Trial Statistical Analysis Plan

c02097092-03

BI Trial No.:	1230.24
Title:	An open-label fixed sequence trial to investigate the potential drug-drug interaction of intravenous volasertib co-administered with a P-gp and CYP3A4 inhibitor (itraconazole p.o.) in patients with various solid tumors.
Investigational Product(s):	Volasertib, BI 6727
Responsible trial statistician:	[redacted] Phone: [redacted] Fax:
Date of statistical analysis plan:	24 July 2014 REVISED
Version:	Revised

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2. LIST OF ABBREVIATIONS

Include a list of all abbreviations used in the TSAP

Term	Definition / description
AE	Adverse Event
AUC	Area under the plasma concentration-time curve
$AUC_{0-\infty}$	Area under the plasma concentration-time curve over the time interval from 0 to infinity
AUC_{0-tz}	Area under the plasma concentration-time curve over the time interval from 0 to the time of the last quantifiable data point
BLQ	below the limit of quantification
bpm	Beats per minute
CI	Confidence Interval
CL	Total clearance of the analyte in plasma following intravenous infusion
C_{max}	Maximum measured concentration of the analyte in plasma
$C_{max,ss}$	Maximum measured concentration of the analyte in plasma at steady state
$C_{pre,ss,N}$	Predose steady state plasma concentration of the analyte in plasma immediately before administration of the Nth dose
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CYP3A4	Cytochrome P_{450} 3A4
DDI	Drug-drug interaction
DILI	Drug-induced Liver Injury
DMC	Data Monitoring Committee
DRT	Dose Reducing Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form

Term	Definition / description
EDC	Electronic Data Capture
EDTA	Ethylendiaminetetraacetic acid
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
GCP	Good Clinical Practice
[redacted]	
HR	Heart rate
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ISF	Investigator Site File
i.v.	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web-based Response System
MDR1	Multidrug resistance protein 1
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRT	Mean residence time after intravenous infusion
ms	Milliseconds
MST	Medical Subteam
MTD	Maximum Tolerated Dose
NOA	not analyzed
NOP	no peak detectable
NOR	no valid result
NOS	no sample
OPU	Operative Unit
PD	Progression of Disease
PG	Pharmacogenomics
PLK	Polo-like kinase
p.o.	per os (oral)
PCC	Protocol Challenge Committee

Term	Definition / description
P-gp	P-glycoprotein
PR interval	ECG interval from the start of P wave to the start of the QRS complex
q.d.	quaque die (once a day)
QRS complex	Combination of a Q wave, an R wave, and an S wave
QT interval	ECG interval from the start of the QRS complex to the end of the T wave
QTc interval	General term for QTcF and QTcB intervals
QTcB interval	QT interval, heart rate corrected using Bazett's formula
QTcF interval	QT interval, heart rate corrected using Fridericia's formula
RR interval	ECG interval from the peak of the R wave to the peak of the subsequent R wave
SAE	Serious Adverse Event
s.c.	Subcutaneous
SPC	Summary of Product Characteristics
$t_{1/2}$	Terminal half-life of the analyte in plasma
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
t.i.d.	ter in die (3 times a day)
t_{max}	Time to maximum analyte plasma concentration
$t_{max.ss}$	Time to maximum analyte plasma concentration at steady state
TMM	Team Member Medicine
TMW	Trial Medical Writer
TSAP	Trial Statistical Analysis Plan
V_{ss}	Apparent volume of distribution at steady state after intravenous infusion
V_z	Apparent volume of distribution during the terminal phase following an intravenous infusion

3. INTRODUCTION

As per ICH E9, the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This TSAP assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomization.

SAS® Version 9.2 (or later version) will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

The changes to the planned analysis are as follows:

The CTP lists primary endpoint AUC0-tz as AUC0-336, which is a typographical error and has been corrected as AUC0-504 in its second revision.

The CTP specifies that "in case that MTD of co-administration of itraconazole and volasertib is less than 300mg, dose will be considered in the ANOVA model to correct for the different starting doses of the patients." However, after first three patients treated on the initial dose level 300mg for the combination therapy, MTD de-escalated immediately to 250mg and all subsequently enrolled patients were treated on 250mg in cycle 1. Very few patients had further intra-individual dose reduction to 200mg during cycle 2 mono-therapy. Due to the sparse data available on the dose levels other than the MTD 250mg, the primary analysis set for pharmacokinetic endpoints will be restricted among the patients who were treated on 250mg in both cycle 1 and cycle 2. The single patient who was treated on 300mg in both cycle 1 and cycle 2 will also be included in the primary analysis. In addition, a sensitivity analysis will be conducted by including patients with intra-dose reduction during cycle 2 after dose normalization.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Relative bioavailability of volasertib and its main metabolite CD10899 will be investigated primarily on the basis of the following pharmacokinetic parameters:

CTP: *The following primary endpoints will be determined for volasertib and its main metabolite CD 10899:*

- $AUC_{0\text{-}tz}$ *(area under the plasma concentration-time curve of the analyte in plasma over the time interval from zero to 504 hours or last actual measure time)*
- C_{max} *(maximum measured plasma concentration of the analyte in plasma)*

The primary objective is to estimate the relative bioavailability of a single dose of volasertib and its main metabolite CD10899 when administered alone (volasertib monotherapy) compared with co-administered with itraconazole (200mg once daily) in cancer patients with various solid tumors. The relative bioavailability is primarily to be determined on the basis of geometric mean ratios of the primary pharmacokinetic endpoints $AUC_{0\text{-}tz}$, and C_{max} measured under the combination therapy period relative to mono therapy period. The derivation of these primary pharmacokinetic endpoints is given in the internal SOP 001-MCS-36-472_RD-01(6).

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

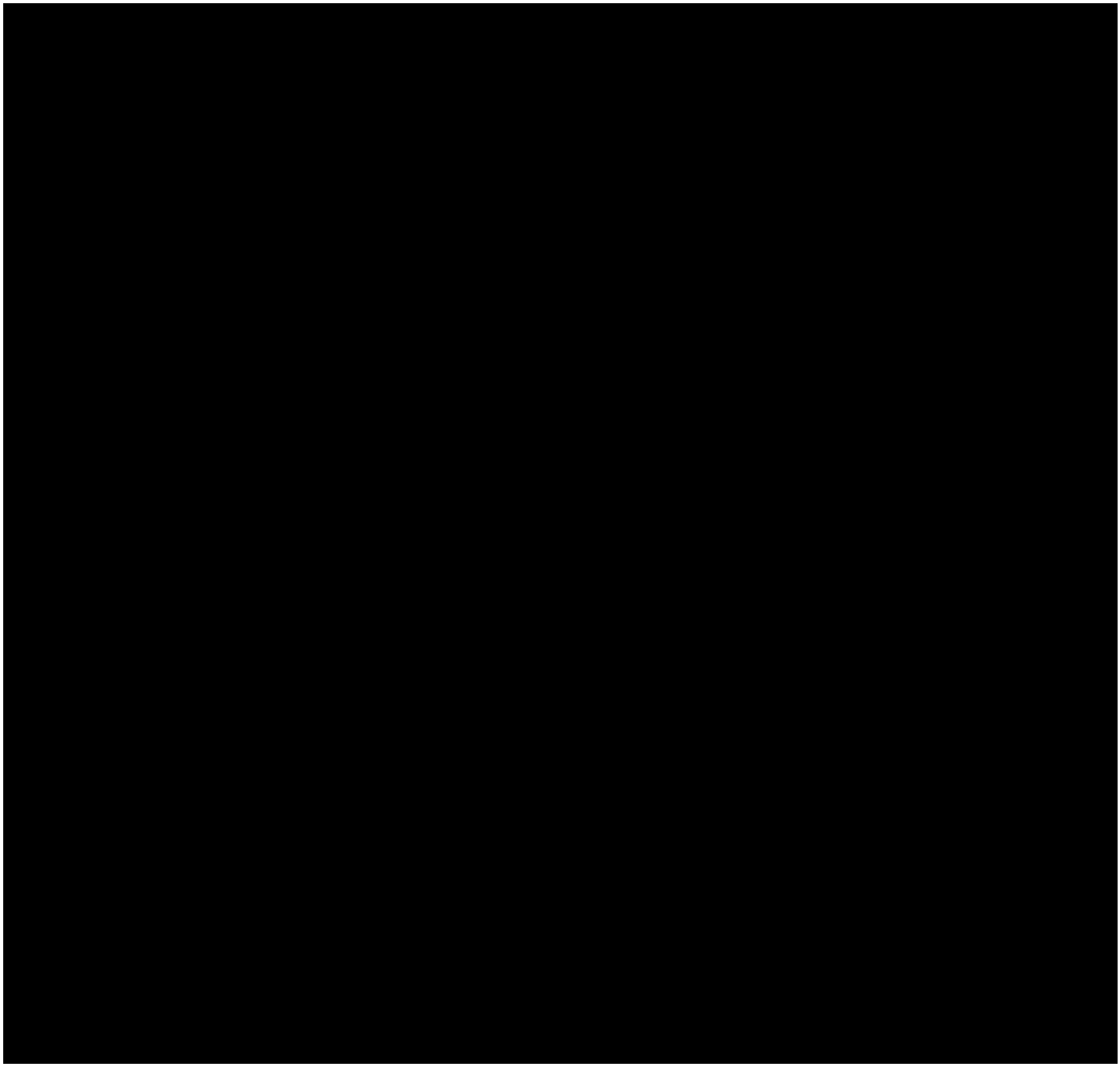
As no key secondary endpoints have been specified in the protocol, this section is not applicable.

5.2.2 Other Secondary endpoints

PK endpoints

The $AUC_{0\text{-}\infty}$ of volasertib and its main metabolite CD 10899 will be statistically assessed using the same methods as described for the primary endpoint.

[redacted]



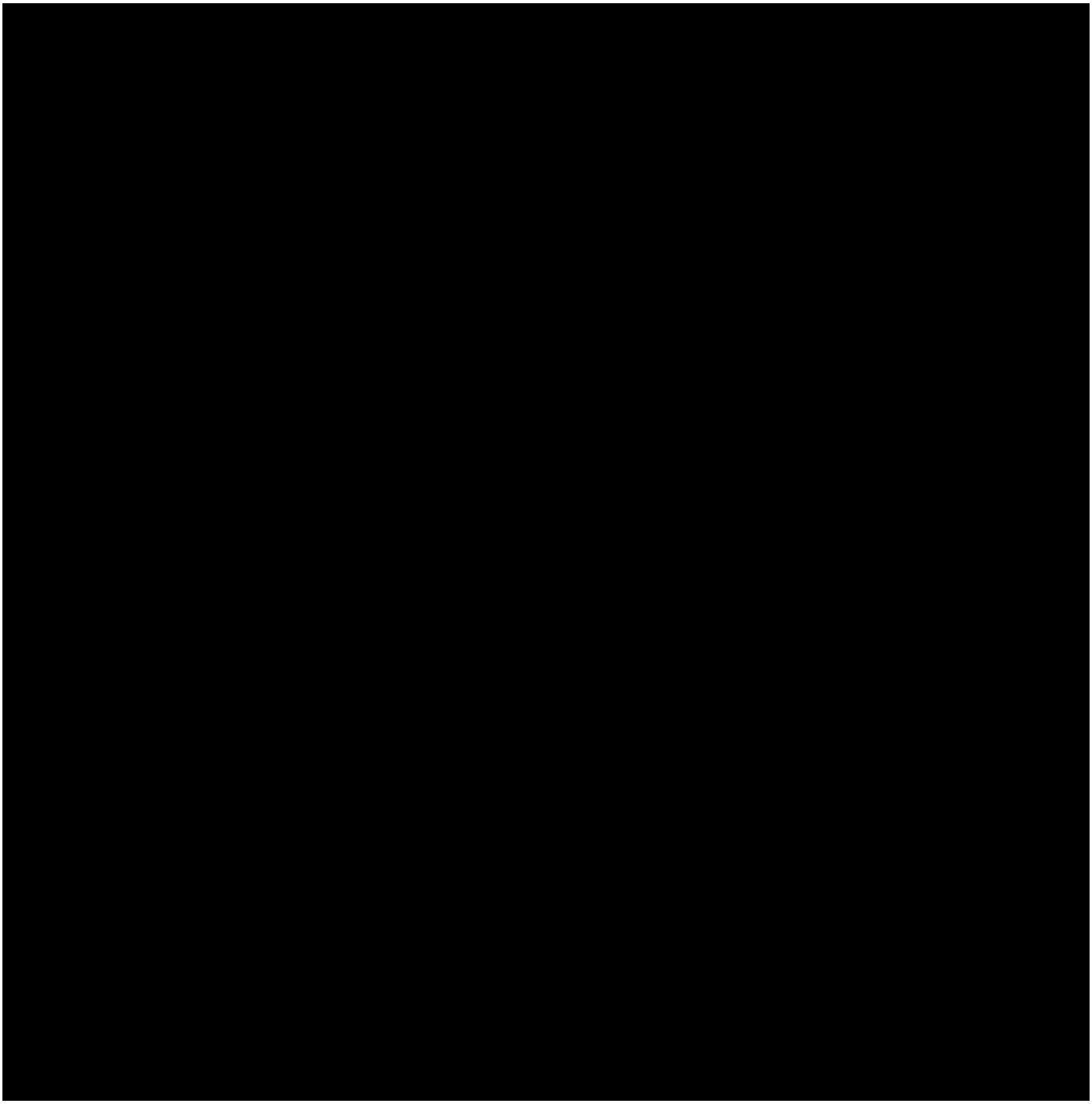
5.4.1 Safety and tolerability endpoints

The assessment of safety and tolerability will be based on

- Adverse events
    - Drug related AE
    - AE leading to dosage reduction
    - AE leading to permanent treatment discontinuation
    - Serious AE

- Safety laboratory tests
- Physical examination (height, weight, ECOG)
- Vital signs (blood pressure and pulse rate)

For details please refer to the CTP Section 5.2 and 5.3.



5.4.4 Electrocardiogram

The following endpoints will be regarded for the electrocardiogram (ECG) analysis:

- Absolute QTcF intervals at each time point
- QTcF changes from individual baseline at each point in time: (QTcF post-baseline measurement obtained at each time point) – (individual baseline QTcF measurement)

The above endpoints will also be computed for the uncorrected QT interval, for heart rate (HR), PR interval and QRS complex. HR will be derived from RR intervals as described in section 7.8.3.

. The classifications will be performed separately for cycle 1 and cycle 2 as well as using the maximum on-treatment value over the entire mono-therapy period (≥ 2 cycles) per patient.

- QTcF values at individual baseline and maximum post-baseline:
  - ≤450 ms
  - >450 ms to ≤470 ms
  - >470 ms to ≤500 ms
  - >500 ms

- QT values at individual baseline and maximum post-baseline:
  - ≤500 ms
  - >500 ms

- QTcF increase from individual baseline to the maximum post-baseline value:
  Intervals for a given patient as
  - ≤30 ms
  - >30 ms to ≤60 ms
  - >60 ms

- QT increase from individual baseline to the maximum post baseline value:
  Intervals for a given patient as
  - ≤60 ms
  - >60 ms

- Increase from individual baseline ≥ 25% and absolute value >200 ms of all on-treatment values in PR interval for a given patient
- Increase from individual baseline ≥ 25% and absolute value >110 ms of all on-treatment values in QRS interval for a given patient

All endpoints derived for the QTcF interval will also be derived for the QTcB interval. The derivation of each QTc interval from the RR and QT intervals is described in section 7.8.3.

The QTc threshold of 470 ms is used to be consistent with the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, which is widely accepted as a standard for describing and managing safety findings in clinical studies of anticancer therapy. The other QT/QTc thresholds are in accordance with the ICH E14 Guideline.

Notable findings (defining outliers for the QT/QTc interval) at any on-treatment time point for a given patient are defined as

- Maximum increase from individual baseline to on-treatment value in QTc interval > 60 ms
- QT/QTc > 500 ms in any on-treatment value which is not present at individual baseline

All endpoints involving the 'individual baseline' will also be derived for the 'combined baseline' (refer to Section 6.7).

ECG endpoints will also include cardiologist's assessments. In particular, findings of abnormal rhythm, conduction, morphology, ST segment changes, T wave abnormalities and myocardial infarction will be explored.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

In total, it was planned to include 24 patients in this two period trial with a fixed treatment sequence:

Treatment A: Day -3 to Day 15 of cycle 1: daily 200mg itraconazole

Day 1 of cycle 1: Single dose volasertib infusion 300mg

Treatment B: Day 1 of cycle 2 (Day 23 starting from Day 1 of cycle 1): Single dose volasertib infusion 300mg

For detail of dosage and formulation see section 4.1 in CTP. For detailed information on the handling of the treatment in the O*C views refer to Technical TSAP ADS plan

Time intervals for safety analysis are defined below. The analyses for safety endpoints will focus the on-treatment period of volasertib and contrast the safety profile within first cycle and second cycle during the study period. In addition, the safety endpoints will be summarized for the entire volasertib mono-therapy period.

Screening period: Screening to first dose of Itraconazole.

Itraconozole induction period: Start of first dose of Itraconazole to start of first dose of volasertib.

First cycle combo-therapy period: Start of first dose of volasertib to the start of the second cycle if patients received the second cycle mono-therapy, or to the 21 days after the first volasertib administration date if patients discontinued after the first cycle.

Second cycle mono-therapy period: Start of second dose of volasertib to the start of the cycle 3 if patients received cycle 3 mono therapy, or to the 21 days after second volasertib administration date if patients discontinued after the second cycle.

Mono-therapy period: Start of the second dose of volasertib to the last dose of volasertib plus 21 days.

Post-treatment period: After 21 days after last dose of volasertib.

6.2 IMPORTANT PROTOCOL VIOLATIONS

Table 6.2: 1 contains the categories in which important PVs are classified. Categories for manually assessed important PVs, i.e. important PVs that are detected manually at the sites and cannot be detected through the database, are not shown in this table but will be finalised before DBL and documented in the final BRPM minutes.

Consistency checks will be prepared for identifying violations of time windows.

Table 6.2: 1 Important protocol violations

Category/ Code		Description	Example/Comment
A		**Entrance criteria not met**	
	A1	Inclusion criteria not met	Inclusion criteria 6 not met as specified in the protocol as this is safety related; see SOP) Other inclusion criteria violation will be manually reviewed.
	A2	Exclusion criteria not met	Laboratory criteria 6-11, 19. Violations on other exclusion criteria will be manually reviewed.
B		**Informed consent**	
	B1	Informed consent not available/not done	Informed consent date missing
	B2	Informed consent too late	Informed consent date <*actual consent date*> was after Visit 1 date <*Visit 2 date*>
C		**Trial medication and randomization**	

Table 6.2: 1 (continued) Important protocol violations

Category/ Code		Description	Example/Comment
	C1.1	Non-compliance	Missing itraconazole doses during either pre-volasertib administration period or on the day of volasertib administration is considered IPV..
	C1.2	Non-compliance	Missing itraconazole doses in the post-volasertib administration period will be documented and reviewed case by case
	C2.1	Volasertib infusion late	Volasertib infusion not immediately after medicine preparation will be documented and reviewed case by case
D		**Concomitant medication**	
	D2	Prohibited medication use	• Strong inhibitors of CYP3A4 • Inducers of CYP3A4 • Inhibitors of P-gp • Inducers of P-gp (CTP 4.2.2.1)
E		**Missing data (for primary endpoints)[1]**	
	E4	Certain violations of procedures used to measure primary and secondary data	Un-evaluable PK results for reasons other than study discontinuation.
F		**Incorrect timing (for primary and secondary endpoints)[2]**	
	F5	Certain violations of the time schedule used to measure primary and secondary data	

KEY: Hb = haemoglobin, Hct = Haematocrit, Tx = transfusion, PPS – Per Protocol Set

6.3 PATIENT SETS ANALYSED

- Treated set (TS):
  This patient set includes all patients who were documented to have taken at least one dose of volasertib. This is the full analysis set population in the sense of ICH-E9. It is used for safety analysis.

- Primary pharmacokinetic set (pPKS):
  This subject set includes all patients in the TS who were treated on the same dosage

(250mg and 300mg) in the first two cycles and provided complete PK measures without important protocol violations.

- Sensitivity pharmacokinetics set (sPKS)

This subject set includes all patients in the TS who provided complete PK measures in the first two cycles without important protocol violations.

- ECG analysis set (ECGS): This patient set includes all patients in the treated set who provide at least one matching pair of QT measurements available pre-dose and after drug administration. Patients with an artificial pacemaker will be excluded.

Table 6.3: 1 Patient sets analyzed

	Patient set			
Class of endpoint	TS	pPKS	sPKS	ECGS
Primary (PK) endpoints		X	X	
[redacted]				
Safety endpoints	X			
ECG endpoints				X
Demographic data/Medical history and Concomitant diagnosis, Concomitant therapy	X			
Important PVs	X			
Disposition	X			

[redacted]

6.5 POOLING OF CENTRES

This section is not applicable because the study was performed in only two centres.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

6.6.1 AE dates and times

It is not planned to impute missing values, with exception of missing AE start dates and times. These are imputed according to BI standards (see DM&SM "Handling of missing and incomplete AE dates")(3)

6.6.2 Missing plasma concentrations and pharmacokinetic parameters

Handling of missing PK data will be performed according to the BI standard procedure "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" [001-MCS-36-472_RD-01] (4) and [001-MCS-36-472] (6).

Plasma concentration-time profiles and descriptive statistics of concentration data

CTP: *Drug concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analyzed), BLQ (below the lower limit of quantification), or NOP (no peak detectable) will be displayed as such and not replaced by zero at any time point (this rule also applies also to the lag phase, including the predose values).*

Pharmacokinetic parameters and their descriptive statistics

CTP: In the non-compartmental analysis, concentration data identified with NOS, NOR, and NOA will not be considered. BLQ and NOP values in the lag phase will be set to zero. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit. All other BLQ/NOP values of the profile will be ignored.

6.6.3 ECG

If replicate ECG recordings are missing, the arithmetic means per time point will be computed with the reduced (1 or 2) number of recordings. If single cardiac cycles (also denoted as beats or waveforms) are missing, the arithmetic means per single ECG will be computed with the reduced (1, 2 or 3) number of cardiac cycles. If individual baseline values (i.e. pre-infusion ECGs) of all treatment cycles are missing, the combined baseline will be imputed by the screening value, while the individual baseline will be considered missing. If the screening value is missing, both baselines will be considered missing. The combined baseline will be computed as the mean of all available individual baselines over all treatment cycles. In all cases where the recording time of the planned pre-infusion ECG is after the start of infusion, change from individual baseline will be set to missing and the mistimed pre-infusion ECG will be flagged in the listing displaying the individual baseline values. The combined baseline will be computed without mistimed individual baselines. If individual baselines of all infusions/courses are mistimed, the combined baseline will be imputed by the screening value (in accordance with the rules above).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline for cycle 1 analyses is the last measurement before the first drug intake in first period; The baseline for cycle 2 analyses is the last measurement before the first drug intake in the second period. The baseline for the mono-therapy is the last measurement before the first drug intake in the second peirod.

ECG

1. Individual baseline of ECG is defined as the mean of the triplicate at the time point closest to but prior to the start of infusion for each administration of volasertib.

2. Combined baseline of ECG is defined as the mean of all individual baselines of ECG across the volasertib administrations.

CTP: *For planned individual plasma concentration sampling times refer to the* CTP *Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for determination of pharmacokinetic parameter.*

Adherence to time windows will be checked via consistency check listings at the RPM/DBLM. The PK measure at 1 hour 45 mins after Volasertib infusion starts will be checked to make sure if it is measured before stop of the infusion.

7. PLANNED ANALYSIS

The format of the listings and tables will follow the standards defined in the BI corporate guideline "Reporting of clinical trials and project summaries" (5).

The individual values of all subjects will be listed, sorted by treatment sequence, subject number and visit. The listings will be included in Appendix 16.2 (SDL) of the CTR.

The following standard descriptive statistical parameters will be displayed in summary tables of continuous variables for non-PK parameters.

N	number of non-missing observations
Mean	arithmetic mean
SD	standard deviation
Min	minimum
Median	median
Max	maximum

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category, as well as the percentage (%) for each treatment. Percentages will be rounded to one decimal place. The category 'missing' will be displayed only if there are actual missing values. Percentages will be based on all subjects in each subject set.

Units of variables should be given in the titles or column/row descriptors in square brackets (e.g. [mg]).

CTP: *The following descriptive statistics will be calculated for plasma concentrations as well as for all primary and secondary PK parameters: N, arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of PK parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with 3 significant digits in the clinical trial report.*

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report, based on TS. The following variables will be displayed: Gender, Race, Age, Baseline height, weight, body surface area, and body mass index. smoking and alcohol status, baseline ECOG

7.2 CONCOMITANT DISEASES AND MEDICATION

Frequency tables are planned for this section of the report, based on the TS.

Concomitant disease will be coded using the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). The coding version number will be displayed as a footnote in the respective output.

The diagnoses and medications will be listed. Subjects without any concomitant diagnoses or concomitant therapies should be noted by a "No" in the respective column.

7.3 TREATMENT COMPLIANCE

It is not intended to list compliance separately. Any deviations from complete intake will be addressed in the RPM/DBLM (see Section 6.2).

7.4 PRIMARY ENDPOINTS

The relative bioavailability will be investigated based on the PK parameters $AUC_{0\text{-}tz}$ and C_{max} for volasertib and its main metabolite CD10899, respectively.

The statistical model used for the analyses will be a repeated measure ANOVA (analysis of variance) model on the logarithmic scale and will be based on both the primary and sensitivity PKS.

CTP: *The statistical model used for the analysis of $AUC_{0\text{-}tz}$, C_{max} of volasertib and CD10899 will be an analysis of variance (ANOVA) model with repeated measure on the logarithmic scale. The effect 'subject' will be considered as random, whereas the effect 'treatment' will be considered as fixed. The model is described by the following equation:*

$y_{km} = \mu + \tau_k + s_m + \varepsilon_{km}$, *where*

y_{km} = *logarithm of response ($AUC_{0\text{-}tz}$ or C_{max}) in subject m receiving treatment k,*

μ = *the overall mean,*

τ_k = *the k-th treatment effect, k = 1, 2,*

s_m = *the effect associated with the m-th subject, m=1,…n,*

ε_{km} = *the random error associated with the m-th subject receiving treatment k.*

CTP: *The PK parameters $AUC_{0\text{-}tz}$ and C_{max} will be log-transformed (natural logarithm) prior to fitting the ANOVA model. The difference between the expected means for log(T)-log(R) will be estimated by the difference in the corresponding least square means (point estimate) and 2 sided 90% confidence intervals based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to give the point estimator*

(geometric mean) and interval estimates for the intra-subject ratio of the geometric means for treatments test and reference.

As stated in the CTP, in case the tolerable dose of volasertib is less than the initial dose level 300mg, dose would be included as a covariate in the ANOVA model. However, as a consequence of immediate dose de-escalation after first three patients treated on 300mg and two of them discontinued after cycle 1, tolerable dose was de-escalated to 250mg and all subsequently enrolled patients were treated on 250mg. Due to the limited dose levels and sparse data available on 300mg, instead of including dose as an additional covariate in the ANOVA model according to the CTP, primary analysis using ANOVA model on log transformed PK endpoints will be performed based on the clean cohort of patients who were treated on equal dose levels (either 250mg or 300mg) throughout both cycles 1 and 2. In addition, a sensitivity analysis will be performed by including the patients with further intra-individual dose reduction from 250mg to 200mg in cycle 2. In the sensitivity analysis, dose proportionality (BI 1230.5, BI 1230.23) will be applied on individuals with dose reduced to 200mg during cycle 2 volasertib mono therapy to rescale the PK measures. However, since dose proportionality was not established for the combination therapy of volasertib + itraconazole, dose normalization will not be applied on the patient who was treated on 300mg in both cycle 1 and 2.

7.5 SECONDARY AND FURTHER ENDPOINTS

7.5.1 Key secondary endpoint

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.2 Other Secondary endpoints

CTP: The AUC0-∞ of volasertib and its main metabolite CD 10899 will be statistically assessed using the same methods as described for the primary endpoint. Relative bioavailability will not be assessed for secondary pharmacokinetic parameters.

Relative bioavailability will be assessed for secondary pharmacokinetic parameters for volasertib and CD10899.

7.7 EXTENT OF EXPOSURE

Descriptive statistics are planned for this section of the report based on the TS.

7.8 SAFETY ANALYSIS

All patients who receive at least one dose of volasertib will be included in the safety analyses. This is the treated set defined in Section 6.3.

7.8.1 Adverse Events

The analysis of adverse events will focus on events that occurred during the on-treatment period, defined from the first treatment administration until 21 days after the last administration for all patients who receive at least one administration of the study treatment regimen. Tables will display the results within each cohort defined by the starting dosage of volasertib.

The analysis of adverse events will be performed within each of the following three time periods separately (Section 6.1):

- First cycle volasertib+ itraconazole combo-therapy period
- Second cycle volasertib mono-therapy period
- Continued volasertib mono-therapy period.

The AEs occurred during screening period, itraconazole induction period, and post-study period (Section 6.1) will be listed.

Standard tabulations arranged by MedDRA SOC and preferred term (PT) will include:

- the overall incidence of adverse events (AE)
- AE intensity graded according to the common terminology criteria for adverse events (CTCAE) version 3

- AE judged to have been related to trial medication
- AE leading to dosage reduction
- AE leading to permanent treatment discontinuation
- AE identified associated with the protocol-specified significant event
- Serious AE

Listings will be produced for the following AEs

- Infections

Listings will be prepared of patients who are identified as having experienced any of the following AEs. Identification will be based upon modified MedDRA SMQ and HLT groupings.

- Mucositis
- QT prolongation
- Cardiac, combining the following SMQ
    - Cardiac failure
    - Ischaemic heart disease
    - Cardiac arrhythmia terms
- Hemorrhages SMQ
- Hepatic
    - AE identified by the SMQ
    - Listing of all ALT, AST, Tbili, and ALK over time, for patients with
    - 1) any ALT or AST ≥3x ULN combined with elevation of total bilirubin ≥ 2x ULN at the same time or
    - 2) an isolated elevation of AST and/or ALT≥5x ULN (without an elevation of bilirubin)

7.8.2 Laboratory tests

Special care must be taken to review the lab data because the data are entered manually at the sites. Any corrections will be documented.

Primary laboratory tests are defined as:

- Low values (-):calcium, creatinine clearance, haemoglobin, neutrophils, platelets, potassium, sodium, and total WBC
- High values (+): Alkaline Phosphatase, ALT, AST, CK, Creatinine, LDH, Total Bilirubin, troponin T, and uric acid

All other labs collected will be classified as secondary.

The following analyses will be presented for the primary laboratory tests:

- descriptive statistics for change from baseline (uses normalized values)
    - for the worst value during treatment, and
    - the last value during treatment
- frequency of patients with transitions in CTCAE grade from baseline to worst and last values during treatment (excludes Troponin I, uses standardized values), and
- frequency of patients with possible clinically significant abnormalities (uses standardized values).

For secondary parameters, the analyses will be restricted to:

- frequency of patients with possible clinically significant abnormalities.

GFR will be calculated from creatinine using the Cockcroft-Gault transformation. GFR will be calculated from normalized creatinine using Cockcroft-Gault. In this calculation, if normalized creatinine is less than the standard lower limit, then it was set equal to the limit.

All lab tables should be footnoted to indicate that values were excluded if they were collected more than 21 days after the stop of treatment.

7.8.3 ECG

Derivation of ECG variables

Three replicate digital ECG recordings will be collected at each time point. Each of the 3 recorded single ECGs will then be evaluated for cardiac intervals, which comprise the RR interval, PR interval, QT interval, and QRS complex. Measurements of these intervals will be made on the 4 (possibly consecutive) cardiac cycles (also denoted as beats or waveforms) from the lead chosen (usually lead II). The measurements of the cardiac cycles will be stored in the database, i.e. usually 12 values per time point. The 4 cardiac cycles will be averaged prior to the calculation of HR and HR-corrected QT intervals QTcF and QTcB.

HR will be derived from the RR interval as:

$$HR\ [bpm] = 60\ 000 / RR\ [ms]$$

QTc intervals will be calculated using Fridericia's and Bazett's formulae (QTcF and QTcB, respectively):

$$QTcF\ [ms] = (1000 / RR)^{1/3} \times QT\ [ms]$$

$$QTcB\ [ms] = (1000 / RR)^{1/2} \times QT\ [ms]$$

Further aggregation of the 3 replicate QT/QTc intervals and HRs at each scheduled time point will be performed using arithmetic means. These values will be used for the derivation of the ECG endpoints as they are specified in Section 5.4.4.

ECG analysis

The analyses of the ECG endpoints will be based on the FAS ECG, i.e., patients with artificial pacemakers will be excluded from the evaluation (descriptive statistics, frequency tables). Any notable finding (see Section 5.4.4) occurring in these patients will be flagged in the listings and has to be described separately in the clinical trial report.

All analyses described below will be applied to 'change from individual baseline' and 'change from combined baseline' (see Section 6.7). The interpretation will focus on the results involving "change from individual baseline". The analysis involving "change from combined baseline" will serve as sensitivity analysis.

Absolute values and change from baseline in QTcF interval, QTcB interval, QT interval, PR interval, HR, and QRS complex will be summarised descriptively by cycle and measurement timepoints.

Frequency tables will be provided for all categorical endpoints. Frequencies of the increases in QTcF, QTcB and QT intervals above thresholds such as 450 ms, 470 ms, and 500 ms between baseline and treatment period will be displayed in two-way shift tables.

Frequencies of patients with notable findings will be displayed as well.

Frequency tables by overall clinical interpretation and a new onset (not present at baseline) of an abnormal finding will be generated.

To evaluate the appropriateness of the QT correction methods, slopes of the relationship of QT/QTc interval versus RR interval will be estimated by applying a random coefficient model. The model will be applied to log-transformed single ECG data (i.e., to the mean of four cardiac cycles). The corresponding model includes the (natural) logarithm of RR as fixed continuous covariate and the (natural) logarithm of QT/QTc as the dependent variable and a random intercept and slope to account for inter-individual variability.

7.8.4 Vital signs

Blood pressure (BP) and pulse rate (PR) will be described with respect to changes compared to baseline values at each of the follow-up time points.

7.8.5 Physical examination

Height, weight, ECOG will be summarized using mean, median and range at each assessment time point.

8. REFERENCES

1 *001-MCG-160_RD-01*: "TSAP annotations", current version; IDEA for CON.

2 *001-MCG-156_RD-01*: "Handling of missing and incomplete AE dates", current version; IDEA for CON.

3 *001-MCG-156*: "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.

4 *CPMP/ICH/137/95*: “Structure and Content of Clinical Study Reports”, ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version.

5 *001-MCG-157*: "Display and Analysis of Laboratory Data", current version, IDEA for CON.

6 001-MCS-36-472_RD-01: “Noncompartmental Pharmacokinetic/Pharmacodynamic Analyses of Clinical Studies”.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
Final	**5-May-14**	[redacted]	None	This is the first version TSAP.
Revision 1	**23-July-14**		Section	ECG analyses sections revised. Safety endpoints are moved out of secondary endpoints to align with the protocol..