarmaco will review the individual deviations and classify them as major or minor. Protocol deviation classification process will be detailed in a separate document.

The number and percentage of participants with at least one major protocol deviations (classified by major deviation category) will be summarized by population group and overall, for the All Treated Analysis Set. Major protocol deviations will also be summarized by population group and overall, for each site.

Details of all protocol deviations (date, deviation category, specific details and classification of major or minor and participants eligibility) will be listed and deviations due to COVID-19 flagged (if applicable).

8. Demographic data and baseline characteristics

Demographic and baseline characteristics will be presented on the All Treated Analysis Set.

8.1. Demographic data

The participants' demographic characteristics (age, sex, race, ethnicity, height, weight and body mass index (BMI) recorded at screening and Day -1, and child-Pugh score for participants with HI recorded at screening and Day -1) will be summarized by population group and overall, and listed.

8.2. Other baseline characteristics

Participants' habits (history of consumption and consumption since screening and Day -1 of tobacco, alcohol, xanthine, and grapefruit) will be summarized by population group and overall and listed.

Positive results will be listed for:

- Serology:
    - For participants with normal hepatic function: hepatitis B surface antigen, anti-hepatitis B core antibodies, anti-hepatitis C virus antibodies anti-human immunodeficiency virus (HIV) 1 and 2 antibodies
    - For participants with HI: anti-HIV 1 and 2 antibodies
- Urine drug screen (Amphetamine, Benzodiazepine, Cannabinoids, Cocaine, Opiate, Barbiturates),
- Alcohol breath test.

All corresponding individual data will be listed.

Childbearing potential (for females only) and birth control method (for both males and females) as well as follicle-stimulating hormone (FSH), if available, will only be listed.

8.3. Medical and surgical histories and concomitant procedures

Information on medical and surgical histories recorded at the screening visit and procedures will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 27.1 or higher.

A table with the number and percentage of participants having at least one previous/ongoing medical history or one surgical history will be generated by population group and overall (by System Organ Class (SOC) and Preferred Term (PT) and overall).

A table with the number and percentage of studied disease history for participants with HI will be provided.

The time since initial diagnosis of the studied disease will be described for participants with HI.

Previous/ongoing medical history will be listed as well as prior surgeries and concomitant procedures.

8.4. Previous and concomitant medications

Information on previous and concomitant medications will be coded according to the WHO Drug Dictionary version of September 2024 or higher.

A previous medication will be defined as a medication stopped prior to the date and time of the administration of IMP.

A concomitant medication will be defined as a medication that is taken by participants at any time during the treatment period (on or after the date and time of IMP administration for each participant).

In case of missing information not directly allowing allocation to either of the two above categories of medications, the following rules will be followed to impute the missing:

- If medication end date is partial, first impute the end date as described in section 6.2, then:
    - If medication end date < date of IMP administration, assign as prior; otherwise, assign as concomitant
- or if the date is completely missing: assign as concomitant.

A table with the number and percentage of participants having taken at least one previous medication and a table with the number and percentage of participants having taken at least one concomitant medication will be generated by population group and overall (overall and by medication class [2nd level of Anatomical Therapeutic Chemical (ATC)] and medication name, where medication class and medication name will be sorted alphabetically). Previous and concomitant medications will be listed separately.

8.5. Compliance

The number of administrated subjects and the dose of suspension drunk (mL) will be described by population group on the All Treated Analysis set.

A listing with IMP administration dates and times and dose of suspension drunk (mL) will be generated, as well as reason not taken, if any. Time of meals intake as well as water consumption will also be listed.

9. Pharmacokinetic data

The pharmacokinetic analysis will be performed on the PK-evaluable analysis set.

The study pharmacokineticist will be responsible for determining if adequate concentration data are available and in addition, the final analysis set will be validated during the study data review meeting.

9.1. Generalities

The following rules for **PK parameter calculation** 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 and PK parameters:
  - Pre-dose BLQ values will be replaced by "0".
  - If the pre-dose value is ≤ 5% of the C_{max} value of the corresponding period for a particular participant, that participant's data, without any adjustments, will be included in all pharmacokinetic and statistical analysis. If the pre-dose value is > 5% of C_{max} value of the corresponding period for a particular participant, that participant's data will be flagged and reported in the listing, but the participant will be dropped from all descriptive and inferential statistical analyses. This is applicable only before the IMP administration.
  - All other BLQ values occurring prior to the first detectable concentration will be replaced by "0".
- All BLQ values occurring after the first detectable and embedded BLQ values (BLQ values between two quantifiable concentrations) will be treated as missing.
  - 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.
  - The values higher than the upper limit of quantification (ULQ) will be replaced by the ULQ value.
  - Some conditions for plasma PK parameters have to be fulfilled:
    1) the percentage of the extrapolated AUC (AUC_{ext}) 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 (Rsq_{adj}) > 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 be flagged in the listings and will be excluded from the analysis:

    1) if the time interval used for the determination of the elimination rate constant is inferior to 2 x $t_{1/2}$ and/or not with a minimum of 3 data points and/or if the $Rsq_{adj} \leq 0.7$: λ_z, $t_{1/2}$, $AUC_{0\text{-}inf}$, CL/F, Vz/F.
    2) if AUC_{ext} > 20%: $AUC_{0\text{-}inf}$, CL/F, Vz/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., participants 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 analyzable and not missing: statistics will be calculated with the available values.
- If more than half of the values are not analyzable 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 not determined (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

Blood samples will be drawn (see section 15.1) at the following timepoints:

- pre-dose (within 30 minutes before administration),
- H0.5, H1, H2, H2.5, H3, H4, H5, H6, H8, H10, H12 post-dose (D1),
- H24, H36 post-dose (D2),
- H48, H60 post-dose (D3),
- H72 post-dose (D4),
- H96 post-dose (D5).

Blood samples for the assessment of the free fraction will be used at the following timepoints: H2, H4, H5 and H12 post-dose (D1).

Relevant plasma PK parameters of ITF2357 and its metabolites (ITF2374 and ITF2375) will be calculated by standard non-compartmental methods for the participants with sufficient plasma concentration data (a PK profile with at least 3 quantifiable concentrations). 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: the linear trapezoidal method for increasing or equal concentrations and the logarithmic trapezoidal method for decreasing concentrations.

The following plasma PK parameters will be calculated for ITF2357 and its metabolites:

Parameters (unit)	**Definition**
C_{max} (ng/mL)	Maximum plasma concentration
t_{max} (h)	Time to reach maximum plasma concentration
$AUC_{0\text{-}last}$ (ng.h/mL)	Area under the plasma concentration-time curve from time zero to the last quantifiable concentration
$AUC_{0\text{-}inf}$ (ng.h/mL)	Area under the plasma concentration-time curve from time zero to infinity, calculated as follows: $AUC_{0\text{-}inf} = AUC_{0-t} + \frac{C_t}{\lambda_z}$, where C_t is the last observed quantifiable concentration at time t, λ_z is the apparent terminal elimination rate constant
$t_{1/2}$ (h)	Terminal elimination half-life, calculated as follows: $t_{1/2} = Ln(2)/\lambda_z$
λ_z (/h)	Apparent terminal elimination rate constant

The following plasma PK parameters will be calculated only for ITF2357:

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

Unbound PK parameters will be calculated only for parents (ITF2357) and metabolites with high protein binding (ITF2374 and ITF2375):

Parameters (unit)	**Definition**
f_u	Unbound fraction**
C_{maxu} (ng/mL)	Unbound maximum plasma concentration calculated as follows: $C_{maxu} = C_{max} \times f_u$
AUC_{lastu} (ng.h/mL)	Unbound area under the plasma concentration time curve from time zero to the last quantifiable concentration calculated as follows: $AUC_{lastu} = AUC_{last} \times f_u$
AUC_{infu} (ng.h/mL)	Unbound are under the plasma concentration time curve extrapolated to infinity calculated as follows: $AUC_{infu} = AUC_{inf} \times f_u$
CL/F_u* (L/h)	Unbound apparent total body clearance calculated as follows: $CL/F_u = (CL/F) / f_u$
Vz/F_u* (L)	Unbound apparent volume of distribution calculated as follows: $Vz/F_u = (Vz/F) / f_u$

* Only for ITF2357.

** The unbound fraction will be calculated at different time points. In case the unbound fraction is substantially different at the available timepoints (i.e., >20% difference), a linear interpolation method will be implemented between timepoints to accurately correct the analyte(s) concentrations over time.

Corrected concentrations will then be used to directly calculate AUC_{lastu} and AUC_{infu}. If the difference is <20% then an average f_u among the available timepoints will be used to correct the PK parameters as proposed in the table above.

9.2.2. Plasma pharmacokinetic analysis

Listings with plasma concentrations (including PK blood sampling dates and times), unbound plasma concentrations, PK parameters and unbound PK parameters will be provided by population group and participant. These listings will be generated for all participants with an available PK profile (complete or incomplete), including those who are excluded from the PK-evaluable Analysis set.

Plasma concentrations, PK parameters, fraction unbound and unbound PK parameters of ITF2357 and its metabolites (ITF2374 and ITF2375), including descriptive statistics will be presented in tables separately for each population group.

Individual plasma concentration versus time profiles of ITF2357 and its metabolites (ITF2374 and ITF2375) will be presented graphically on linear and log/linear coordinates for each participant.

The graph of arithmetic mean ± SEM over time will be provided for plasma concentration and of ITF2357 and its metabolites (ITF2374 and ITF2375 separately) on linear and log/linear coordinates with all population groups on the same graph.

Scatter plots will be generated for the comparison of the C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ (if applicable) parameters of ITF2357 and its metabolites (ITF2374 and ITF2375) between the population groups.

9.2.3. Hepatic impairment effect

9.2.3.1. Primary analysis

For log transformed C_{max}, AUC_{last} and $AUC_{0\text{-}inf}$, the effect of HI group on ITF2357 and its metabolites (ITF2374 and ITF2375) will be analyzed using a linear model with fixed terms for HI group (normal, mild and moderate) and gender and with age and body weight at baseline as covariates*.

The following SAS® code will be used:

```
proc glm data= ADNCA;
    model <ln(CMAX)>/<ln(AUCLAST)>/<ln(AUC0INF)> = HI_GRP SEX AGE
    WEIGHT_BSL;
    estimate “HI_normal vs HI_mild” HI_GRP -1 1 0;
    estimate “HI_normal vs HI_moderate” HI_GRP -1 0 1;
run;
```

(*) The inclusion of covariates in the model will be first assessed by the Akaike’s information criterion (AIC). The model with the lowest AIC value will be selected for the final analysis. Models lack-of-fit will be assessed by residual plots.

Point estimates and 90% confidence intervals (CIs) for the geometric means ratio of each HI group versus the normal control group will be provided for C_{max}, AUC_{last} and $AUC_{0\text{-}inf}$. Moreover, for C_{max}, AUC_{last} and $AUC_{0\text{-}inf}$, a point estimate and 90% CI for the geometric mean of each population group will be provided. Corresponding plots of geometric mean ratio and geometric mean will be also provided.

9.2.3.2. Secondary analysis

Relationships between PK parameters C_{max}, AUC_{last}, $t_{1/2}$, $AUC_{0\text{-}inf}$, C_{maxu}, $AUC_{last\ u}$, AUC_{infu} (for total and unbound ITF2357 and its metabolites ITF2374 and ITF2375), CL/F, Vz/F (for ITF2357 only) and hepatic function measures (Child-Pugh score) will be explored.

For this, scatter plots will be generated between total and unbound PK parameters and Child-Pugh score for ITF2357 and its metabolites ITF2374 and ITF2375. All groups will be on the same graph with different symbols formatting for the population groups.

10. Pharmacodynamics data

Not applicable.

11. Safety data

The safety analyses will be performed on the All Treated Analysis set.

11.1. Adverse events

Adverse events, including pre-treatment events, will be recorded from the time of informed consent through the end-of-trial visit.

Adverse events will be coded according to MedDRA Version 27.1 or higher and for severity (the maximum intensity of an AE during a day) according to the definition of the Common Terminology Criteria for Adverse Event (CTCAE) version 5.0 or higher. The version used will be indicated in the data summaries and listings.

A treatment-emergent adverse event (TEAE) is defined as an AE that started or worsened on or after IMP dosing.

Partial dates will be imputed as defined in section 6.2 before deriving the TEAE flag. If the start date is completely missing, then it will be assumed to be treatment emergent unless stop date indicates differently. If the AE start time is missing and the AE is on the same day than IMP dosing, then it will be assumed to be treatment emergent unless stop date/time indicates differently.

Each AE will be described by the:

- Seriousness
- Duration (start and end dates)
- National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE) Grade
- Relationship with the study drug
- Outcome

If the AE has a missing relationship it is assumed to be related to the study treatment for analysis purposes.

Adverse events will be summarized by population group and overall, for the All Treated Analysis Set.

An overall summary table will present the following:

- TEAEs (events and subjects).
- TEAEs leading to withdrawal from study (subjects).
- TEAEs according to CTCAE grade (1 to 5) (events and subjects).

- TEAEs (related/not related) to study treatment (events and subjects).
- Serious TEAEs (events and subjects).
- Serious study treatment related TEAEs (events and subjects).
- TEAEs leading to death (subjects only).

In the above summary, if a subject experienced more than one TEAE, the subject will be counted once using the most related event for the "by relationship to study treatment" and "related to study treatment" summaries and at the worst severity for the "by severity" summary.

The following tables will be presented:

- TEAEs by SOC and PT (events and subjects).
- TEAEs by SOC, PT and CTCAE grade (events and subjects).
- TEAEs by SOC, PT and relationship (related/not related) to study treatment (events and subjects).
- Serious TEAEs by SOC and PT (events and subjects).

All AEs 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 participants with at least one TEAE for a given PT will also correspond to the number of TEAEs whatever the number of occurrences during the studied period.
ii. In case of a change of intensity or causality for an event, the intensity will be the highest recorded intensity, and the causality will be the highest likelihood recorded.

11.2. Clinical laboratory data

The following clinical laboratory parameters will be measured (see section 15.1):

- at screening,
- on D-1,
- at H24 (D2), H48 (D3), H72 (D4), H96 (D5),
- at EOS (D10 ±1 day).

Hematology parameters will be listed and grouped as follows:

- Red blood cells: erythrocytes (10^12/L), hemoglobin (HGB) (g/L) and hematocrit (ratio)
- White blood cells: basophils (10^9/L), basophils/leukocytes (%), eosinophils (10^9/L), eosinophils/leukocytes (%), leukocytes (10^9/L), lymphocytes (10^9/L), lymphocytes/leukocytes (%), monocytes (10^9/L), monocytes/leukocytes (%), neutrophils (10^9/L) and neutrophils/leukocytes (%).
- Other parameters: platelets (10^9/L).

Blood chemistry parameters will be listed and grouped as follows:

- Liver function: alanine aminotransferase (ALT) (IU/L), alkaline phosphatase (IU/L), aspartate aminotransferase (AST) (IU/L), bilirubin (µmol/L), gamma glutamyl transferase (GGT) (IU/L),
- Renal chemistry: creatinine (µmol/L), and urea (mmol/L),

- Electrolytes: calcium (mmol/L), chloride (mmol/L), potassium (mmol/L) and sodium (mmol/L),
- Metabolism parameters: glucose (mmol/L), cholesterol (mmol/L), triglycerides (mmol/L),
- Other proteins: albumin (g/L), creatinine kinase (IU/L), and protein (g/L).

Coagulation parameters will be listed and grouped as follows:

- Coagulation parameters: activated partial thromboplastin time (aPTT) (sec), Prothrombin Intl. Normalized Ratio (INR) (ratio) and prothrombin time (sec),

Urinalysis parameters will be listed and grouped as follows:

- Planned urinalysis parameters: dipstick determination of pH, erythrocytes, glucose, ketones, leukocytes, nitrite and protein,
- Direct microscopy (in case of abnormal urinalysis parameters and in the listing only).

For hematology, blood chemistry and coagulation, raw data and changes from baseline will be described by summary statistics by population group and overall and visit /measurement timepoint.

Shift in hematology, chemistry and coagulation values from baseline to each visit/measurement timepoint for low, normal, high, missing and total results based on reference ranges will be summarized by population group, for the All Treated Analysis Set.

For urinalysis, raw data (planned parameters) will be described by summary statistics or frequency tables by population group and visit/measurement timepoint.

For hematology, blood chemistry, coagulation, values higher or lower than the laboratory reference range (H, L) or abnormal values for urinalysis will be listed.

For hematology and blood chemistry, a summary table with the number and percentage of participants with potentially clinically significant abnormal (PCSA) values (defined in section 15.2) will be generated by population group and visit/measurement timepoint.

A specific listing of participants with PCSA values will be generated.

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

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

11.2.1. Pregnancy test (for females only)

For women of childbearing potential only, serum pregnancy test (β-HCG) will be performed (see section 15.1) at screening, D-1 and EOS (D10 ±1 day).

Positive results will be listed on the All Treated Analysis set and all individual data will be listed on the Enrolled set.

11.3. Other safety parameters

11.3.1. Vital signs data

Supine systolic and diastolic blood pressure (mmHg), pulse rate (beats/min) and respiratory rate (breaths/min) will be measured (see section 15.1):

- At screening,
- D-1,

- At pre-dose 30 minutes before administration, H2, H3, H5, H8, H12 post-dose (D1),
- H96 post-dose (D5),
- EOS (D10 ±1day).

Blood pressure will be also measured in standing position at screening and D-1.

Body temperature (C°) will be measured (see section 15.1) at screening, D-1 and EOS (D10 ±1day).

The presence of orthostatic hypotension will be derived as follows for a pair of values (supine and standing) corresponding to the same examination:

- Orthostatic hypotension: standing SBP - supine SBP ≤ -20 mmHg or
  standing DBP - supine DBP ≤ -10 mmHg.

Raw data and changes from baseline (for supine position only) will be described by population group and visit/measurement timepoint.

A summary table with the number and percentage of participants with PCSA values (defined in section 15.2) will be generated by population group and visit /measurement timepoint.

A specific listing of participants with PCSA values will be generated.

The number and percentage of subjects with at least one orthostatic hypotension will be presented by population group and visit /measurement timepoint.

Values (raw data and changes from baseline) will be listed and PCSA values will be flagged with clinical significance information.

A listing of subjects having at least one orthostatic hypotension will be provided.

11.3.2. Electrocardiogram data

Standard 12-lead ECG parameters (including heart rate (beats/min), PR interval (msec), QRS duration (msec), QT interval (msec), Bazett QTc interval (QTcB) (msec), Fridericia QTc interval (QTcF) (msec) and ECG abnormalities will be recorded (see section 15.1):

- At screening,
- D-1,
- At pre-dose (30 minutes before administration), H2, H5, H8 and H12 (D1),
- H96 (D5),
- EOS (D10 ±1day).

If ECG demonstrates a prolonged QTcF interval >450 msec, 2 additional ECGs will be obtained. The average of the non-missing values (even if more than 3 values are collected) of the ECGs will be calculated and will serve as analyzable data.

Only interpretable ECGs will be analyzed.

Raw data and changes from baseline (except for ECG abnormalities) will be described by population group and visit /measurement timepoint.

In addition, the overall interpretation of the ECG (Normal, Abnormal NCS, Abnormal CS, missing) will be summarized over time by population group and overall.

Shift in ECG interpretation from baseline to each visit/measurement timepoint for normal, abnormal NCS, abnormal CS, missing and total results will be summarized using the “worst case” scenario for each set of triplicate readings as required. Subjects will only be included in the missing category if they attended the visit but have no data available for the ECG interpretation. Withdrawn subjects will not be included in the missing category.

A summary table with the number and percentage of participants with PCSA values (defined in section 15.2) will be generated by population group,visit/measurement timepoint and overall.

A specific listing of participants with PCSA values will be generated.

Values [raw data/ECG abnormalities and changes from baseline] will be listed and data out of the PCSA ranges will be flagged with clinical significance information. Only the mean of the triplicate values will be listed (if applicable).

11.3.3. Physical examination

Physical examinations (include, at a minimum of assessments of the cardiovascular, respiratory, gastrointestinal, dermatological and neurological, musculoskeletal in addition to head, eyes, ears, nose, throat, neck and lymph nodes systems) will be performed:

- At screening,
- On D-1,
- At H96 (D5),
- At EOS (D10 ±1day).

Abnormal physical examination findings will be listed as well as individual data.

12. Procedures and data formats

Biotrial standard operating procedures (SOP) will be followed, and in particular on SOP GL-6.3.6: Programming of the statistical analysis, results editing and quality control.

Derived data produced for the generation of TFLs will follow CDISC ADaM standard (ADaM Model v. 2.1 / ADaM implementation guide version 1.3).

ADaM and SDTM datasets will be provided to Italfarmaco.

13. Reporting conventions

All tables, figures and listings are detailed in section 15.3. 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 ITF/2357/60 / <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.xxx)
	Median	xx.xx

Parameter (Unit)	**Statistics / Category**	**Group X (N=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. SD will be provided with two additional decimals compared to the variable itself. Coefficients of variation for PK analyses will be provided with one decimal place.

14. References

1. Karvanen J. The statistical basis of laboratory data normalization. Drug Information Journal. 2003;37(1):101-107.
2. United States. Food and Drug Administration. Guidance for industry. Pharmacokinetics in patients with impaired hepatic function: study design, data analysis, and impact on dosing and labeling, U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, May 2003. Clinical Pharmacology.

15. Appendices

15.1. Appendix 1 - Schedule of Activities of the study

15.1.1. Overall Study - Schedule of Activities (SOA)

Epoch	**Enrollment**		**Treatment period**					**Follow-up**
Phase	**Screening**	**Admission**	**Hospitalization**					**End-of-Study**
Day (D)	**D-28 to D-2**	**D-1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D10 (±1 day)**
Informed consent	X							
Demographic characteristics[a]	X							
Institutionalization		X						
Discharge							X	
Outpatient visit	X							X
Inclusion/exclusion criteria	X	X						
Medical/surgical history	X	X						
Child-Pugh score[b]	X[b]	X[b]						
Prior/concomitant medications	←------	----------	-----	-----	-----	-------	-------	---------→
Inclusion			X					
Investigational Medicinal Product (IMP) administration								
Givinostat (-)			X					
Safety								
Physical examination	X	X					X	X
Height	X							
Body weight	X	X						X

Epoch	**Enrollment**		**Treatment period**					**Follow-up**
Phase	**Screening**	**Admission**	**Hospitalization**					**End-of-Study**
Day (D)	**D-28 to D-2**	**D-1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D10 (±1 day)**
Body temperature (oral)	X	X						X
Vital signs (§)	X	X	X				X	X
Electrocardiogram (ECG)	X	X	X				X	X
Hematology[c], biochemistry, coagulation, urinalysis	X	X		X[c]	X[c]	X[c]	X[d]	X
Serology tests	X							
Serum pregnancy test if applicable	X	X						X
Serum follicle-stimulating hormone (FSH), if applicable	X							
Urine drug screen, alcohol breath test	X	X						
Adverse event collection	←- - - - - - -	- - - - - - - - - -	- - - - - -	- - - - - -	- - - - - -	- - - - - -	- - - - - - -	- - - - - - - - - →
Pharmacokinetics (PK)								
PK samples			X	X	X	X	X	
Blood samples for ITF2357, and metabolites ITF2374 and ITF2375 free fraction			X					

a Including age (years), race and ethnicity, and gender.
b Only in Hepatic Impairment (HI) patients
c Additional samples will be taken only for hematology test.
d On D5 at hour (H)96, urinalysis may be performed within a ± 2 hour time-window.
(') Dose of the IMP is expressed as givinostat hydrochloride monohydrate.
(§) Blood pressure (both supine and standing position at screening and D-1, supine only thereafter), pulse rate and respiratory rate.

15.1.2. Period - Schedule of Activities (SOA)

Day	**D1**													**D2**		**D3**		**D4**	**D5**
Time (hour/minute)	**-0H30**	**0H**	**0H30**	**1H**	**2H**	**2.5**	**3H**	**4H**	**5H**	**6H**	**8H**	**10H**	**12H**	**24H**	**36H**	**48H**	**60H**	**72H**	**96H**
Indicative clock time		8:00	8:30											8:00		8:00		8:00	8:00
Concomitant medications		←	-	-	-		-	-		-	-	-	-	-	-	-	-	-	→
Discharge (breakfast will be provided)																			X
Standard meals[a]										X									
IMP administration																			
Givninostat		X																	
Safety																			
Physical examination																			X
Archival blood sample	X																		
Vital signs[c]	X				X		X		X		X		X						X
ECG	X				X				X		X		X						X
Hematology, biochemistry, coagulation, urinalysis														X		X		X	X[b]
Adverse event collection		<	-	-	-		-	-		-	-	-	-	-	-	-	-	-	>
Pharmacokinetics																			
PK samples	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood samples for ITF2357, ITF2374 and ITF2375 free fraction					X			X	X				X						

a Standardized meals will be provided during the inpatient period. However, and for the dosing on Day 1, an overnight fast will be imposed, so that no food is taken within at least 10 hours before IMP administration. Participants will remain fasted for at least 2 hours after dosing, a snack at H2 post-dose, be served lunch at H4 post-dose, possible snack in the afternoon and dinner around H10 post-dose. Drinking of water will be allowed ad libitum except for 1 h before and 1 h after dosing; before and after that period, drinking water will be permitted ad libitum.

b On D5 at H96, urinalysis may be performed within a ±2 hours' time-window.

c Supine blood pressure, pulse rate and respiratory rate.

Note: when several assessments take place at the same time, the following order should be respected: ECG, vital signs, safety samples, meals, PK, drug administration. **To respect the exact timing of PK samples, ECG and vital signs will be done ahead of the scheduled time.**

15.2. Appendix 2 - Criteria for Potentially Clinically Significant Abnormalities (PCSA)

PARAMETER	LOWER PCSA VALUE	UPPER PCSA VALUE
Laboratory parameters		
AST		≥ 3 ULN and < 5 ULN (High) ≥ 5 ULN and < 20 ULN (High+) ≥ 20 ULN (High++)
ALT		≥ 3 ULN and < 5 ULN (High) ≥ 5 ULN and < 20 ULN (High+) ≥ 20 ULN (High++)
Gamma GT		≥2,5 ULN <5 ULN (High) ≥5 ULN and < 20 ULN (High +) ≥20 ULN (High++)
Alkaline phosphatase		≥ 1.5 ULN
Total bilirubin		≥ 1.5 ULN
Creatinine		≥ 150 µmol/L
Sodium	≤ 129 mmol/L	≥ 160 mmol/L
Potassium	< 3 mmol/L	≥ 5.5 mmol/L
Glucose	≤ 3.9 mmol/L and < LLN	≥ 7 mmol/L
Hemoglobin	≤ 100 g/L	
Platelets	< 100 10^9/L	
Leukocytes	< 3 10^9/L (< 2 10^9/L for Black or African American)	
Neutrophils	< 1.5 10^9/L (< 1 10^9/L for Black or African American)	
Eosinophils		> 0.5 10^9/L or > ULN if ULN > 0.5 10^9/L
Triglycerides		>300 – 500 mg/dL >500 – 1000 mg/dL >1000 mg/dL
Cholesterol		>300- 400 mg/dL >400 – 500 mg/dL >500 mg/dL
Vital signs		
Supine HR	≤ 40 beats/min and change from baseline ≤ -20 beats/min	≥ 100 beats/min and change from baseline ≥ 20 beats/min
Supine SBP	≤ 95 mmHg and change from baseline ≤ -20 mmHg	≥ 140 mmHg and change from baseline ≥ 20 mmHg
Supine DBP	≤ 45 mmHg and change from baseline ≤ -10 mmHg	≥ 90 mmHg and change from baseline ≥ 10 mmHg
Standard 12-lead ECG parameters		
HR	≤ 40 beats/min and change from baseline ≤ -20 beats/min	≥ 100 beats/min and change from baseline ≥ 20 beats/min
PR		≥ 220 msec
QRS		≥ 120 msec

PARAMETER	LOWER PCSA VALUE	UPPER PCSA VALUE
QTc		> 450 msec and ≤ 480 msec (High) > 480 msec and ≤ 500 msec (High+) > 500 msec (High++) change from baseline > 30 msec and change from baseline ≤ 60 msec (High) change from baseline > 60 msec (High+)