Clinical Trial Protocol

Doc. No.: c01677062-09

EudraCT No.:	2011-002367-23
BI Trial No.:	1230.24
BI Investigational Product:	Volasertib (lab code: BI 6727)
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 tumours
Clinical Phase:	I
Trial Clinical Monitor:	[redacted] Tel: [redacted] Fax:
Co-ordinating Investigator:	[redacted] Tel.: [redacted] Fax:
Status:	Final Protocol (Revised Protocol (based on global amendment 3)
Version and Date:	**4.0** **30 Jan 2017**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: n.a.			
Name of active ingredient: volasertib			
Protocol date: 18 Oct 2012	**Trial number:** 1230.24		**Revision date:** **30 Jan 2017**
Title of trial:	An open-label fixed sequence trial to investigate the potential drug-drug interaction of intrveneous volasertib co-administered with a P-gp and CYP3A4 inhibitor (itraconazole p.o.) in patients with various solid tumours		
Co-ordinating Investigator:	[redacted]		
Trial sites:	2 study centres		
Clinical phase:	I		
Objectives:	Primary objective: To investigate the influence of co-administration of itraconazole (a potent dual inhibitor of cytochrome P450 3A4 and P-gp) and volasertib on the pharmacokinetic profile of volasertib without co-administration of itraconazole Secondary objectives: To determine safety, tolerability and preliminary therapeutic effects following intravenous administration of volasertib		
Methodology:	Uncontrolled, open-label, phase I volasertib DDI (drug-drug interaction) study with a dual P-gp and CYP3A4 inhibitor (itraconazole)		
No. of patients:			
total entered:	24		
each treatment:	All 24 patients will receive volasertib in combination with itraconazole and volasertib alone in two consecutive treatment cycles		
Diagnosis :	Histo- or cytologically confirmed diagnosis of advanced/metastatic solid tumour refractory or not amenable to standard therapy		
Main criteria for inclusion:	Adult males and females with histologically or cytologically confirmed diagnosis of advanced, non resectable and / or metastatic solid tumour, for whom conventional treatment has failed, or for whom no therapy of proven efficacy exists, or who are not amenable to established forms of treatment		
Test product:	volasertib		
dose:	300 mg		
mode of admin.:	Intravenous 2 hour infusion on day 1 of each 21 day treatment cycle		

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: n.a.			
Name of active ingredient: volasertib			
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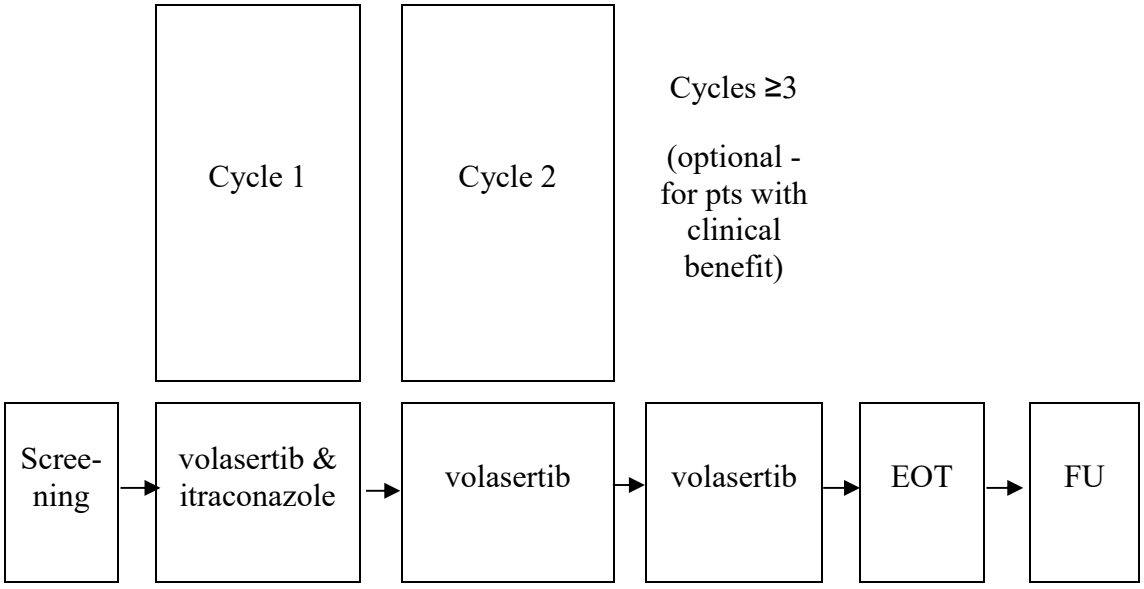
Perpetrator products:	itraconazole
dose:	200 mg qd for 18 days (total: 3600 mg)
mode of admin.:	oral
Duration of treatment:	Two cycles of treatment (with and without co-administration of itraconazole); repeated treatment cycles (volasertib monotherapy) in patients for whom clinical benefit is obtained
Pharmacokinetics endpoints:	Primary endpoints: AUC0-tz and Cmax of volasertib and its metabolite CD 10899 Secondary endpoints: AUC0-oo of volasertib and its metabolite CD 10899 [redacted] Plasma concentrations of itraconazole at selected time points All PK measurements will be performed only in first two treatment cycles.
Efficacy assessment:	Preliminary therapeutic effects will be evaluated by investigator assessment of response and clinical benefit
Safety assessment:	Adverse events according to Common Terminology Criteria for Adverse Events v3.0 (CTCAE v3.0) changes in safety lab, and in ECG
Statistical methods:	AUC_{0-tz} and C_{max} will be log-transformed prior to fitting an ANOVA model. This model will include effects for "treatment" and "subjects". 90% confidence intervals will be computed for the primary endpoints, then back-transformed to the original scale to give the point estimator and interval estimates for the geometric mean ratio (Test / Reference). Descriptive statistics for all other parameters and endpoints will be calculated.

FLOW CHART

OVERALL DESIGN



TREATMENT CYCLE 1 (volasertib **with itraconazole)**

Visit	Day #	Planned Time [h:min]	Approximate clock time of actual day [h.min]	Event and comment	Safety Laboratory[2] (S), Coagulation (C)	PK_{plasma} volasertib + CD 10899, itraconazole	Vital signs (BP and PR), ECG (digital, triplicate)	Adverse events/ Con. med
SCREEN	-14 to -4			screening[1], ECOG blood samples for additional screening lab parameters	S[2], C		X	
1	-4	-88:00	16:00	admission to trial site[3] review of in-and exclusion criteria				↑
	-3	-72:00	8:00	itraconazole 200 mg				
	-2	-48:00	8:00	itraconazole 200 mg				
	-1	-24:00	8:00	itraconazole 200 mg		X[10, 12]		
	1	-0:30	7:30	blood samples for pharmacogenomics[9]	S	X	X	
	1	-0:05	7:55	itraconazole 200 mg				
		0:00	8:00	start of iv volasertib infusion, ECOG				
		0:30	8:30				X[4]	
		1:00	9:00			X	X[4]	
		1:45[7]	9:45	physical examination		X	X	
		2:00	10:00	end of iv volasertib infusion, ECOG				
		3:00	11:00				X	
		4:00	12:00			X		
		6:00	14:00			X[11]	X[6]	
		8:00	16:00			X[11]		
		12:00	20:00			X		
	2	24:00	8:00	itraconazole 200 mg	C	X[12]	X[6]	
		36:00	20:00			X[11]		
	3	48:00	8:00	itraconazole 200 mg		X[12]		
	4	72:00	8:00	itraconazole 200 mg discharge from trial centre subjects will continue to take itraconazole 200 mg once daily until Day 15 and would receive a diary card to note down the date and time of itraconazole intake at home		X[11, 12]		
2	8	168:00	8:00	itraconazole 200 mg	S	X[11, 12]	X[4]	

Visit	Day #	Planned Time [h:min]	Approximate clock time of actual day [h.min]	Event and comment	Safety Laboratory[2] (S), Coagulation (C)	PK_{plasma} volasertib + CD 10899, itraconazole	Vital signs (BP and PR), ECG (digital, triplicate)	Adverse events/ Con. med
3	15	336:00	8:00	itraconazole 200 mg last dose physical examination, body weight, ECOG, tumour assessment, eligibility for further treatment cycle[5]	S, C	X[11, 12]	X[4]	———
4[8]	22	504:00	8:00			X[11]		

Days are calculated as calendar days (example: in case a patient is starting (day 1) on Thursday, all visits (day 8, day 15, day 22,) should occur on a Thursday

1. Screening (to be performed between 14 and one day before drug administration) including patient information, informed consent, physical examination and review of vital signs/ECG/laboratory including drug, alcohol and virus screening; also to include demographics, determination of the body weight, smoking and alcohol history, relevant medical history, concomitant medication, review of inclusion/exclusion criteria at screening and pregnancy test in women of childbearing potential
2. Safety lab includes haematology, and serum biochemistry. For detail see 5.2.3. Urinalysis (dipstick) is only performed at screening and EOT.
3. Patients should be admitted to hospital at day -4 and stay until 72h after start of infusion
4. Vital signs only
5. Only patients with clinical benefit after volasertib treatment based on investigator´s assessment (clinical response, or absence of progression, or symptom improvement) will qualify for further participation in the trial. In case of symptom improvement despite disease progression a repeated cycle may be allowed upon the agreement of the clinical monitor and the investigator.
6. ECG only
7. Shortly before end of infusion.
8. This visit may co-incide with visit 1 of treatment cycle 2
9. Can be taken also at any later time point from those patients who received at least first cycle of volasertib.
10. Analysed for itraconazole only
11. Analysed for volasertib and CD 10899 metabolite only
12. PK sampling should be taken just before itraconazole intake

TREATMENT CYCLE 2 (volasertib **without itraconazole)**

Visit	Day	Planned Time [h:min]	Approximate clock time of actual day [h.min]	Event and comment	Safety Laboratory[5] (S), Coagulation (C)	PK_{plasma} volasertib and CD 10899	Vital signs (BP and PR), ECG (digital, triplicate)	Adverse events/ Con. med
1	-1	-17:00	15:00	admission to trial site[1,2]				↑
	1	-0:30[6]	7:30	review of in-and exclusion criteria	S	X	X	
		0:00	8:00	start of iv volasertib infusion, ECOG ▲				
		0:30	8:30	|			X[3]	
		1:00	9:00	|		X	X[3]	
		1:45[8]	9:45	| physical examination		X	X	
		2:00	10:00	▼ end of iv volasertib infusion, ECOG				
		3:00	11:00				X	
		4:00	12:00			X		
		6:00	14:00			X	X[7]	
		8:00	16:00			X		
		12:00	20:00			X		
	2	24:00	8:00		C	X	X[7]	
		36:00	20:00			X		
	3	48:00	8:00			X		
	4	72:00	8:00	discharge from trial centre		X		
2	8	168:00	8:00		S	X	X[3]	
3	15	336:00	8:00			X		
4[9]	22	504:00	8:00	physical examination, body weight, ECOG, tumour assessment, eligibility for further treatment cycle[4]	S, C	X	X[3]	

1. Patients should be admitted to hospital and stay until day 4 (72h after start of infusion)
2. Pregnancy test in women of childbearing potential
3. Vital signs only
4. Only patients with clinical benefit after volasertib treatment based on investigator´s assessment (clinical response, or absence of progression, or symptom improvement) will qualify for further participation in the trial. In case of symptom improvement despite disease progression a repeated cycle may be allowed upon the agreement of the clinical monitor and the investigator.
5. Safety lab includes haematology, and serum biochemistry. For detail see 5.2.3. Urinalysis (dipstick) is only performed at screening and EOT.
6. For predose sampling of volasertib and CD 10899 in plasma, metabolic profiling, the time window is 2 hours before start of infusion.
7. ECG only
8. Shortly before end of infusion
9. This visit may co-incide with visit 1 of treatment cycle 3

SUBSEQUENT TREATMENT CYCLES (for patients with clinical benefit)

Study period	**Treatment**				**EOT[1]**	**FU[2]**
Visit	**V1**	**V2[6]**	**V3[6]**	**V4[7]**		
Day	**1**	**8**	**15**	**22**		
(day range)		(±1)	(±1)	(±2)		
Physical examination[10]	X			X	X	
ECOG performance score[10]	X			X	X	X
Body weight[10]	X			X	X	
Vital signs[10]	X	X	X	X	X	X
ECG	X[3]				X	
Tumour assessment[8]	X			X	X	
Infusion of volasertib	X					
Safety lab parameters[4]	X	X	X	X	X	
Coagulation parameters[4]	X			X	X	
Pregnancy test[9]				X		
Adverse events	X	X	X	X	X	X[5]
Concomitant therapy	X	X	X	X	X	
Termination of trial medication					X	
Treatment with any other anti-tumour drug						X
Patient status					X	X
Eligibility for further treatment cycle	X			X		

1. EOT, end of treatment. Assessments which are to be performed at the last visit (when a patient discontinues the study treatment)
2. FU, follow-up. Follow-up visit should be performed 21 days after discontinuation of study drug
3. ECG on visit V1 should be performed according to 5.2.4. After approval of the Protocol revision 3, ECG should be performed prior to and at the end of volasertib infusions as single reads using a local ECG machine. No central analysis of ECGs will be performed.
4. Safety lab includes haematology and serum biochemistry. For detail see 5.2.3. Urinalysis (dipstick) is only performed at EOT. After approval of the Protocol revision 3, safety laboratory including coagulation parameters should be done only as medically indicated at discretion of the investigator. The results should be recorded in the source data only; documentation in the eCRF is not required.
5. In case adverse events were not yet recovered at the EOT visit or if new AEs occur that are considered drug related
6. Optional visits at the investigators discretion, can be performed by phone as well
7. Visit V4 may coincide with V1 of the following cycle in case the patient continues the study treatment
8. Clinical response assessment after every cycle, radiological assessment at the investigator's discretion. After implementation of the Protocol revision 3, this efficacy data will be recorded in the source data only; documentation in the eCRF is not required.
9. Pregnancy test in women of childbearing potential after every other cycle, i,e. C4, C6, C8 etc.
10. After approval of the Protocol revision 3, physical examination, ECOG performance score, body weight, vital signs will be performed assessed/checked only as medically indicated at discretion of the investigator.

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ABBREVIATIONS

AE	Adverse Event
AUC	Area under the plasma concentration-time curve
$AUC_{0-\infty}$	Area under the plasma concnentration-time curve over the time interval from 0 to infinity
AUC_{0-tz}	Area under the plasma concnentration-time curve over the time interval from 0 to the time of the last quantifiable data point
BLQ	below the limit of quantification
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
EDC	Electronic Data Capture
EDTA	Ethylendiaminetetraacetic acid
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
GCP	Good Clinical Practice
HPC	Human Pharmacology Centre
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
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
P-gp	P-glycoprotein
q.d.	quaque die (once a day)
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

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Most advanced or metastatic human tumours are incurable despite the availability of a variety of conventional treatment modalities like surgery, cytotoxic drugs, radiation therapy, and combinations of these. Objective responses in patients with advanced disease, though frequently seen using conventional treatments, are often followed by tumour progression and death. Therefore the search for new therapeutic strategies has become an urgent priority.

Our understanding of tumour biology and cell cycle regulation in particular has increased considerably in recent years, preparing ground for novel targeted treatment principles. Mitotic kinases of the Polo family which are highly conserved in all eukaryotes have been identified as important regulators of cell division and its checkpoints (R04-0421). Polo-like kinase 1 (PLK-1) controls several key steps in the passage of cells through M phase: 1) initiation of entry into mitosis, 2) centrosome separation and maturation necessary for the formation of a bipolar mitotic spindle, 3) metaphase to anaphase transition and mitotic exit and 4) onset of cytokinesis (R04-0028). PLK-1 is a target of the DNA damage checkpoint (R04-0422). Failure of cell cycle checkpoints to arrest the cell after appropriate stimuli such as DNA damaging agents or radiation is a hallmark of tumour. These findings provide a rationale for pursuing PLK-1 inhibition as a therapeutic principle in oncology.

Recently mammalian PLK-1 was shown to be over-expressed in various human malignancies such as non-small cell lung cancer (R04-0031), colorectal cancer (R04-0034) and AML (P09-09644). The functional relevance of PLK-1 was demonstrated in *in vitro* "knock down" experiments where PLK-1 inhibition induced cell cycle arrest and apoptosis in tumour cell lines (R04-0030, R04-0423). A potential role for PLK-1 over-expression in carcinogenesis was shown both *in vitro* and *in vivo* (R04-0321). Therefore PLK-1 inhibition represents a promising new therapeutic approach with a novel mode of action in oncology.

The 1230.24 trial will investigate the potential influence of co-administration of volasertib, a highly selective and potent PLK-1 inhibitor, with itraconazole, a potent P-gp inhibitor and cytochrome P450 3A4 inhibitor.

1.2 DRUG PROFILE

Volasertib is a highly selective and potent small molecule PLK inhibitor (P09-06192). The pharmacological profile of volasertib was evaluated *in vitro* in enzymatic assays, cellular cytotoxicity assays and assays examining cell cycle progression. *In vivo* efficacy of volasertib was determined in human tumour xenografts in nude mice.

In an enzymatic assay using human recombinant kinases volasertib potently inhibited Plk1 as well as the two closely related kinases Plk2 and Plk3 (IC50 values 0.87, 5, and 56 nmol/L, respectively). In contrast, assays using a panel of >50 other kinases failed to identify any inhibitory activity at concentrations up to 10 µmol/L demonstrating the high molecular

specificity of the compound. The compound was also tested for its cellular activity on a panel of tumour cell lines. Cytotoxicity *in vitro* and inhibition of PLK-1 in enzymatic assays was achieved at comparable concentrations. Activity was not dependent on cellular origin or molecular phenotype. Cell biological profiling revealed that volasertib induces a typical PLK-1 mitotic arrest phenotype (G2/M arrest, abnormal mitotic figures) at similar concentrations. When comparing the activity in parental cell lines to the activity in the respective chemo-resistant counterparts activity of volasertib was much better conserved than the activity of conventional chemotherapeutics such as taxanes or vincristine.

Efficacy of volasertib was shown in various xenograft models. Tumour regression up to complete cures of animals was demonstrated. Tumour regression was also shown in models of larger tumours. Doses shown to be effective were well tolerated and were administered to nude mice 1-2 times per week intravenously (P09-06192).

The non-clinical safety profile of volasertib is considered favourable regarding the oncological indication and the anti-proliferative principle. In 3-cycle toxicity studies in dogs and rats mechanism -related side effects were observed in organs with high turnover as expected. Main target organs were the gastrointestinal tract (mucosal lesions), bone marrow and lymphoid. Complete reversibility even of severe lesions at higher doses was observed. Moreover no evidence for unspecific toxicity affecting other organs such as kidney or liver was found. However, an exploratory investigation on the cardiovascular system in pigs, given at very high doses of up to 30 mg/kg volasertib, showed that volasertib induced QT prolongation starting at a plasma level of 3700 nmol/L and slight QTcSE prolongation in chronically treated dogs starting at 36 mg/m2 at plasma levels of about 880 – 1090 nmol/L. The hERG channel was inhibited with an IC50 value of 2.4 µmol/L while the action potential in guinea pig papillary muscle was not affected up to 10 µmol/L. Based on these results, QT-monitoring is continued in the clinical phase I and II trials with volasertib. More detailed information is provided in the Investigator's Brochure (IB) (U05-2201).

Until October 2011 (time of data cut off for IB version 7), a total of 553 patients have been treated in clinical phase I and phase II trials with volasertib. Clinical Phase I safety data and preliminary Phase I and II data from ongoing trials show the compound to be safe with reversible suppression of haematopoiesis constituting the main side effect. The MTD for the d1q3w schedule was defined at 400 mg. 300 mg is used as the initial Phase II dose in the ongoing Phase II program in solid tumours (P10-07075).
Besides suppression of haematopoiesis (resulting in anaemia, leuko-/neutropenia, thrombocytopenia), complications associated with cytopenias (e.g. neutropenic fever / infection, bleeding) and QT prolongation no other relevant non-specific effects of volasertib have been identified so far at the dose used in solid tumor trials (300 mg d1q21d). In the AML trial volasertib is administered more frequently (d1+15q28d) and the dose per administration was further escalated. At the higher doses investigated in AML mucositis was reported, an AE that is expected from the mode of action.

1230.P1/P3/P4 7 106In the electrocardiogram (ECG) monitoring available data indicate the potential for dose dependant prolongations of QT using Fridericia's correction algorithm (QTcF) at the time of C_{max}, but no associated clinical events were reported. No other relevant unspecific toxicity has been observed as yet.

More detailed information is provided in the Investigator's Brochure (U05-2201).

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Although considerable progress has been made in understanding tumour biology as well as in developing more effective treatment regimens, most patients with locally advanced or metastatic tumours will succumb to their disease. Thus, there is a substantial need for novel therapeutic strategies to improve the outcome for patients with advanced or metastatic malignancies for whom conventional treatment has failed, or for whom no therapy of proven efficacy exists.

Cell-cycle targeted therapies represent a novel and promising approach in these patients (R04-0415). Mitotic kinases regulating cell division and its checkpoints are considered particularly attractive targets for new therapies (R04-0421). Volasertib represents a new class of small molecules targeting and blocking activation of PLK with high selectivity and specificity. This compound induces cell cycle arrest, apoptosis and tumour shrinkage at tolerable doses in preclinical tumour models. In the clinical setting antitumour activity was reported in phase I and phase II trials (see IB).

This open label phase I trial 1230.24 will investigate the influence of co-administration of volasertib and itraconazole, a potent inhibitor of P-gp and cytochrome P450 3A4 in comparison to administration of volasertib without influencing itraconazole.

In vitro tests have shown that volasertib is a substrate of cytochrome P450 3A4 as well as a highly potent inhibitor of P-gp (U08-2116, U08-3450).

Volasertib distributes rapidly into a large volume (>4000 liters). The current PK data suggest that the terminal elimination half-life represents rather the slow re-distribution of Volasertib from deeper compartments into the blood stream than the elimination from the systemic circulation. Since that Volasertib is a P-gp substrate the distribution might be influenced by P-gp inhibitors.

Male and female patients with various solid tumours for whom conventional treatment has failed, or for whom no therapy of proven efficacy exists, or who are not amenable to established forms of treatment will be treated with volasertib in this study. Volasertib will be given as a single infusion over 120 minutes on day one of the study. Based on the safety profile from study 1230.1, the first in man trial of volasertib, the recommended phase II dose of 300 mg will be given.

Determination and quantification of the influence of co-administration of itraconazole and volasertib compared to volasertib without influencing factors is the primary endpoint of this trial. This effect will be evaluated in the first two treatment cycles.

If clinical benefit from volasertib treatment is indicated, patients may receive additional cycles of volasertib. In these additional cycles no drug-drug interaction will be evaluated. Patients who experience a clinical benefit, i.e. an objective tumour response or symptom

improvement or the absence of tumour progression and who have recovered from drug-related adverse events from previous cycles are eligible for additional cycles of volasertib according to protocol.

Secondary endpoints of this trial are safety, tolerability and the assessment of preliminary therapeutic effects of volasertib.

2.2 TRIAL OBJECTIVES

The primary objective of the present study is to investigate the influence of co-administration of itraconazole (a potent dual inhibitor of cytochrome P450 3A4 and P-gp) and volasertib on the pharmacokinetic profile of volasertib without co-administration of itraconazole.
Secondary objectives are to investigate safety, tolerability and preliminary therapeutic effects following intravenous administration of volasertib.

2.3 BENEFIT - RISK ASSESSMENT

The most relevant side effect of volasertib administration is expected to be a transient inhibition of proliferation of normal dividing cells in bone marrow and mucosal tissue. The side effects on bone marrow stem cells lead to a temporary decrease in the number of blood cells and platelets(reversible events of neutropenia, febrile neutropenia, thrombocytopenia and anaemia), as reported by the DLTs and adverse events in clinical trials. . Transient inhibition of haematopoiesis may be followed by clinical symptoms and complications as e.g. infections in neutropenic patients, bleedings in thrombocytopenic patients and fatigue in anaemic patients; respective drug related adverse event were reported in the clinical trials with volasertib. The majority of adverse events of CTCAE grade 3 or higher reported in clinical trials and considered related to volasertib are decrease of blood cells (anaemia, neutropenia and thrombocytopenia) and associated complications. Inhibition of mucosal proliferation may lead to gastrointestinal symptoms such as nausea or diarrhoea, although this finding was reported only in a limited number of patients so far. Other frequently reported adverse events were reported mostly with mild to moderate severity (nausea, decreased appetite, vomiting, constipation, alopecia).. These side effects are frequently seen in tumour patients treated with conventional cytotoxics or kinase inhibitors and can easily be monitored. Supportive treatment for these effects is available.
QT prolongation was seen in preclinical models. QTcF prolongations in the 20-30ms range at C_{max} were observed in the first phase I trial without occurrence of relevant clinical events. This observation will be further characterized by ECG monitoring in the phase I and II program. Mild to moderate cardiac lesions were seen in chronically treated dogs. Given that no cardiac events were reported in patients but clinical benefit was already observed in a heavily pre-treated Phase I patient population a positive risk-benefit ratio was concluded. Nevertheless, biomarkers for cardiotoxicity (Troponin, CK) and ECGs including QTc assessment will remain a part of the clinical safety monitoring in any phase I/II study.

Cancer patients with advanced tumours and no further treatment options may benefit from tumour shrinkage, tumour stabilization or improvement of tumour-related symptoms as a result of treatment with volasertib. The potential benefit of therapy with volasertib is expected to outweigh the treatment related risks.

Restrictions for CYP3A4/Pgp inhibitors/inductors are only relevant for the drug-drug interaction part of the study, as these drugs may potentially interfere with the metabolism and distribution of volasertib. For the non-drug-drug interaction part other cytotoxic and anticancer immunotherapies are not allowed while CYP3A4/Pgp inhibitors/inductors are allowed.

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this study requires timely detection, evaluation and follow-up of laboratory alterations of selected liver laboratory parameters to ensure patients´ safety.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This trial is an uncontrolled, open-label, sequential drug-drug interaction study of volasertib and itraconazole in tumour patients. Patients with advanced, non-resectable and/or metastatic solid tumours will be eligible for the study if conventional treatment has failed or if they are not amenable to established treatment options. Patients will be assessed for eligibility at a screening visit within 14 days prior to first drug administration. For the first treatment cycle patients will receive 200 mg of itraconazole starting 3 days before the first intravenous infusion of volasertib. On day 1 patients will receive an intravenous infusion with volasertib, whilst itraconazole dosing continues for 14 days/until 336 hours after volasertib infusion. PK samples will be taken until 504 hours after start of infusion.

After this 504 hours blood sample has been withdrawn and if none of the criteria for removal of patients from therapy or assessments is met (see section 3.3.4), patients will receive a second infusion of volasertib with clinical activities as outlined in the flow chart for treatment cycle 2. This cycle will be identical to the first cycle with the exception that no administration of itraconazole occurs in cycle 2.

The patients will be admitted to hospital for the time period of itraconazole administration from 88 hours before until 72 hours after start of infusion of volasertib in cycle 1 and the night before until 72 hours after start of infusion in treatment cycle 2, subsequent treatment cycles can be administered on an outpatient basis at the discretion of the investigator. The patients will visit the investigator at regular intervals as specified in the flow chart for determination of safety laboratory parameters, recording of adverse events and additional investigations as outlined in the flow chart. A radiological assessment of tumour response will be performed at discretion of the investigator.

Initially, patients will be treated sequentially. Single patient cohorts will be treated for the first cycle until three patients have completed the first cycle.
Thereafter, cohorts of 3 patients will be treated until the preliminary safety of volasertib in combination with itraconazole is confirmed (for details see section 4.1.3.1).

After implementation of Protocol revision 3, safety laboratory parameters and additional investigations (weight, ECOG, vital signs, physical examination etc) as outlined in the Flow chart will be done as medically indicated at discretion of the investigator. Investigator will continue recording ECG prior and at the end of volasertib infusion to ensure patient safety. For this purpose investigator will use local ECG machine, centralized ECG analysis will be discontinued.
Clinical response assessment after every cycle and radiological assessment at the investigator's discretion will be continued to support the investigator´s decision on treatment continuation/discontinuation.

3.1.1 Administrative structure of the trial

The trial will be performed by investigators and study nurses experienced in phase I trials and in conducting drug-drug interaction trials. Safety laboratory tests will be performed at the investigator site. Pharmacokinetic evaluations will be performed by Boehringer Ingelheim.

On-site monitoring will be performed by a CRO appointed by Boehringer Ingelheim.

All trial relevant documentation will be stored at a CRO and will be harmonised with Boehringer Ingelheim's CTMF at the end of the trial. Trial relevant documentation which must remain at the trial site will be filed in the investigator site file (ISF) at the investigator site.

The principal investigator who will sign the clinical trial report of this trial has been appointed by Boehringer Ingelheim. The principal investigator has experience in these types of trials and investigations.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

The primary objective of this study is to determine the influence of co-administration of volasertib with itraconazole on the pharmacokinetics of volasertib in comparison to volasertib alone in cancer patients. No control group will be recruited.

The intra-individual comparison is preferred as each of the subjects will serve as his own control and the precision is therefore expected to be higher than with a group comparison.

The fixed sequence is considered appropriate for an unbiased investigation of the volasertib PK due to the neglible carry-over effect from the first treatment cycle and because unspecific time effects on the volasertib PK are not to be expected.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 24 patients, at least 8 male and 8 female, will be recruited for this study (see Section 7.6). Patients not completing treatment cycle 2 will be replaced (see Section 3.3.4.1).

24 patients will be recruited for this study in order to have at least data for 24 patients completing the first treatment cycle with co-administration of itraconazole and volasertib and the second cycle with volasertib. The recruitment period is expected to last approximately 12 months.

A log of all patients included into the study (i.e. having given informed consent) will be maintained in the ISF at the investigational site irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for study entry

Adult male and female patients with histo- or cytologically confirmed diagnosis of advanced / metastatic solid tumour.

3.3.2 Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for entry into the trial:

1. Patients with histologically or cytologically confirmed diagnosis of advanced, non resectable and / or metastatic solid tumour, for whom conventional treatment has failed, or for whom no therapy of proven efficacy exists, or who are not amenable to established forms of treatment based on the investigator's assessment
2. Male or female
3. Age ≥18 and ≤70 years
4. Written informed consent consistent with ICH-GCP and local legislation
5. Eastern Cooperative Oncology Group (ECOG) performance score ≤ 2
6. Recovery from CTCAE Grade ≥ 2 therapy-related toxicities from previous chemo-, hormone-, immuno-, or radiotherapy (except alopecia)

3.3.3 Exclusion criteria

Patients presenting with any of the following will not be included in the trial:

1. Serious concomitant non-oncological disease considered by the investigator to be incompatible with the protocol
2. Active infectious disease
3. Viral hepatitis, HIV infection
4. Clinical evidence of active brain metastasis or leptomeningeal disease during the past 6 months
5. Second malignancy currently requiring active therapy (except for hormonal / antihormonal treatment e.g. in prostate or breast cancer)
6. Absolute neutrophil count less than 1,500/mm^3
7. Platelet count less than 100,000/mm^3
8. Total bilirubin greater than 1.5 mg/dL (> 26 µmol/L, SI unit equivalent)
9. Aspartate amino transferase (AST) and / or alanine amino transferase (ALT) greater than 2.5 times the upper limit of normal (if related to liver metastases greater than five times the upper limit of normal)
!"# Serum creatinine greater than 2x ULN.
11. QTcF prolongation > 470 ms or QT prolongation deemed clinically relevant by the investigator (e.g., congenital long QT syndrome).The QTcF will be calculated as the mean of the 3 ECGs taken at screening

12. Male patients who are sexually active and having a partner with childbearing potential and unwilling to use a medically acceptable method of contraception during the trial and for at least six months after end of active therapy
13. Female patients with childbearing potential and unwilling to use a medically acceptable method of contraception during the trial and for at least six months after end of active therapy. Woman of childbearing potential (premenopausal female) is defined as the female who is not surgically sterilised by hysterectomy or bilateral tubal ligation or post-menopausal for at least 12 months.
14. Treatment with other investigational drugs or participation in another clinical trial within the past four weeks prior to start of therapy or concomitantly with this trial
15. Chemo-, radio- immuno-, or molecular-targeted cancer-therapy within the past four weeks prior to start of therapy or concomitantly with this trial. This restriction does not apply to steroids, bisphosphonates hormonal / antihormonal treatment (e.g. in prostate or breast cancer).
16. Patients unable to comply with the protocol
17. Alcohol abuse more than an average 3 units of alcoholic beverages per day or more than 21 units per week (1 unit equals 0.5 pint [285 mL] of beer or lager, 1 glass [125 mL] of wine, 25 mL shot of 40% spirit)) or drug abuse
18. Life expectancy less than 12 weeks
19. Potent CYP 3A4 and P-glycoprotein inhibitors other than the study drug or inducers between one week prior to first drug administration or expected treatment with a respective drug until the last PK sample is collected
    a) Strong CYP 3A4 inhibitors: atazanavir, clarithromycin, indinavir, itraconazole (other then study drug), ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin
    b) CYP 3A4 inducers: carbamazepine, rifampicin
    c) P-gp inhibitors: cyclosporine, erythromycin, itraconazole (other then study drug), ketoconazole, quinidine, phenobarbital salt with quinidine, ritonavir, valspodar, verapamil
    d) P-gp inducers: hypericum perforatum, rifampicin
20. History of allergy/hypersensitivity (including allergy to study drug or its excipients) based on the investigator's assessment
21. Excessive physical activities (within one week prior to administration and until the last PK sample is taken)

Exclusion criteria specific for this study:

22. Veins unsuitable for blood sampling and infusion

For study restrictions refer section 4.2.2.

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

A patient must be withdrawn from the trial if any of the following criteria apply:

- The patient withdraws consent (patients are free to discontinue their participation in this study at any time without the need to justify the decision).

In this event, the patient will be asked to have an end of treatment investigation and the data collected until the point in time when withdrawal occurred will be included in the final analysis of the trial data. No further follow-up will be performed if the patient does not agree to further visits however patients might be contacted to obtain information on patient's status.

A patient must be withdrawn from active treatment if any of the following apply:

- The patient requests discontinuation of active treatment but agrees to be followed-up
- The patient is no longer able to receive active treatment (e.g. due to adverse events, surgery, concomitant diagnoses, concomitant therapies or administrative reasons). The investigator may also stop a patient's treatment if the patient is no longer able to attend study visits e.g. due to worsening of disease
- Unacceptable toxicity occurs which does not recover to a degree that allows treatment continuation
- Further dose reductions are considered necessary but would not be permitted according to the protocol

Treatment may be stopped in an individual patient after discussion between the sponsor and the investigator if eligibility criteria are violated and/or the patient fails to comply with the protocol, e.g. no adherence to restrictions, non-attendance at study assessments.

The EOT information should be obtained. All patients who end active treatment (but not the trial) will be followed up as described in section 6.2.3.

Patients who were withdrawn during the first treatment cycle with co-administration of itraconazole and volasertib or during second treatment cycle with volasertib will be replaced, whereas patients withdrawn at a later stage will not be replaced.

3.3.4.2 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site,
2. Emergence of any efficacy/safety information that could significantly affect continuation of the trial
3. Violation of GCP, the CTP, or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial.

4. Any other administrative reasons, including discontinuation of the clinical development program with volasertib

The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

3.3.5 Re-treatment criteria for repeated cycles

To continue treatment with further cycles, the following criteria must be met:

1. Clinical benefit after volasertib treatment based on investigator´s assessment (clinical response, or absence of progression, or symptom improvement). In case of symptom improvement despite disease progression a repeated cycle may be allowed upon the agreement of the clinical monitor and the investigator
2. a) Neutrophils ≥ 1 500/mm^3 and platelets ≥ 100 000/mm^3
   b) In case criterion 2a) is not fulfilled, the peripheral blood should be re-evaluated at weekly intervals. As soon as criterion 2a) is met, the treatment should be continued unless other criteria for discontinuation or withdrawal apply (see section 3.3.4.1).
3. Acceptable tolerability (according to the investigator judgment) and recovery from drug related AEs to CTCAE levels that allow further treatment
4. Unacceptable toxicities (according to 5.2.6) are recovered to pre-treatment values or CTCAE Grade 1, whichever is higher

3.3.6 Handling of patients removed from active treatment/trial

All withdrawals will be documented and the reason for end of treatment recorded and discussed, as necessary, in the final report of the trial.

As soon as a patient is withdrawn from the trial, the next scheduled visit and the EOT should be performed if feasible. Every effort should be made to follow-up patients in case an AE is still ongoing at the time of withdrawal / at the EOT visit.

Patients who withdraw prior to first treatment will not be included in the analysis. They will be entered into the trial data base, the reason for withdrawal documented and reported descriptively and by patient listing in the final report of this trial.

Patients who do not complete the first two cycles will be replaced.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

Volasertib will be administered to the patients in two consecutive treatment cycles on day 1 of a 21 day treatment cycle. The first volasertib infusion will occur after pretreatment with itraconazole from Day-3 to Day 1. Itraconazole will be continued for another 14 days after volasertib administration. In the second cycle, volasertib will be administered without itraconazole.

Repeated treatment cycles (≥3) of volasertib monotherapy can be administered in patients for whom clinical benefit is obtained.

Volasertib doses will be calculated as free base of the chloride salt. 1.00 mg volasertib (free base) equals 1.18 mg volasertib chloride salt.

In case of unexpected toxicity due to concomitant medication of volasertib and itraconazole, a reduced dose of 250 mg or 200 mg may be administered to the patients.

4.1.1 Identity of BI investigational product and comparator product(s)

Substance:	volasertib
Pharmaceutical form:	Solution for infusion (to be diluted with saline 0.9% before administration)
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	2 mg/mL (200 mg/ 100 mL vial or 350 mg / 175 mL vial)
Posology:	Infusion over 120 minutes
Route of administration:	intravenous
Daily dose:	300 mg
Duration of use:	Single dose on day 1 of a 3 week cycle

Perpetrator Drug:

Substance:	itraconazole (Orungal®)
Pharmaceutical form:	capsules
Source:	[redacted]
Unit strength:	100 mg / capsule
Posology:	daily 200 mg
Route of administration:	oral
Daily dose:	200 mg
Duration of use:	18 days (three days before administration of volasertib, continuing from Day 1 till Day 15)

4.1.2 Method of assigning patients to treatment groups

This section is not applicable in this study.

4.1.3 Selection of doses in the trial

The data obtained from clinical studies performed to date does not indicate a deviation from dose-proportionality for volasertib within the dose ranges 12-125 mg and 200-450 mg when volasertib is administered as a constant intravenous infusion.

To meet the objectives of the study, the dose investigated was designed to cover the dose where clinical efficacy is anticipated. The selected dose for iv administration in the present study is the recommended phase II dose for solid tumour trials (P11-14366).

4.1.3.1 Potential dose reduction

Reduction of starting dose

Initially, patients will be treated sequentially. Single patients will be treated for the first cycle until three patients have completed the first cycle.

Thereafter, cohorts of 3 patients will be treated until the preliminary safety of volasertib in combination with itraconazole is confirmed.

If more than 1 out of 6 patients experiences unacceptable toxicity (DRT, Section 5.2.6) during the first treatment cycle, the dose of volasertib for subsequent patients will be deescalated to 250 mg in the first and second treatment period.

If more than 1 out of 6 patients treated at a volasertib dose of 250 mg experiences unacceptable toxicity during the first treatment cycle, the dose of volasertib for subsequent patients will be further deescalated to 200 mg in the first and second treatment period.

The highest dose for which the incidence of unacceptable toxicity is no more than 1 out of 6 will be used as the dose of volasertib for the first and second treatment cycle of all further patients included in the trial (MTD, cf. Section 5.2.6).

Dose reduction in individual patients

If a patient experiences unacceptable toxicity (DRT, Section 5.2.6) the patient can continue volasertib treatment at a lower dose if criteria for retreatment are met (see Section 3.3.5). Each occurrence of DRT will lead to a dose reduction by 50 mg of any subsequent volasertib infusion(s). No dose reduction of volasertib below 200 mg is allowed.

If a patient experiences a DRT at the 200 mg dose, i.e. a dose reduction to <200 mg would be required, the volasertib treatment will be permanently discontinued and the patient will move to the EoT visit.

When a dose reduction of volasertib occurs, this applies to all subsequent cycles with no possibility to dose escalation back to the previous dose.

4.1.3.2 Dose escalation scheme

A patient who is eligible to continue therapy with volasertib beyond the 2nd cycle (see Section 3.3.5) may either be treated with the original dose or may receive a higher dose in the third and subsequent cycles. The dose can be increased by 50 mg after each cycle ≥2 up to a maximum dose of 350 mg in case of clinical benefit and good tolerability in the completed cycle (i.e., non-hematological drug related adverse events of less than CTCAE Grade 2 and / or hematological drug related adverse events of less than CTCAE Grade 3). Dose escalation will occur only upon agreement between investigator and sponsor. Patients should continue on the higher dose in all subsequent treatment cycles if well tolerated. The decision to escalate the dose can be made at the end of cycles ≥2. No dose increases above 350 mg are allowed. After dose escalation to the 350 mg subsequent dose reductions are allowed as per Section 4.1.3.1.

4.1.4 Drug assignment and administration of doses for each patient

4.1.4.1 First cycle (combined volasertib and itraconazole administration)

The treatment to be evaluated is as outlined in Table 4.1.4.1: 1 below:

Table 4.1.4.1: 1 Treatments to be administered in the first treatment cycle

Treat-ment	Substance	Formulation	Unit strength	To be reconstituted with	Total dose [mg]
oral	itraconazole	capsules	100 mg per capsule	N/A	3600 mg (18 times 200 mg)
iv	volasertib	solution for infusion	vial of 200 mg (calculated as free base) /100 ml, 2 vials to be used or vial of 350 mg (calculated as free base) / 175 ml, 1 vial to be used	isotonic saline	300, potential dose reductions according to section 4.1.3.1

Itraconazole will be administered to the patients in 24 hour intervals, after meal, starting 72 hours before administration of the first intravenous infusion of volasertib and will continue to be given in 24 hour intervals up to Day 15 / 336 hours thereafter.

On day 1, volasertib will be administered to the patients as a two hour infusion between 8:00 and 10:00 h in the morning. The administration of the formulation will be performed under the supervision of the investigating physician or a designee. Cancer patients will receive an iv volasertib (dose according to section 4.1.3.1).

For preparation of the volasertib infusion solution, the preconcentrate of volasertib will be diluted in 0.9% physiological NaCl. For further details on the preparation of the infusion solution, please refer to the “Dilution and Handling of Clinical Trial Drug” document filed in the ISF.

4.1.4.2 Second cycle (volasertib without itraconazole administration)

The treatment to be evaluated is as outlined in Table 4.1.4.2: 1 below:

Table 4.1.4.2: 1 Treatments to be administered in the second treatment cycle

Treat-ment	Substance	Formulation	Unit strength	To be reconstituted with	Total dose [mg]
iv	volasertib	solution for infusion	vial of 200 mg (calculated as free base) /100 ml, 2 vials to be used or vial of 350 mg (calculated as free base) / 175 ml, 1 vial to be used	isotonic saline	300 potential dose reductions according to section 4.1.3.1

On day 1 of treatment cycle 2, volasertib will be administered to the patients as a two hour infusion between 8:00 and 10:00 h in the morning. The administration of the formulation will be performed under the supervision of the investigating physician or a designee. Cancer patients will receive an iv dose of 300 mg volasertib (calculated as free base) whereas dose reduction is possible.

The procedure for preparing the infusion solution is as described for treatment cycle 1.

4.1.4.3 Subsequent treatment cycles

Patients who are eligible for subsequent cycles (>2) of treatment with volasertib (for criteria to continue treatment see section 3.3.5) will receive volasertib as long as neither patient nor investigator requests treatment discontinuation. Volasertib will be administered as described for treatment cycle 1.

For possible dose reduction and dose escalation see sections 4.1.3.1 and 4.1.3.2.

4.1.5 Blinding and procedures for unblinding

Not applicable. This trial will be performed according to an open-label design.

4.1.6 Packaging, labelling, and re-supply

For details of packaging and the description of the label, refer to the ISF.

Investigational product

Volasertib will be supplied in **100 and 175** mL vials containing 200 / 350 mg volasertib, respectively. Examples of the labelling of the medication will be found in the investigator site file (ISF). Volasertib will be labelled according to Annex 13 with trial number, medication number, name of product and strengths or identification code, pharmaceutical dosage form, quantity of dosage units, route and mode of administration, term ‘clinical trial use‘ (domestic language), sponsor name and address, storage conditions, use-by date, investigator name.

Medication will be delivered to the investigators pharmacy where the total dose per patient will be prepared upon request from the investigator. For preparation of the volasertib infusion solution, the preconcentrate will be diluted in 0.9% sodium chloride. The content of more than one vial may be needed for the administration of the requested dose. For further details, please refer to the ISF.

Perpetrator

Itraconazole will be acquired as commercial product from the European market. According to Hungarian regulations, itraconazole will be regarded as IMP. Itraconazole primary packaging will be unchanged and will be re-labelled by Boehringer Ingelheim Pharma GmbH & Co. KG according to Annex 13 with trial number, medication number, name of product and strengths or identification code, pharmaceutical dosage form, quantity of dosage units, route and mode of administration, term ‘clinical trial use‘ (domestic language), sponsor name and address, storage conditions, use-by date, investigator name and the term "Keep out of reach of children" (domestic language).

Please refer to section 4.1.8 for drug accountability. All used, partially used and unused IMP will be destroyed at the site and will not be returned to the sponsor. Double signatures of study staff will be required for this on-site destruction.

4.1.7 Storage conditions

Volasertib solution for infusion as well as itraconazole will be stored in the hospital pharmacy in a limited access area at the temperature indicated on the trial drug label.

4.1.8 Drug accountability

The investigator will receive the investigational drugs (volasertib and itraconazole) delivered by the sponsor when the following requirements are fulfilled:

- approval of the study protocol by the IRB / ethics committee,
- availability of a signed and dated clinical trial contract between the sponsor and the Head of Trial Centre,
- approval/notification of the regulatory authority, e.g. competent authority,
- availability of the curriculum vitae of the principal investigator,
- availability of a signed and dated clinical trial protocol or immediately imminent signing of the clinical trial protocol,

The investigator must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or alternative disposition of unused products.

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the investigational product(s) and trial patients. The investigator will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational product(s) received from the sponsor. At the time of return to the appointed CRO, the investigator / pharmacist / investigational drug storage manager must verify that no remaining supplies are in the investigator's possession.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

All concomitant therapies to provide adequate care may be given as clinically necessary (for restrictions see 4.2.2). All concomitant therapies administered during the course of the study must be recorded in the eCRF. Trade name, indication, and dates of administration will be documented.

4.2.1 Rescue medication, emergency procedures, and additional treatment(s)

Rescue medication to reverse the action of volasertib is not available. Potential side effects of volasertib should be treated symptomatically. Symptomatic treatment of side effects or tumour-associated symptoms is allowed. During the first cycle, the use of growth factors such as granulocyte colony stimulating factor (G-CSF) for treatment of haematotoxicity is not encouraged except for life-threatening circumstances. After the first cycle, G-CSF is allowed at the discretion of the investigator and must be recorded in the eCRF.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Additional chemo-, immuno-, hormone, radio-, or molecular-targeted cancer-therapy is not permitted during the study. These restrictions do not apply to steroids and bisphosphonates as well as to hormonal / antihormonal treatment e.g. in prostate or breast cancer. For symptom control, palliative radiotherapy may be permitted after discussion with the BI Clinical Monitor.

The following potent CYP 3A4 and P-glycoprotein inhibitors or inducers are not permitted from one week prior to first drug administration until the last PK sample is collected:

Strong CYP 3A4 inhibitors: atazanavir, clarithromycin, indinavir, ketoconazole, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin
CYP 3A4 inducers: carbamazepine, rifampicin
P-gp inhibitors: cyclosporine, erythromycin, ketoconazole, itraconazole, quinidine, phenobarbital salt with quinidine, ritonavir, valspodar, verapamil
P-gp inducers: hypericum perforatum (St. John´s wort), rifampicin

4.3 TREATMENT COMPLIANCE

The study medication will be administered orally every 24 hours (itraconazole) or as an intravenous 120 minute infusion (volasertib) under supervision of the investigator or designee.

5. VARIABLES AND THEIR ASSESSMENT

A total amount of 238.5 mL blood will be taken per patient during the first two treatment cycles of the study. This amount includes blood samples for laboratory parameters and pharmacokinetic purposes. This volume of blood is considered to be acceptable from medical point of view.

Blood samples for PK should be processed as soon as possible and within 30 minutes of collection while stored on ice.

Table 5:1 Number of blood samples and total blood volume collected for the DDI part of the trial (cycles 1 and 2)

Assessment	total # samples	mL of blood per sample	Total volume of blood (mL)
Clinical Laboratory	Haematology (2)	3.0	40.5
(Screening and Follow-up visits)	Biochemistry (2)	8.5	
	Coagulation (2)	4.5	
	Serology (1)*	8.5	
Coagulation	3	4.5	13.5
Haematology	5	3.0	15.0
Biochemistry	5	8.5	42.5
Pharmacokinetic samples - volasertib and CD 10899 in plasma, itraconazole**	29	4.0	116.0
Pharmacogenomic sample	2	2.0+9.0	11.0
Total volume of blood to be drawn			**238.5**

* Only at screening
** For itraconazole aliquot only in cycle 1

5.1 EFFICACY - CLINICAL PHARMACOLOGY

5.1.1 Endpoint of efficacy

Preliminary therapeutic effects (clinical benefit as e.g. tumour response, stable disease or symptom improvement) will be assessed by investigator response assessment (clinical assessment after every cycle, radiological and other assessments at investigator's discretion).

The investigator will perform a clinical assessment at the time points specified in the Flow Chart (i.e. at time points for physical examination). An evaluation will be performed to determine whether the patient appears to be clinically benefitting from trial drugs. The clinical assessment together with other assessments (e.g. radiology) if applicable will be the basis for the investigator´s decision on continuation or discontinuation of an individual patient in the trial.

After implementation of the Protocol revision 3, the efficacy data (clinical response assessment performed after every cycle, radiological assessment at the investigator's

discretion) will not be recorded in the eCRF, investigator should capture this information only in the source data.

5.2 SAFETY

5.2.1 Endpoint(s) of safety

ECG and clinical lab tests. Furthermore, adverse events will be assessed.

After implementation of the Protocol revision 3, safety laboratory tests should be done as medically indicated at discretion of the investigator. The results are not required to be entered in the eCRF, only to be captured in the source data (see section 5.2.3).

ECG should be performed prior to and at the end of volasertib infusions as single reads using a local ECG machine without performing central ECG review (see section 5.2.4).

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalisation, is a congenital anomaly / birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Intensity of adverse event

During the study, all AEs will be recorded in the eCRF. The events will be graded according to the NCI-CTCAE Version 3 (R04-0474).

Causal relationship of adverse event

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the case report forms.

Yes: There is a reasonable causal relationship between the investigational product administered and the AE.
No: There is no reasonable causal relationship between the investigational product administered and the AE.

If a SAE is reported, the causal relationship must be provided by the investigator for all trial drugs, i.e. the BI trial drug and for all other trial drugs (i.e. perpetrator).

Worsening of underlying disease or other pre-existing conditions

Worsening of the underlying disease or of other pre-existing conditions will be recorded as an (S)AE in the (e)CRF.

Changes in vital signs, ECG, physical examination and laboratory test results

Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an (S)AE in the (e)CRF , if they are judged clinically relevant by the investigator.

Protocol-Specified Significant Events

The following is considered as Protocol-Specified Significant Event:
Hepatic injury defined by the following alterations of liver parameters:

- an elevation of AST and/or ALT ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample or
- an isolated elevation of AST and / or ALT ≥ 5 fold ULN (without an elevation of bilirubin)

Patients showing these lab abnormalities need to be followed up according to Appendix 10.1.2 of this clinical trial protocol and the "DILI checklist" provided in the ISF.

Protocol-specified significant events are to be reported in an expedited manner similar to SAEs, even if they do not meet any of the seriousness criteria – for details please see Section 5.2.2.2.

5.2.2.2 Adverse event and serious adverse event reporting

All adverse events, serious and non-serious, occurring during the course of the clinical trial (i.e., from signing the informed consent onwards through the observational phase (=21 days after last drug administration)) will be collected, documented and reported to the sponsor by

the investigator on the appropriate eCRFs / SAE reporting forms. After this defined observational period only AEs and SAEs related to the study drug and/or study design have to be reported by the investigator. Reporting will be done according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the Investigator Site File.

For each adverse event, the investigator will provide the onset date, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug. The investigator will determine the relationship of the investigational drug to all AEs as defined in section 5.2.2.1.

The investigator also has the responsibility to report any AEs occurring once informed consent has been signed and through 21 days after last dose of study administration. Any AEs reported to the sponsor during this phase must be documented in the safety database.AEs that are not yet recovered at the End of Treatment (EOT) visit will be followed until recovery or, in case of persistence, sufficient characterization of the toxic effects has been achieved and the investigator and the BI Clinical Monitor agree not to pursue them further.

Table 5.2.2.2:1 AE/SAE reporting requirements

Time period	**Reporting requirements**
Screening until 21 days after last drug intake	Report all AEs, SAEs regardless of relatedness. This includes all deaths.
Post-treatment (>21 days after last drug intake)	Report AEs and SAEs which are considered related to study drug or study design/ procedures. Please note: Acc. to this rule also Death will only be reported as SAE if considered study drug or study design/procedure related.

Patients may be admitted to hospital during selected phases of the study for administrative reasons, e.g., collection of blood for pharmacokinetic purposes. Hospitalizations for administrative reasons and other hospitalizations already planned at the screening visit need not be reported as a SAE when they are performed "as planned".

The investigator must report the following events via fax using the SAE form immediately (within 24 hours) to the sponsor: SAEs and non-serious AEs occurring at the same time as an SAE and/or which are medically related to the SAE(s), and protocol-specified significant events. With receipt of any further information to these events, a follow-up SAE report has to be provided. SAEs and non-serious AEs must include a causal relationship assessment made by the investigator.

BI has set up a list of AEs which are defined to be always serious. In order to support the investigator with the identification of these "always serious adverse events", if a non-serious AE is identified to be serious per BI definition, a query will be raised. The investigator must verify the description and seriousness of the event. If the event description is correct, the item

"serious" needs to be ticked and an SAE has to be reported in expedited fashion following the same procedure as above. The list of these adverse events can be found via the RDC-system.

The SAE form is to be forwarded to the defined unique entry point identified for the BI OPU (country-specific contact details will be provided in the Investigator Site File). This immediate report is required irrespective of whether the investigational product has been administered or not and irrespective of causal relationship. It also applies if new information to existing SAEs becomes available.

Pregnancy

In rare cases, pregnancy might occur in clinical trials. Once a female subject has been enrolled into the clinical trial, after having taken study medication, the investigator must report immediately any drug exposure during pregnancy to the sponsor. Drug exposure during pregnancy has to be reported immediately (within 24 hours or next business day whichever is shorter) to the defined unique entry point for SAE forms of the respective BI OPU (country-specific contact details will be provided in the Investigator Site File). The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up. In the absence of an (S)AE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B).

5.2.3 Assessment of safety laboratory parameters

Blood samples will be collected from venous blood at the time points indicated in the flow chart. Laboratory tests listed will be performed at the study sites and may be performed within 2 days prior to the visit day to allow a rapid decision whether the patient may be eligible for further therapy or not. All reference values of laboratory tests performed at study site should be provided to Boehringer Ingelheim.

Laboratory tests will include the parameters listed in Table 5.2.3:1.

Table 5.2.3:1 Laboratory tests

Hematology	red blood cell count (RBC), haemoglobin, hematocrit, medium corpuscular volume (MCV), white blood cell count (WBC) with differential count, and platelets
Biochemistry	glucose, sodium, potassium, calcium, creatinine, aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphatase, gamma-glutamyl transferase (GGT) lactate dehydrogenase (LDH), total bilirubin, urea, total protein, albumin, uric acid, creatine phosphokinase (CPK) and troponin T
Coagulation parameters	prothrombin time (PT), international normalized ratio (INR) where therapeutically indicated and partial thromboplastin time (PTT)
Urinalysis (only at screening and EOT)	nitrite, protein, glucose, ketone bodies, urobilinogen, urine bilirubin, erythrocytes, leucocytes, pH (all by urine dipstick)
Additional lab parameters for screening	hepatitis B surface antigen, hepatitis C antibody, HIV-1 and HIV-2 antibody (all qualitative) urine drug screening, alcohol breath test

These parameters will be assessed at time points specified in the flow chart. In case of toxicity, adequate and more frequent blood sampling may be performed at the discretion of the investigator. In case of grade 4 neutropenia, blood must be collected seven days after the first occurrence of grade 4 neutropenia at the latest.

In case of pathological findings, further evaluation should be performed and the findings documented.

After approval of Protocol revision 3, safety laboratory examinations should be done as medically indicated at discretion of the investigator. The results are not required to be entered in the eCRF; documentation in the source data is sufficient. Only in case of findings that are qualifying as an (S)AE the respective (S)AE will be reported (eCRF and SAE form if applicable).

5.2.4 Electrocardiogram

12-lead ECGs of 10 sec duration will be recorded after 5 minutes rest in supine position with every infusion of volasertib (prior to the start of infusion and immediately prior to the end of the volasertib infusion), additional ECGs will be recorded at all time points outlined in the flow chart. If ECG is in the same time point as safety lab, PK or PG sampling ECG should be recoded always before blood sampling. All ECGs must be digitally recorded in triplicate using dedicated equipment provided by a CRO. Study activities will be performed using radio controlled clocks. All other equipment using non-radio controlled clocks will be synchronized to the radio controlled watches before drug administration.

Twelve-lead resting digital triplicate ECGs will be performed at the following visits:

- Screening
- Cycle 1 Visit 1:
    - Day 1, within 30 min prior to start of infusion of volasertib
    - Day 1, immediately prior to the end of infusion of volasertib (1:45 after start of infusion). The infusion should not be finished yet at that sampling time point.
    - Day 1, 3 hours after the start of infusion;
    - Day 1, 6 hours after the start of infusion
    - Day 2, 24 hours after the start of the infusion
- Cycle 2 Visit 1:
    - Day 1, within 30 min prior to start of infusion of volasertib
    - Day 1, immediately prior to the end of infusion of volasertib (1:45 after start of infusion). The infusion should not be finished yet at that sampling time point.
    - Day 1, 3 hours after the start of infusion;
    - Day 1, 6 hours after the start of infusion
    - Day 2, 24 hours after the start of the infusion
- Cycle ≥3 Visit 1
    - Prior to the start of volasertib infusion
    - Immediately prior to the end of infusion of volasertib (1:45 after start of infusion). The infusion should not be finished yet at that sampling time point.
- End of treatment (EoT)

The recording will be checked for pathological results (to be recorded as baseline conditions or AEs according to 5.2.2.1) and signed by the investigator. In addition, a centralized evaluation of all 12-lead ECGs recorded will be performed by a CRO.

The QTcF for each time point will be calculated as the mean of the 3 ECGs taken at that time point. The machine will calculate the QTcF each time but the investigator will calculate the mean of the 3 QTcF values obtained from the machine.

Additional ECGs should be performed whenever the investigator deems necessary.

In case of QTcF > 470 ms PRIOR to the planned start of infusion of volasertib, the trial drug should not be administered. Any other obvious potential reason for the QTcF prolongation (e.g. concomitant medication) should be investigated and eliminated if possible. The patient will be asked to lie down and relax for some time (at least 30 minutes). Then the QTcF will

be re-checked in triplicate. It is acceptable to give the volasertib infusion if the QTcF recovers to ≤470 ms on the repeat triplicate ECG just prior to the infusion. If the patient's ECG does not improve (i.e, QTcF does not become ≤470 ms) upon resting, new ECGs should be performed at later time points;, volasertib should be administered as soon as QTcF is <470 ms.

In case of QTcF change from baseline (meaning prior to start of current infusion) > 60 ms with absolute QTcF ≤500 ms (Grade 2 CTCAE version 3.0) AFTER receiving volasertib, it is mandatory that patient remain at the investigative site after administration of volasertib for further ECG monitoring. The investigator will initiate further diagnostics (e.g. check electrolytes and check concomitant therapy that may be contributing to QTcF prolongation) and if required provide adequate treatment according to medical standards. The patient will be discharged from the investigative site after resolution of ECG findings (e.g. when the QTcF value is ≤470 ms on a single observation). If the patient qualifies for a subsequent volasertib administration (see Section 3.3.5), the dose of volasertib may be reduced by 50 mg (see Section 4.1.3.1) at the investigator's discretion depending on the benefit/risk ratio assessed by the investigator.

In case of QTcF prolongation to > 500 ms absolute (Grade 3 CTCAE version 3.0) AFTER receiving volasertib, it is mandatory that patient remain at the investigative site after administration of volasertib for further ECG monitoring. The investigator will initiate further diagnostics (e.g. check electrolytes and check concomitant therapy that may be contributing to QTcF prolongation) and if required provide adequate treatment according to medical standards. The patient will be discharged from the investigative site after resolution of ECG findings (e.g. when the QTcF value is ≤470 ms on a single observation). If the patient qualifies for a subsequent volasertib administration (see Section 3.3.5), the dose will be reduced (see Section 4.1.3.1). The volasertib infusion subsequent to the occurrence of QTcF >500 ms must be performed under a continuous ECG monitoring, with the possibility to transfer the patient to an intensive care unit in case of any issue.

In case of occurrence of symptoms suggestive of arrhythmia related to QTcF prolongation, patient will be hospitalized, a cardiologic evaluation will be performed and treatment provided according to medical standards. In case of occurrence of symptoms of left ventricular insufficiency, a cardiologic evaluation by a cardiologist and an echocardiogram must be performed.

In case of drug related ECG changes and whenever the investigator deems necessary, additional ECG monitoring will be performed in the respective and later cycles of treatment.

After implementation of the Protocol revision 3, ECG should be performed prior to and at the end of volasertib infusions as single reads using a local ECG machine without performing central ECG review. Only in case of findings that are qualifying as an (S)AE the respective (S)AE will be reported (eCRF and SAE form if applicable).

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

Vital signs (blood pressure (BP) and pulse rate after 5 minutes supine rest) will be recorded at the screening visit and with every volasertib infusion at the following time points: pre-infusion (after ECG) and 30 (+ 10), 60 (±10), 105 (-10) and 180 (±10) minutes after start of infusion of volasertib, on days 8 (168h) and 15 (336h) in the first two treatment cycle, at every visit during subsequent cycles, EOT and at FU.

After implementation of the Protocol revision 3, Vital signs should be collected as medically indicated at discretion of the investigator. The results are not required to be entered in the eCRF; documentation in the source data is sufficient. Only in case of findings that are qualifying as an (S)AE the respective (S)AE will be reported (eCRF and SAE form if applicable).

5.2.6 Dose reducing volasertib toxicity

Dose reducing volasertib toxicity (DRT) (i.e. unacceptable volasertib toxicity) is defined as:

- Drug related CTCAE Grade 3 or greater non-haematological toxicity (except emesis or diarrhoea responding to supportive treatment; if drug related nausea, vomiting or diarrhea is sufficiently treated but nevertheless of grade ≥3 severity, this is considered),

or

- Drug related CTCAE Grade 4 neutropenia for more than 7 days

or

- Drug related CTCAE Grade 4 thrombocytopenia.

Patients who have experienced an unacceptable toxicity are eligible for re-treatment with volasertib at a reduced dose of volasertib as per section 4.1.3.1.

The maximum tolerated dose of co-administration of itraconazole and volasertib (MTD) is defined as the highest dose for which the incidence of DRT is no more than 1 out of 6 patients.

5.3 OTHER

5.3.1 Other endpoint(s)

This section is not applicable in this study.

5.3.2 Other assessment(s)

5.3.2.1 Physical examination, height, body weight, and performance status

A general physical examination will be performed at screening, at the end of each infusion in cycles 1 and 2, 15 days after start of infusion in cycle 1 and 21 days after start of infusion in cycle 2 as well as at the end of the treatment. The same investigator should perform this examination. Physical examination will include measurement of height and body weight and the evaluation of the ECOG performance score. Height will be documented only once at screening. Weight and ECOG score will also be assessed when volasertib treatment is started and at the end of the treatment. ECOG will also be assessed at the last visit of each cycle.

After approval of Protocol Revision 3, physical examinations, weight, and ECOG performance score should be done as medically indicated at discretion of the investigator. The results are not required to be entered in the eCRF; documentation in the source data is sufficient. In case of findings that are qualifying as an (S)AE the respective (S)AE will be reported (eCRF and SAE form if applicable).

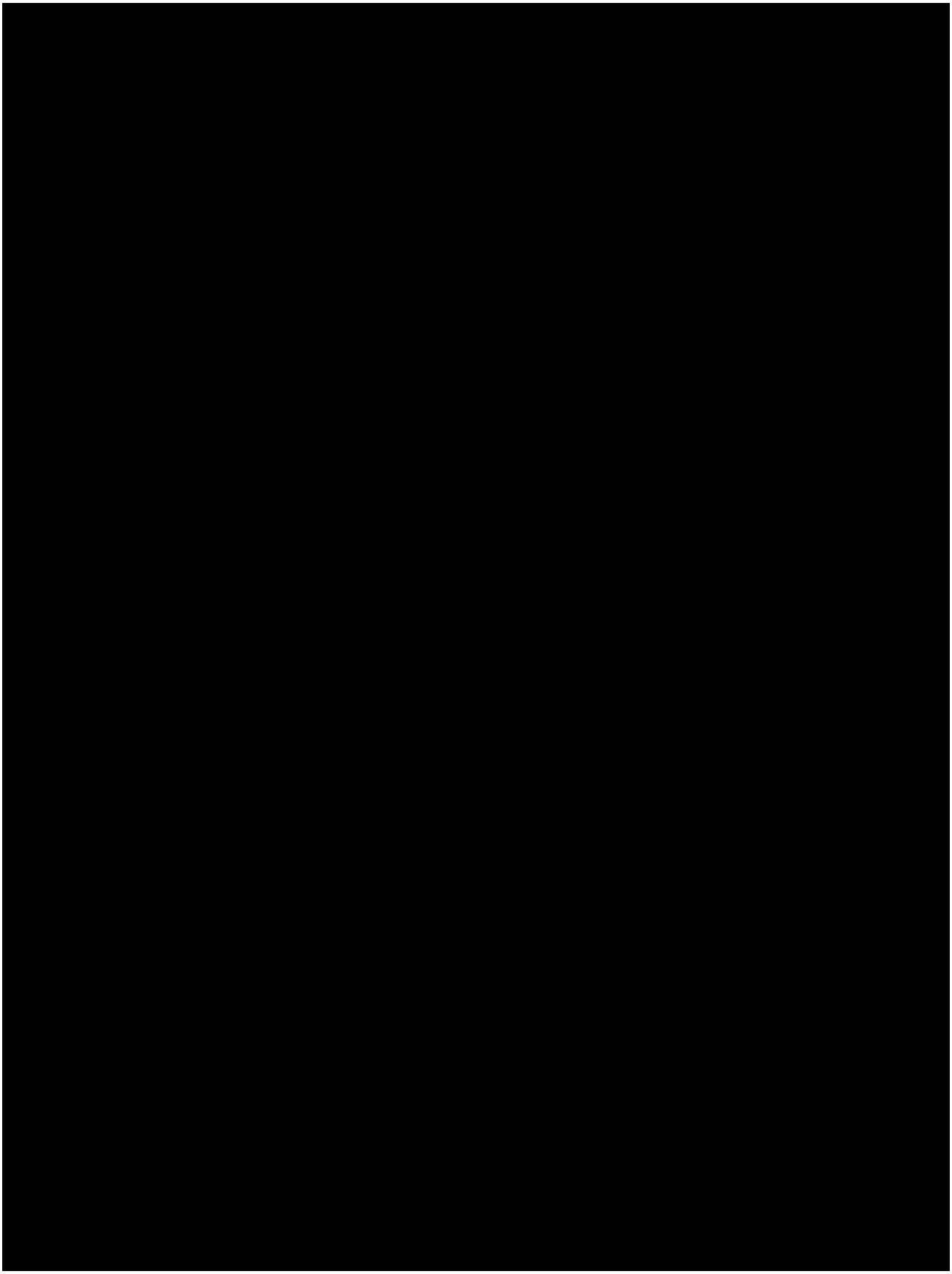
5.3.2.2 Demographics and history

Demographics (sex, birth date, race), information on smoking and alcohol status, and baseline conditions will be collected during the screening.

History of tumour will also be obtained. The type of tumour, the date of first histological diagnosis (month and year may be sufficient), and the primary tumour site will be reported into the eCRF. The differentiation grade (not specified, poorly differentiated, moderately differentiated, well differentiated), the number and location of metastatic sites as well as the stage according to the tumour, (lymph) node, metastasis (TNM) classification and the [redacted] / American Joint Committee on Cancers (AJCC) classification will be provided as obtained at diagnosis. It will also be recorded whether visceral involvement, bone involvement or soft tissue involvement is present (yes, no, unknown). Previous surgery will be reported. Previously administered radio-, chemo-, immuno-, molecular-targeted, and hormone therapy will be reported including start and end dates (month and year may be sufficient), the therapy protocol with the number of cycles (chemo-, immunotherapy), the best response obtained (complete response, partial response, stable disease, progressive disease, unknown) as well as whether the therapy was given as neoadjuvant, adjuvant, or palliative therapy. Concerning previous radiotherapy the total radiation dose and radiation field will be recorded.

5.3.2.3 Concomitant diagnoses and/or therapy

Concomitant diagnoses and/or therapies present at study entry and/or during screening will be recorded in the eCRF.



5.4 APPROPRIATENESS OF MEASUREMENTS

The assessments which will be performed in this study are standard, and generally recognised as being reliable, accurate and relevant.

5.4.1 Timing of assessments

Date and exact clock time of drug administration as well as of PK sampling must be recorded. The designation “before” on study Day 1 refers to the time period of 2 hours prior to drug administration, i.e. study measurements and assessments scheduled to occur “before” must be performed and completed within 2 hours prior to drug administration. For data management purposes, this pre-dose period is referred to in the flow chart and section 5.2 as -0:30 h.
A time window of +/- 5 % of the time from dosing to scheduled sample timepoint will be allowed for PK blood sampling. Nominal times should be adhered to as closely as possible. PK sampling time deviations of more than 5% will be identified and their handling discussed no later than at the last RPM before preliminary snapshot generation.

The duration of the volasertib infusion (planned 120 min) as well as interruptions if applicable will be documented (start and end time of the infusion) in the eCRF. Every attempt will be made to adhere to an infusion time of 120 min for volasertib with a constant infusion rate.

In the event assessments are planned for the same scheme time, the order of the assessments should be arranged in such a way that ECG will be performed before vital signs, followed by blood sampling. Blood sampling times should be adhered to as closely as possible.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Blood for pharmacokinetic analysis will be collected at specified time points during the first and the second treatment cycle (see FlowChart) to determine the plasma concentration of volasertib, its clinical relevant metabolite CD 10899 (if feasible) and itraconazole. Further exploratory analysis for identification of drug metabolites could be done if applicable. If these additional analyses are performed, the results will be reported separately. The actual sampling date and time for blood samples will be documented in the eCRF. These actual sampling times will be used for determination of pharmacokinetic parameters.

Please note that for a valid PK analysis, it is of utmost importance to document the exact clock time of trial medication administration. The duration of the volasertib infusion (planned 2 hours) will be documented (start and end time of the infusion as well as interruptions) in the eCRF. Every attempt will be made to adhere to an infusion time of 2 hours for volasertib with a constant infusion rate.

5.5.1 Pharmacokinetic endpoint(s)

Pharmacokinetic parameters will be evaluated by means of noncompartmental analysis. The derivation of pharmacokinetic parameters is described in detail in the internal SOP 001-MCS-36-472_RD-01.

Primary endpoints (volasertib and CD 10899):

- maximum measured plasma concentration (C_{max})
- area under the plasma concentration-time curve over the time interval from zero to the last quantifiable drug plasma concentration after dose administration (AUC_{0-tz})

Secondary endpoint (volasertib and CD 10899):

- area under the plasma concentration-time curve over the time interval from zero extrapolated to infinity ($AUC_{0-\infty}$)

[redacted]

All pharmacokinetic measurements will be performed only in first two treatment cycles.

5.5.2 Methods of sample collection

Actual date and time of blood collection together with the patient number should be recorded in the eCRF.

5.5.2.1 Blood sampling

During the trial PK blood samples will be collected to determine the concentration of volasertib, its metabolite CD 10899 (if feasible) and itraconazole in plasma.

PK blood samples before start of infusion and shortly before end of infusion will be taken from a forearm vein contralateral to the infusion site. For patients having a central venous catheter, volasertib may be administered using this device and PK blood samples should be obtained from either forearm. For planned times please refer to the Flow Chart.

Cycle 1:

For quantification of plasma concentrations of volasertib, the metabolite CD 10899, and itraconazole, around 4 mL of venous blood will be taken in a potassium EDTA (ethylendiaminetetraacetic acid)-anticoagulant blood drawing tube (e.g. Vacutainer® or Monovette) at the time points specified in the FlowChart.

The sampling tubes have to be mixed immediately with the anticoagulant by gently inverting about 10 times. Vigorous shaking should be avoided to prevent haemolysis. The whole blood is to be centrifuged at 4-25°C at approximately 3000 rpm (~2100 g) for at least 15 minutes. Centrifugation should be done within 60 min after sampling. The blood samples should be stored at room temperature or below until centrifugation.

From each blood sample, transfer immediately three aliquots of EDTA plasma (at least 500 µL each, aliquot 1 for volasertib/CD 10899, aliquot 2 for itraconazole, and aliquot 3 as

back-up) into carefully and unique labelled cryovials. Blood sample should be transferred always into three aliquots independent of analysis that will be performed for this time point. Please check the patient number and planned sampling time. The visit, the exact time (hh:mm, 24 h-clock time) and date (month in letter) of sampling are to be recorded in the eCRF.

Cycle 2:

For quantification of plasma concentrations of volasertib and its metabolite CD 10899 around 4 mL of venous blood will be taken in a potassium EDTA (ethylendiaminetetraacetic acid)-anticoagulant blood drawing tube (e.g. Vacutainer® or Monovette) at the time points specified in the FlowChart.

The sampling tubes have to be mixed immediately with the anticoagulant by gently inverting about 10 times. Vigorous shaking should be avoided to prevent haemolysis. The whole blood is to be centrifuged at 4-25°C at approximately 3000 rpm (~2100 g) for at least 15 minutes. Centrifugation should be done within 60 min after sampling. The blood samples should be stored at room temperature or below until centrifugation.

From each blood sample, transfer immediately two aliquots of EDTA plasma (at least 600 µL each, aliquot 1 for volasertib/CD 10899 and aliquot 2 as back-up) into carefully and unique labelled cryovials. Please check the patient number and planned sampling time. The visit, the exact time (hh:mm, 24 h-clock time) and date (month in letter) of sampling are to be recorded in the eCRF.

The plasma samples have to be stored at -20°C or below at the clinical site until shipment on dry ice to the analytical laboratory. They also will be stored at the analytical laboratory at -20°C or below until analysis.

5.6 BIOMARKER(S)

During the course of the study no biomarker will be determined.

5.6.1 Endpoints based on biomarker(s)

This section is not applicable in this study.

5.6.2 Methods of sample collection

This section is not applicable in this study.

5.6.3 Analytical determinations

This section is not applicable in this study.

5.7 PHARMACODYNAMICS

This section is not applicable in this study.

5.7.1 Pharmacodynamic endpoints

This section is not applicable in this study.

5.7.2 Methods of sample collection

This section is not applicable in this study.

5.8 PHARMACOKINETIC - PHARMACODYNAMIC RELATIONSHIP

In this study, no pharmacokinetic-pharmacodynamic relationship will be studied.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

The patients will stay at the investigator site from the evening before first itraconazole administration (day -4) until day 4 of the first cycle as well as from the day before intravenous infusion of volasertib until 72 hours after start of infusion of the second cycle (day -1 until day 4). Ambulatory visits will happen 168 hours (day 8), 336 hours (day 15) and 504 hours (day 22) after start of infusion, where the last visit may coincide with day 1 of consecutive treatment cycles. In this case the blood sample for PK has to be taken before administration of the study drug.

Procedures will be performed as outlined in the flow chart. In third and subsequent treatment cycles the patient will visit the investigator at regular intervals as specified in the flow chart (visit 2 and 3 are optional visits at the investigator's discretion) for determination of safety laboratory parameters, recording of adverse events and additional procedures as outlined in the flow chart. If a patient misses a visit and the patient reports to the investigator between this and the next scheduled visit, the missed visit should be performed with the actual date and the reason should be given for the delayed visit. The next visit, however, should take place as scheduled relative to the first administration of the trial drug in the treatment cycle.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in period

The screening phase (screen visit) i.e. after informed consent and prior to the first administration of the trial drug may be up to 14 days in duration. After written informed consent has been obtained, the investigator should perform the procedures required for screening within 14 days and prior to the first treatment within the trial.

The following will be obtained and / or performed:

- Informed consent and patient information
- Demographics (sex, birth date, race)
- Medical history (oncological, relevant non-oncological, smoking status, alcohol consumption)
- Physical examination including body height, weight, vital signs and ECOG performance score
- Patient eligibility (inclusion and exclusion criteria)
- Concomitant therapy
- Drugs of abuse in urine and alcohol breath test
- Resting 12-lead ECG
- Safety laboratory (no repeat examination in case a safety laboratory investigation has been performed within 14 days before the screening visit), including urine dipstick

- Coagulation parameters
  pregnancy test for women of childbearing potential - women of childbearing potential (premenopausal female patient) is defined as the female patient who is not surgically sterilised by hysterectomy or bilateral tubal ligation, or post-menopausal for at least 12 months.

6.2.2 Treatment period

6.2.2.1 First Treatment Cycle

The first treatment cycle will be performed under partially hospitalised conditions: For detailed timing of the assessments please refer to the flow chart.

- Physical examination
- Review of in- and exclusion criteria
- ECOG performance score
- Body weight
- ECG
- Vital signs
- Oral administration of itraconazole in 24 hour intervals
- Intravenous administration of volasertib
- Blood sampling for determination of volasertib, CD 10899 [redacted] concentrations in plasma
- Blood sampling for pharmacogenetics
- Safety lab parameters (without urinalysis)
- Coagulation parameters
- Occurrence of AEs since enrolment
- Changes in concomitant therapy
- Clinical tumour assessment
- Review of patient eligibility for repeated treatment cycles

6.2.2.2 Second Treatment Cycle

The second treatment cycle will be performed under partially hospitalised conditions: For detailed timing of the assessments please refer to the flow chart.

- Physical examination
- Review of in- and exclusion criteria
- ECOG performance score
- Body weight
- ECG
- Vital signs
- Intravenous administration of volasertib
- Blood sampling for determination of volasertib and CD 10899 concentrations in plasma

- Safety lab parameters (without urinalysis)
- Coagulation parameters
- Occurrence of AEs since enrolment
- Changes in concomitant therapy
- Clinical tumour assessment
- Review of patient eligibility for repeated treatment cycles
- pregnancy test for women of childbearing potential - women of childbearing potential (premenopausal female patient) is defined as the female patient who is not surgically sterilised by hysterectomy or bilateral tubal ligation, or post-menopausal for at least 12 months.

6.2.2.3 Subsequent treatment cycles (non-DDI)

After implementation of Protocol revision 3, safety laboratory parameters and additional investigations (body weight, ECOG, vital signs, physical examination etc) at subsequent treatment cycles will be done as medically indicated at discretion of the investigator. Investigator will continue recording ECG prior and at the end of volasertib infusion to ensure patient safety. For this purpose investigator will use local ECG machine, centralized ECG analysis will be discontinued. Findings that are qualifying as an (S)AE the respective (S)AE will be reported (eCRF and SAE form if applicable).
Clinical response assessment will be done after every cycle, radiological assessment at the investigator's discretion. After implementation of the Protocol revision 3, this efficacy data will be recorded in the source data only; documentation in the eCRF is not required.

6.2.2.3.1 Visit 1 (Day 1 of volasertib administration)

On the treatment day, the following will be obtained and / or performed:

- Physical examination
- ECOG performance score
- Body weight
- ECG
- Vital signs
- Clinical tumour assessment
- Safety lab parameters (without urinalysis)
- Coagulation parameters
- Administration of volasertib
- Occurrence of AEs since enrolment
- Changes in concomitant therapy

6.2.2.3.2 Visits 2 and 3 (day 8 and 15)

Visits 2 and 3 are optional from the second cycle onwards; the visits may be omitted at the discretion of the investigator. At these visits, the following will be obtained and / or performed:

- Vital signs
- Occurrence of AEs since last visit
- Changes in concomitant therapy
- Safety lab parameters (without urinalysis)

6.2.2.3.3 Visit 4 (day 22)

Visit 4 (day 22) is the last visit in the repeated treatment cycle. This visit may coincide with day 1 of the following treatment cycle. Examinations which are due at both the present visit and the day of volasertib administration need only to be documented once:

- Physical examination
- ECOG performance score
- Body weight
- Vital signs
- Occurrence of AEs since last visit
- Changes in concomitant therapy
- Safety lab parameters (without urinalysis)
- Coagulation parameters
- Tumour assessment at the end of each cycle
- Review of patient eligibility for repeated treatment cycles
- pregnancy test after every other cycle for women of childbearing potential - women of childbearing potential (premenopausal female patient) is defined as the female patient who is not surgically sterilised by hysterectomy or bilateral tubal ligation, or post-menopausal for at least 12 months.

6.2.3 End of trial and follow-up period

6.2.3.1 Visit at the end of treatment

The end of treatment (EOT) information should be obtained when the patient concludes active treatment in the trial, along with the information obtained at the visit scheduled for that time point. If the patient concludes the trial mid-way through a treatment cycle and not at the end of a treatment cycle, the required end of cycle information should also be collected at this time.

The following will be obtained and / or performed:

- Termination of patient's active treatment (including reason for termination or if applicable premature discontinuation of trial, date of last administration of the trial drug)
- Patient status: in case the patient had PD the date of first diagnosis of PD has to be recorded
- Physical examination, ECOG score, body weight, and vital signs
- ECG
- Safety laboratory, including coagulation parameters and urinalysis
- Occurrence of AEs since last visit
- Changes in concomitant therapy
- Clinical tumour assessment

6.2.3.2 Follow-up visit

Follow-up visits will be performed after the EOT visit for patients who are not eligible for further treatment cycles until progression of disease, death, treatment with any other anti-tumour therapy, patient is lost to follow-up, or agreement between sponsor and principal investigator not to pursue further follow up visits.

Follow-up visits should be performed at 3 months intervals or earlier if appropriate. Follow-up visits may also be performed by telephone interview in case the patient is unable to visit the investigator.

The following will be obtained and / or performed.

- Occurrence of AEs since last visit in case they are considered drug-related
- Follow-up of AEs in case they were not yet recovered at EOT
- ECOG performance score
- Treatment with any other anti-tumour drug
- Patient status: date of and reason for death (if applicable), date of progression (in case, the patient experienced PD)

If visit is performed by telephone interview at least information on progression, date of progression and date of death should be obtained.

After approval of Protocol Revision 3, Follow-up is completed 21 days after discontinuation of study drug.

6.2.3.3 End of trial

The clinical trial will be considered completed as soon as the last patient has died or was lost to follow-up. If patients are still on treatment at the time the trial report is written, these patients will either be included in a follow-up trial or alternatively kept on treatment in this trial. If patients are kept on treatment in this trial then additional data will be reported in an adequate format in appropriate reporting timelines after all of these patients will have completed follow-up.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

Objectives

The primary objective of the present study is to investigate the influence of co-administration of itraconazole, a potent dual inhibitor of cytochrome P450 3A4 and P-gp, and volasertib (Test, T) on the pharmacokinetic profile of volasertib without co-administration of itraconazole (Reference, R). Therefore the relative bioavailability of volasertib will be assessed.

Design

The study will be conducted according to an open-label, randomised, fixed sequence design. The comparisons will be intra-individual (each subject serves as his own control) and the precision is therefore expected to be higher than with a between-subject comparison [R94-1529]. The uncontrolled design with respect to potential time effects is unavoidable but still expected to deliver valid results on the volasertib PK.

Primary endpoints

Relative bioavailability of volasertib and its main metabolite CD 10899 is primarily to be determined on the basis of the parameters AUC_{0-tz}, and C_{max} (see Section 5.5.1). The derivation of these primary parameters is given in the internal SOP 029-DCP-102.

Secondary endpoints

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

The derivation of these PK parameters is presented in the internal SOP 029-DCP-102.

Safety and tolerability will be determined on the basis of the following parameters: adverse events, ECG, and clinical lab tests.

[redacted]

The derivation of these PK parameters is presented in the internal SOP 001-MCS-36-472_RD-01.

If deemed necessary, statistical assessments will be conducted.

Model

The statistical model used for the analysis of the primary and secondary PK endpoints will be an ANOVA (analysis of variance) model on the logarithmic scale. This model will include effects accounting for the following sources of variation: 'subject' and 'treatment'. The effect 'subject' will be considered as random, whereas the 'treatment' effect will be considered as fixed. For tests on treatment effects, the denominator sum of squares will be the sum of squares for error in the comparison R – T. The model is described by the following equation

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

y_{km} = logarithm of response measured on subject m receiving treatment k,

μ = the overall mean,

s_m = the effect associated with the mth subject, m = 1, 2, ..., n,

τ_k = the kth treatment effect, k = 1, 2,

e_{km} = the random error associated with the mth subject who received treatment k.

The subdivision into male / female subjects is not expected to have influence on the intra-individual treatment comparisons and therefore 'sex' is not a model term.

In case the 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. The model will take into account the dose proportionality established for volasertib.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of volasertib in combination with itraconazole compared volasertib alone will be investigated descriptively by applying the average bioequivalence method to the ratio between PK parameters (AUC_{0-tz} and C_{max}). No confirmatory hypothesis will be tested.

7.3 PLANNED ANALYSES

7.3.1 Primary analyses

The pharmacokinetic 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 and interval estimates for the geometric mean intra-subject ratio between response under test and response under reference.

All evaluable subjects who received at least one dose of volasertib will be included in the pharmacokinetic analysis. Subjects who are considered as not evaluable will be listed with their individual plasma concentrations and individual pharmacokinetic parameters, however, will not be included in descriptive statistics for plasma concentrations, pharmacokinetic parameters or other statistical assessment.

Concentrations will be used for graphs and calculations in the format that is reported in the bioanalytical report. Noncompartmental pharmacokinetic analyses of the plasma concentration-time data will be performed using a validated software program, e.g. Winnonlin Version 5.2. Only concentrations within the validated concentration range will be used for the calculation of pharmacokinetic parameters. For pre-dose samples, the actual sampling time will be set to zero.

Plasma concentrations will be plotted graphically versus time for all evaluable subjects as listed in the drug plasma concentration-time tables. For the presentation of the mean profiles, the geometric and arithmetic mean and the planned blood sampling times will be used. If the actual sampling time deviates significantly from the planned time, the corresponding plasma concentration will be excluded from the calculation of descriptive statistics.

The following descriptive statistics will be calculated for analyte concentrations as well as for all pharmacokinetic 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 pharmacokinetic 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 three significant digits in the clinical trial report.

7.3.2 Secondary analyses

7.3.2.1 Secondary pharmacokinetic parameters

Relative bioavailability will not be assessed for secondary pharmacokinetic parameters. Apart from this, the same methods as described for primary pharmacokinetic endpoints will be used to analyse the secondary endpoints.

7.3.2.2 Safety and tolerability analyses

Refer to section 7.3.3 for a description of the analysis of safety and tolerability.

7.3.3 Safety analyses

All patients who receive at least one dose of study drug will be included in the safety evaluation. Safety analyses will be performed in accordance with BI standards.

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Adverse events occurring prior to drug administration will be assigned to the screening period. Adverse events occurring within 21 days of most recent volasertib infusion will be considered to be on treatment.

Independent of this rule, the relationship of an adverse event to the study drug treatments will be assessed by the investigator. Adverse event information as reported in the eCRFs will be aggregated in a two step process. First, multiple recordings (AE occurrences) of the same adverse event will be combined into one AE episode (collapsing). The second step will combine all of the AE episodes of an adverse event into one AE record as needed for by-patient summaries (condensing).

Reporting of adverse events and laboratory data will follow the standard BI procedures. The analysis of adverse events will comprise various frequency tabulations. Tables will be produced for treatment cycle 1 (co-administration of volasertib and itraconazole), treatment cycle 2 (volasertib alone) and for all treatment cycles combined. DRTs and the MTD (see Section 5.2.6) will be reported.

Laboratory values will be listed, tabulated and compared with their reference ranges. They will also be assessed with regard to possible changes compared to baseline values and with regard to the comparison of the first and second treatment cycle. The frequency of possible clinically significant abnormalities will be tabulated.

Safety will also be assessed by evaluation of physical examination (see Section 7.3.8), vital signs (blood pressure, pulse rate) and 12-lead ECG. Change from screening and/or baseline as well as change between treatment cycle 1 and 2 will be compared descriptively.

7.3.4 Interim analyses

No formal interim analysis is planned. However a review of all data relevant for safety will be performed after the first three patients were included. In case of unacceptable toxicity, the dose of drug might be reduced to 250 mg or 200 mg according to the dose deescalation scheme in Section 3.1. Therefore, reviews of safety will be performed after cohorts of three patients have been dosed.

7.3.5 Pharmacokinetic analyses

Refer to Section 7.3.1, 7.3.2.1 and 7.3.8 for primary, secondary [redacted] analyses.

7.3.6 Biomarkers, pharmacodynamic analyses and pharmacokinetic – pharmacodynamic relationship

This section is not applicable in this study.

[redacted]

7.3.8 Other analyses

Preliminary therapeutic effects of volasertib based on the investigator response assessment will be summarised descriptively.

[redacted]

Physical examination data will be summarised descriptively.

Demographics, tumour history as well as concomitant diagnoses and/or therapy will be summarised descriptively.

7.4 HANDLING OF MISSING DATA

7.4.1 Safety

With respect to safety evaluations, it is not planned to impute missing values.

7.4.2 Plasma concentration - time profiles

Concentration data identified with NOS (no sample), NOR (no valid result), NOA (not analyzed), BLQ (below the limit of quantification), and NOP (no peak detectable) will be ignored and not replaced by zero at any time point (applies also to the lag phase). Descriptive statistics of concentrations at specific time points will be calculated only when at least 2/3 of the individuals have concentrations within the validated concentration range. The overall sample size to decide whether the "2/3 rule" is fulfilled will be based on the total number of samples intended to be drawn for that time point (i.e. BLQ, NOR, NOS, NOA, NOP are included).

7.4.3 Pharmacokinetic parameters

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.

Every effort will be made to include all concentration data in an analysis. If not possible, a case to case decision is required whether the value should only be excluded from half-life estimation or the complete analysis.

- If a concentration is only excluded from half-life determination, it will be used for all other calculations (e.g. descriptive statistics) and for graphical presentation.
- If a concentration value is excluded from all calculations, it will not be presented graphically or used for the calculation of descriptive statistics and parameter determination. However the excluded concentration itself will be listed in the tables in section 15 of the clinical trial report associated with an appropriate flag.

Descriptive statistics of parameters are calculated only when at least 2/3 of the individual parameter estimates of a certain parameter are available. If the actual sampling time will not be recorded or will be missing for a certain time point, the planned time will generally be used for this time point instead. PK parameters which cannot be determined will be identified by "not calculated" (NC).

7.4.4 Efficacy

With respect to efficacy evaluations, it is not planned to impute missing values.

7.5 RANDOMISATION

This is a fixed sequence design; no randomization to a treatment or sequence is necessary.

7.6 DETERMINATION OF SAMPLE SIZE

The planned sample size of 24 evaluable patients is not based on a power calculation, but is conventional, and is judged as being adequate for the objectives of this study. This sample size considers that patients who were withdrawn during the first treatment cycle will be replaced. Ideally, the patients should be subdivided 12+12 into male and female subjects but for practical reasons a minimum of 8 subjects of each sex is acceptable.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study patients against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP.

The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

Hungarian data protection regulations will apply to the personal data generated throughout this trial.

Insurance Cover: The terms and conditions of the insurance cover are made available to the investigator and the patients via documentation in the ISF (Investigator Site File).

8.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

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

The patient must be informed that his / her medical records may be examined by authorised monitors (CML/CRA) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate *IRB / IEC* members, and by inspectors from regulatory authorities.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees or by IRBs or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

Case Report Forms (CRFs) for individual patients will be provided by the sponsor via remote data capture. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial; also current medical records must be available.

For eCRFs all data must be derived from source documents.

8.3.2 Direct access to source data and documents

The investigator / institution will permit trial-related monitoring, audits, IRB review and regulatory inspection, providing direct access to all related source data / documents. eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate (CRA) / on site monitor and auditor may review all eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore a unique reference document for the evaluation of listedness needs to be provided. For the BI 6727 this is *the current version of the Investigator's Brochure (U05-2201) or the*

Company Core Data Sheet (CCDS). The current versions of these reference documents are to be provided in the ISF. No AEs are classified as listed for matching placebo, study design, or invasive procedures.

8.4.2 Expedited reporting to health authorities and IECs/IRBs

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs) to health authorities and IECs/IRBs, will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the Investigator Site File.

8.5 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the *IRB* and the regulatory authorities, *i.e. the CA*.

8.6 COMPLETION OF TRIAL

The EC/competent authority in each participating EU member state needs to be notified about the end of the trial (last patient out, unless specified differently in section 6.2.3 of the CTP) or early termination of the trial.

9. REFERENCES

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10. APPENDICES

10.1 CLINICAL EVALUATION OF LIVER INJURY

10.1.1 Introduction

Alterations of liver laboratory parameters, as described in section 5.2.2.1 (Protocol-Specified Significant Events), are to be further evaluated using the following procedures:

10.1.2 Procedures

Repeat the following laboratory tests: ALT, AST, and bilirubin (total and direct) - within 48 to 72 hours and provide additional blood sample to the central laboratory for automatic reflex testing of the below listed laboratory parameters. Only in case whereby the central laboratory is not immediately available (e.g. if the logistics are such that the patient´s repeat specimen would not reach the central laboratory in a reasonable timeframe), ALT, AST, and bilirubin (total and direct) will be evaluated by local laboratory and results are made available to the investigator and to BI as soon as possible. If in such a case ALT and/or AST ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN or an isolated elevation of AST and / or ALT (without an elevation of bilirubin) are confirmed, results of the laboratory parameters described below must be made available to the investigator and to BI as soon as possible.

In addition,

- obtain detailed history of current symptoms and concurrent diagnoses and medical history according to the “DILI checklist” provided in the ISF
- obtain history of concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets according to the “DILI checklist” provided in the ISF
- obtain history of exposure to environmental chemical agents (consider home and work place exposure) according to the “DILI checklist” provided in the ISF

and report these via the CRF.

Biochemistry:
Alkaline phosphatase, albumin, PT or INR, CK, CK-MB, ceruloplasmin, α-1 antitrypsin, transferrin, amylase, lipase, fasting glucose, cholesterol, triglycerides

Serology:
Hepatitis A (Anti-IgM, Anti-IgG), Hepatitis B (HBsAg, Anti-HBs, DNA), Hepatitis C (Anti-HCV, RNA if Anti-HCV positive), Hepatitis D (Anti-IgM, Anti-IgG), Hepatitis E (Anti-HEV, Anti-HEV IgM, RNA if Anti-HEV IgM positive), Anti-Smooth Muscle antibody (titer), Anti-nuclear antibody (titer), Anti-LKM (liver-kidney microsomes) antibody, Antimitochondrial antibody, Epstein Barr virus (VCA IgG, VCA IgM), cytomegalovirus

(IgG, IgM), herpes simplex virus (IgG, IgM), varicella (IgG, IgM), parvovirus (IgG, IgM), toxoplasmosis (IgG, IgM)

11.DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		**1**
Date of CTP revision		**10 Dec 2012**
EudraCT number		**2011-002367-23**
BI Trial number		**1230.24**
BI Investigational Product(s)		**Volasertib**
Title of protocol		**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 tumours**
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		**TREATMENT CYCLE 1 (**volasertib **with itraconazole) flow chart**
Description of change		Change 1: Footnote 10. was added Change 2: Footnote 11. was added Change 3: Footnote 12. was added
Rationale for change		Changes 1 and 2: To specify volasertib and CD 10899 metabolite and/or itraconazole to be analysed at certain timepoints. Change 3: To clarify PK sampling in relation to itraconazole intake.
Section to be changed		5.2.4 Electrocardiogram

Description of change		Change 1: PGx changed to PG Change 2 and 3: nabios was deleted
Rationale for change		Change 1: Typo correction. Changes 2 and 3: Another vendor will provide central ECG.
Section to be changed		5.3.3 Pharmacogenomic evaluation
Description of change		To specify PG sampling time and correct tubes to be used
Rationale for change		Minor clarifications to PG sampling.
Section to be changed		5.5.2.1 Methods of sample collection, Blood sampling
Description of change		Change 1: A sentence was added for central venous catheter. Change 2: Following sentence was added: "Blood sample should be transferred always into three aliquots independent of analysis that will be performed for this time point."
Rationale for change		Change 1: To clarify taking PK blood sample at patients with central venous catheter. Change 2: To clarify PK sample handling.
Number of global amendment		**2**
Date of CTP revision		**12 June 2014**
EudraCT number		**2011-002367-23**
BI Trial number		**1230.24**
BI Investigational Product(s)		**Volasertib**
Title of protocol		**An open-label fixed sequence trial to investigate the potential drug-drug interaction of intravenous volasertib co-administered with a Pgp and CYP3A4 inhibitor (itraconazole p.o.) in patients with various solid tumours**
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent		☐

Authority to be notified of change with request for approval		
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS
Description of change		Change 1: 'Objective' was changed to 'endpoint'. Change 2: A sentence was added for PK measurements. Change 3: 'Assessment' was added for efficacy and safety.
Rationale for change		Change 1: The mentioned parameters are endpoints no objectives. Change 2: PK samples are taken only in the first two treatment cycles. Change 3: To clarify these parameters.
Section to be changed		ABBREVIATIONS
Description of change		$Ae_{t1\text{-}t2,}$ $CL_{R,t1\text{-}t2}$ and fe t1-t2 parameters were deleted.
Rationale for change		Typo; urine sample is not collected thus these parameters are not calculated.
Section to be changed		4.1.1. Identity of BI investigational product and comparator product(s)
Description of change		Change 1: 175 mL vial was added with content. Change 2: Content for 100 mL vial was deleted for daily dose.
Rationale for change		Changes 1: In next IMP re-supply 175 mL vials will be provided instead of 100 mL; both vial sizes will be permitted to usage. Change 2: Content was applicable only for 100 mL vial.
Section to be changed		Table 4.1.4.1: 1 Treatments to be administered in the first treatment cycle
Description of change		175 mL vial was added with content as well as no. of vial to be used.

Rationale for change		As of next IMP re-supply both vial sizes will be permitted to usage.
Section to be changed		Table 4.1.4.2: 1 Treatments to be administered in the second treatment cycle
Description of change		175 mL vial was added with content as well as no. of vial to be used.
Rationale for change		As of next IMP re-supply both vial sizes will be permitted to usage.
Section to be changed		4.1.6 Packaging, labelling, and re-supply
Description of change		Change 1: 175 mL was also added as well as 350 mg respectively.
Rationale for change		In next IMP re-supply 175 mL vials will be provided instead of 100 mL.
Section to be changed		5.2.1 Endpoint(s) of safety
Description of change		Adverse event was deleted as endpoint, however added that it will be also assessed.
Rationale for change		Adverse event is not an endpoint.
Section to be changed		5.2.2.1 Definitions of adverse events
Description of change		Isolated elevation of AST and / or ALT clarified.
Rationale for change		Typo correction.
Section to be changed		5.5.1 Pharmacokinetic endpoint(s)
Description of change		Change 1: SOP number corrected. Change 2: 'Objective' was changed to 'endpoint'. Change 3: AUC_{0-tz} 336 hours changed to the last quantifiable drug plasma concentration after dose administration. Change 4: Under Other objectives the last three parameters were deleted. Change 5: A sentence was added for PK measurements.
Rationale for change		Change 1: To reflect current applicable SOP. Change 2: The mentioned parameters are endpoints no objectives. Change 3: To clarify AUC_{0-tz} Change 4: Typo; urine sample is not collected thus these parameters cannot be calculated.

		Change 5: PK samples are taken only in the first two treatment cycles.
Section to be changed		7.1 STATISTICAL DESIGN - MODEL
Description of change		Change 1: $Ae_{0\text{-}tz}$, $fe_{0\text{-}tz}$, $CL_{R,t1\text{-}t2}$ parameters were deleted. Change 2: SOP number corrected. Change 3: A sentence was added for statistical assessments.
Rationale for change		Change 1: Typo; urine sample is not collected thus these parameters are not calculated. Change 2: To reflect current applicable SOP. Change 3: Statistical assessments are not described clearly.
Number of global amendment		**3**
Date of CTP revision		**30 Jan 2017**
EudraCT number		**2011-002367-23**
BI Trial number		**1230.24**
BI Investigational Product(s)		**Volasertib**
Title of protocol		**An open-label fixed sequence trial to investigate the potential drug-drug interaction of intravenous volasertib co-administered with a Pgp and CYP3A4 inhibitor (itraconazole p.o.) in patients with various solid tumours**
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐

Section to be changed		Title Page
Description of change		Trial clinical monitor name and telephone number were changed.
Rationale for change		Trial clinical monitor has been changed in the trial.
Section to be changed		Flowchart (subsequent treatment cycles)
Description of change		Change 1: Physical examination, ECOG performance score, body weight, vital signs, ECG Safety lab parameters, coagulation parameters were updated. Change 2: Follow up visit should be performed 21 days after discontinuation of study drug.
Rationale for change		Due to discontinuation of the Volasertib program the procedures of the study have been simplified and to be done in accordance with local standard of care. ECG will not be centrally evaluated and to be performed by using local ECG device.
Section to be changed		3.1 Overall trial design and plan 5.1.1 Endpoints of efficacy 5.1.2 Endpoints of safety 5.2.3 Assessment of safety laboratory parameters 5.2.4 Electrocardiogram 5.2.5.1 Vital signs 5.3.2.1 Physical examination, height, body weight and performance status 6.2.2.3 Subsequent treatment cycles (non-DDI)
Description of change		Text stating that physical examination, ECOG performance score, body weight, vital signs, ECG Safety lab parameters, coagulation parameters will be done in accordance with local standard of care. ECG will not be centrally evaluated and to be performed by using local ECG device. Efficacy data will be recorded in the source data only; documentation in the eCRF is not required.
Rationale for change		Due to discontinuation of the Volasertib program the procedures of the study have been simplified and to be done in accordance with local standard of care.
Section to be changed		6.2.3.2 Follow up visit
Description of change		Follow up visit should be performed 21 days after discontinuation of study drug.
Rationale for change		Due to discontinuation of Volasertib program the procedures of the study have been simplified and to be done in accordance with local standard of care.

APPROVAL / SIGNATURE PAGE

Document Number: c01677062 **Technical Version Number:9.0**

Document Name: clinical-trial-protocol-revision-3

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 tumours

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval–Clinical Monitor	[redacted]	30 Jan 2017 13:56 CET
Approval-Team Member Medicine		30 Jan 2017 15:37 CET
Approval-Therapeutic Area[redacted]		31 Jan 2017 08:54 CET
Author-Trial Clinical Pharmacokineticist		31 Jan 2017 16:40 CET
Author-Trial Programmer		03 Feb 2017 15:41 CET
Verification-Paper Signature Completion		06 Feb 2017 15:33 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**