Boehringer Ingelheim Belgium

Boehringer Ingelheim

[redacted]

Clinical Trial Protocol

EudraCT No.:	2005-002500-42
BI Trial No.:	
Investigational Product(s):	BI 6727
Title:	An open phase I single dose escalation study of BI 6727 administered intravenously in patients with advanced solid tumours with repeated administration in patients with clinical benefit
Clinical Phase:	I
Trial Clinical Monitor:	[redacted] Phone: [redacted] Fax: [redacted] E-mail : [redacted]
Principal Investigator:	[redacted] Phone: [redacted] Fax: [redacted] E-mail: [redacted]
Status, Version, and Date of Protocol:	Final, 3 October 2005
Planned Dates of Trial:	October 2005 – February 2007

SIGNATURE PAGE(S)

Trial Clinical Monitor

Date [redacted]

Trial Statistician

Date [redacted]

Team Member Medicine

Date [redacted]

Therapeutic Area

Date [redacted]

Trial Clinical Pharmacokineticist

Date [redacted]

PRINCIPAL INVESTIGATOR SIGNATURE

_____

STUDY TITLE: An open phase I single dose escalation study of BI 6727 administered intravenously in patients with advanced solid tumours with repeated administration in patients with clinical benefit

STUDY NUMBER: 1230.1.....

I herewith certify that I agree to adhere to the trial protocol and to all documents referenced in the trial protocol.

INVESTIGATOR: [redacted] **SIGNATURE**:_____

AFFILIATION: [redacted]

DATE:

LOCAL SIGNATURES
(PRINCIPAL INVESTIGATOR OF SITE AND CLINICAL MONITOR LOCAL)

CLINICAL MONITOR

LOCAL:

Date [redacted]

Name
Organisation/Department [redacted]

I herewith certify that I agree to adhere to the trial protocol and to all documents referenced in the trial protocol.

PRINCIPAL

INVESTIGATOR (site):

Date [redacted]

Name
Organisation/Department [redacted]

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: [redacted]		**Tabulated Trial Protocol**	
Name of finished product: NA			
Name of active ingredient: BI 6727			
Protocol date 03 October 2005	**Trial number** 1230.1	**Planned study period** 10/2005 – 02/2007	
Title of study:	An open phase I single dose escalation study of BI 6727 administered intravenously in patients with advanced solid tumours with repeated administration in patients with clinical benefit		
Investigator :	[redacted]		
Study centre :	[redacted]		
Clinical phase:	I		
Objectives:	Safety, maximum tolerated dose (MTD), pharmacokinetics, efficacy		
Methodology:	Uncontrolled, open label, dose escalation		
No. of subjects entered:			
total:	Up to 80		
each treatment:	3 to 6 per level, 24 at MTD		
Diagnosis and main criteria for inclusion	Patients with a confirmed diagnosis of an advanced and/or metastatic solid tumour refractory to standard therapy or not amenable to standard therapies		
Test product(s) :	BI 6727		
dose:	Start dose of 12 mg		
mode of admin. :	Intravenous, once every 21 days		
Reference therapy:	n.a.		
dose:			
mode of admin. :			
Duration of treatment:	Single dose, repeated treatment courses in patients with clinical benefit		
Criteria for efficacy:	Tumour response, time to progression, pharmacokinetic profile of BI 6727		
Criteria for safety:	Adverse events according to common terminology criteria for adverse events (CTCAE) v.3.0, laboratory evaluations, patient performance, vital signs		
Statistical methods:	descriptive statistics Kaplan Meier method for time to progression analysis		

FLOW CHART: INITIAL TREATMENT COURSE

Study Periods	Screening	Treat-ment	Observation after Treatment						EOT[f]	FU
		course 1								
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**		
Day	**-14 - 0**	**1**	**2**	**3**	**5**	**8**	**15**	**22**		
(day range)					**(±1)**	**(±1)**	**(±1)**	**(±2)**		
Informed Consent and Subject Information	x									
Demographics	x									
Genotyping		x[j]								
Medical History	x									
In- /Exclusion Criteria	x	x								
Physical Examination	x								x	x[b]
ECOG performance score	x	x						x	x	x
Pregnancy test	x									
MRI, CT[a]	x							x[a]		x
EUS, US (optional)	x							x		x
Body weight	x	x							x	
ECG	x	x[k]						x		x[b]
Infusion BI 6727		**x**								
Vital Signs	x	x	x	x	x	x	x	x	x	
Safety lab parameters	x	x	x	x	x	x	x	x		x[b]
Tumour markers[i]	x							x		
Urine examination	x		x						x	
Pharmacokinetics (plasma)		x[c]	x[c]	x[c]	x[c]	x[c]	x[c]			
Pharmacokinetics (urine)		x[h]	x[h]	x[h]						
Adverse Events		x	x	x	x	x	x	x	x	x[e]
Concomitant Therapy	x	x	x	x	x	x	x	x		
Tumour assessment[a]	x							x[a]		x
Conclusion of Subject Participation									x	

[a] according to RECIST guidelines. Imaging and assessment are required at the end of every other treatment course.
[b] optional
[c] for time schedule of pharmacokinetic sampling refer to table (Appendix 10.2), plasma samples have to be drawn from the opposite arm of the infusion. For patients having central venous access, BI 6727 may be administered using this device and PK samples obtained from either forearm. Intensive PK blood sampling performed in Course 1 only; for repeated courses PK blood sampling performed at the end of infusion (1:00h) after 24:00h, 168:00 h and after 336:00h (Appendix 101.2).
[e] if not yet recovered at the end of the previous course and in case of new adverse events if drug related
[f] end of treatment; investigations which have to be performed at the last visit (when a patient discontinues the study)
[g] data from visit 8 may be used in case EOT examinations were done within the past four weeks
FU= follow up visits until progression, lost to follow up or treatment with another anti-cancer drug

[h] one blank urine will be sampled prior to the infusion on visit 2 (at least two 2 mL aliquots), additionally urine will be collected for 24 h intervals (0-24 and 24-48 h)
[i] in applicable tumour types of the underlying disease (c.f. 5.2.5)
[j] Six (6) mL blood collected into an EDTA tube and processed as outlined in Appendix 10.3.3 for Cytochrome P450 (CYP2D6, CYP2C19, CYP2C9) and N-acetyltransferase (NAT2) genotyping
[k] before administration and directly after completion of infusion

FLOW CHART: REPEATED TREATMENT COURSES

Study Periods	**Repeated treatment courses**					**EOT[f]**	**FU**
Visit	**1**	**2**	**3**	**4**	**5**		
Day	**1**	**2**	**8**	**15**	**22**		
(day range)			**(±1)**	**(±1)**	**(±2)**		
Physical Examination	x[g]					x	x[b]
ECOG performance score	x				x	x	x
Pregnancy test	x						
MRI, CT[a]					x[a]		x
EUS, US (optional)					x		x
Body weight	x					x	
ECG	x[k]				x		x[b]
Infusion BI 6727	**x**						
Vital Signs	x	x	x	x	x	x	
Safety lab parameters	x[g]	x	x	x	x		x[b]
Urine examination	x[g]	x				x	
Pharmacokinetics (plasma)	x[c]	x[c]	x[c]	x[c]			
Adverse Events	x[d]	x	x	x	x	x	x[e]
Concomitant Therapy	x[d]	x	x	x	x		
Tumour assessment[a]					x[a]		x
Conclusion of Subject Participation						x	

[a] according to RECIST guidelines. Imaging and assessment are required at the end of every other treatment course.
[b] optional
[c] for time schedule of pharmacokinetic sampling refer to table (Appendix 10.2), plasma samples have to be drawn from the opposite arm of the infusion. Intensive PK blood sampling performed in Course 1 only; for repeated courses PK blood sampling performed at the end of infusion (1:00h) after 24:00h, 168:00h and after 336:00h (Appendix 10.2).
[d] update only
[e] if not yet recovered at the end of the previous course and in case of new adverse events if drug related
[f] end of treatment; investigations which have to be performed at the last visit (when a patient discontinues the study)
[g] data from last visit of previous course (day 22 ± 2) may be used in case examinations were done within the past four weeks
FU= follow up visit until progression, lost to follow up or treatment with another anti-cancer drug
[k] before administration and directly after completion of infusion of course 3 in eligible patients, further analyses in case of changes during prior courses

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ABBREVIATIONS

AE	Adverse Event
BI	Boehringer Ingelheim
CA	Competent Authority
CML	Clinical Monitor Local
CRA	Clinical Research Assistant/Associate
CRF/eCRF	Case Report Form / electronic Case Report Form
CTMF	Clinical Trial Master File
CRO	Clinical Research Organisation
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DLT	Dose limiting toxicity
DNA	Desoxyribonucleic acid
ECC	Endogenous creatinine clearance
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EDTA	Ethylendiaminetetraacetic acid
EOT	End of treatment
EUS	endoultrasonography
FDA	Food and Drug Administration
$fe_{0-24/48}$	Fraction of analyte eliminated in urine from time point 0 to time point 24/48
fe_{t1-t2}	Fraction of analyte eliminated in urine from time point t1 to time point t2
FU	Follow up
GCP	Good Clinical Practice
gCV	geometric coefficient of variation
gMean	geometric mean
HR	heart rate
HPLC-MS/MS	High performance liquid chromatography, tandem mass spectrometry
ICH	International Conference on Harmonisation
IEC /EC	(Independent) Ethics Committee

IND	Investigational New Drug
INR	International normalised ratio
IRB	Institutional review board
ISF	Investigator Site File
LDH	Lactate dehydrogenase
MCV	Medium corpuscular volume
MRI	Magnetic resonance imaging
MRT	Mean residence time of the analyte in the body after intravenous administration
MTD	Maximum tolerated dose
NC	Next course
NOA	Not analyzed
NOP	No peak detectable
NOR	No valid result
NOS	No sample
No.	Number
OPU	Operative Unit (of BI)
PD	Progressive disease
PK	Pharmacokinetics
PLK-1	Polo-like kinase 1
PR	Partial response
PR-interval	interval between the beginning of the P wave and beginning of the Q wave (seconds). Also called the PQ interval
PT	Prothrombin time
PTT	Partial thromboplastin time
QRS	duration of the QRS wave form (seconds)
QT-interval	interval from the beginning of the Q wave to the end of the T wave on an ECG (seconds)
QTc	QT interval, corrected for heart rate (seconds)
QTcB	QT interval, corrected for heart rate according to Bazett's formula (seconds) = measured QT / (square root of preceding RR interval)
QTcF	QT interval, corrected for heart rate according to Fridericia's formula (seconds) = measured QT / (cube root of preceding RR interval)
RBC	Red blood cell count

RECIST	Response evaluation criteria in solid tumours
RR-interval	interval between R waves (seconds)
SAE	Serious Adverse Event
SD	Stable disease
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	terminal half-life of the analyte in plasma
t_{max}	time from dosing to maximum concentration
[redacted]	
US	Utrasonography
V_{ss}	Apparent volume of distribution at steady state following intravascular administration
V_z	Apparent volume of distribution during the terminal phase λ_z following an intravascular dose
WBC	White blood cell count

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Many advanced or metastatic human cancers 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 cancer 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 cancer. These findings provide a rationale for pursuing PLK-1 inhibition as a therapeutic principle in oncology.

Recently mammalian PLK-1 was shown to be overexpressed in various human cancers such as non-small cell lung cancer (R04-0031) and colorectal cancer (R04-0034). 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 cancer cell lines (R04-0030, R04-0423). A potential role for PLK-1 overexpression 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 1230.1 trial will investigate safety and preliminary efficacy of BI 6727, a highly selective and specific PLK-1 inhibitor to be administered intravenously to patients with advanced or metastatic cancers.

1.2 DRUG PROFILE

BI 6727 is a highly selective and potent small molecule Polo-like kinase 1 inhibitor. The pharmacological profile of BI 6727 was evaluated in vitro in enzymatic assays, cellular cytotoxicity assays and assays examining cell cycle progression. In vivo efficacy of BI 6727 was determined in human tumour xenografts in nude mice.

In an enzymatic assay using human recombinant PLK-1 the molecular potency of BI 6727 was in the low nanomolar range. More than 45 kinases tested in parallel with PLK-1 were not inhibited 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 BI 6727 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 BI 6727 was much better conserved than the activity of conventional chemotherapeutics such as taxanes or vincristine.

Efficacy of BI 6727 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.

The non-clinical safety profile of BI 6727 is considered favorable regarding the oncological indication and the antiproliferative 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. More detailed information is provided in the Investigator's Brochure.

No clinical data exist for BI 6727 administered to patients. Clinical data from the Polo-like kinase 1 inhibitor BI 2536 currently under investigation in clinical trials show good tolerability with haematotoxicity (neutropenia) constituting the dose limiting toxicity. No relevant unspecific toxicity has been observed as yet. Evidence for clinical antitumour activity has been observed.

1.3 RATIONALE FOR PERFORMING THE TRIAL

This open label Phase I dose escalation trial 1230.1 is the first in man trial with BI 6727 in cancer patients. The trial will investigate safety and efficacy of this specific Polo-like kinase 1 inhibitor in cancer patients.

Patients with various solid tumours who have either failed conventional treatment, or for whom no therapy of proven efficacy exists, or who are not amenable to established forms of treatment will be treated with BI 6727 in this study. BI 6727 will be given as a single infusion over 60 minutes on day one of the study. Based on the 3-cycle non-clinical safety studies a recommended starting dose of 12 mg will be given.

Determination of the maximum tolerated dose (MTD) is the primary endpoint of this trial. MTD will be evaluated in patients receiving the first course of BI 6727. Depending on the drug related toxicity observed in this study three to six patients will be treated per dose tier. To increase the safety database at the MTD a total of 24 patients will be enrolled at MTD.

Secondary endpoints of this trial are safety, pharmacokinetic profile of BI 6727 and the assessment of antitumour efficacy.

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 courses are eligible for an additional course of BI 6727 according to protocol.

1.4 BENEFIT / RISK ASSESSMENT

Although considerable progress has been made in understanding cancer 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 who have failed conventional treatment, 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). BI 6727 represents a new class of small molecules targeting and blocking activation of PLK-1 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 these effects may hopefully translate into tumour remissions in patients without further treatment options.

The most relevant side effect of BI 6727 administration is expected to be a transient inhibition of proliferation of normal dividing cells in mucosal tissue and bone marrow. Thymic atrophy seen in toxicological studies is not deemed relevant in the target population of adult cancer patients. Inhibition of mucosal proliferation may lead to gastrointestinal symptoms such as nausea or diarrhoea. The side effects on bone marrow stem cells may lead to a temporary decrease of blood cells and platelets. These side effects are frequently seen in cancer patients treated with conventional cytotoxics or targeted therapies and can easily be monitored. Supportive treatment for these effects is available. In contrast to many established antiproliferative agents no unspecific toxic effects have been identified for BI 6727 in preclinical studies. The QT-prolongation observed at high doses in an animal model are not expected to impair clinical development of the compound. Nevertheless ECG monitoring will be performed and analysed centrally by a core lab.

In ongoing clinical trials with the Polo-like kinase 1 inhibitor BI 2536 good tolerability has been demonstrated. Haematotoxicity with predominant neutropenia constituted dose limiting toxicity. The neutropenia was quickly reversible and did not accumulate after repeated courses in the patients treated so far. No unspecific toxicity, no toxicity relating to kidneys or liver and no cardio-or neurotoxicity have been documented so far. Evidence for antitumour efficacy has been observed.

Cancer patients with advanced tumours and no further treatment options may benefit from tumour shrinkage, tumour stabilisation or improvement of tumour-related symptoms induced by BI 6727. The potential benefit of therapy with BI 6727 is expected to outweigh the treatment related risks.

2. TRIAL OBJECTIVES

2.1 GENERAL AIM / PRIMARY OBJECTIVE

The primary objective of this trial is to identify the maximum tolerated dose (MTD) of BI 6727 therapy in terms of drug-related adverse events.

Secondary objectives are the collection of overall safety and antitumour efficacy data and the determination of the pharmacokinetic profile of BI 6727.

2.2 PRIMARY ENDPOINT

The primary endpoint of this trial is the determination of the Maximum Tolerated Dose (MTD) of BI 6727.

2.3 SECONDARY ENDPOINT(S)

1) Incidence and intensity of drug-related adverse events according to common terminology criteria for adverse events (CTCAE) v.3.0, laboratory evaluations, patient performance and vital signs

2) Tumour responses and time to progression after BI 6727 treatment

3) Pharmacokinetic parameters of BI 6727 (for parameters cf. section 7.1.2.).

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN - DESCRIPTION

Due to the methodology of this trial (dose escalation), it is not possible to predict the number of patients necessary to reach the objectives. An estimated total of up to 80 patients might be necessary to establish MTD. A total of 24 patients will be treated at MTD. Actual accrual will depend on the number of dose levels tested and the adverse events observed. Patients non evaluable with respect to MTD will be replaced. Patients with a histologically or cytologically confirmed diagnosis of a malignant solid tumour refractory or not amenable to standard therapies are eligible for this trial. It is planned to have the trial performed at one centre, depending on enrolment more centres may be initiated.

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

This is an open label, uncontrolled trial in patients with advanced solid tumours following a fixed dose escalation design. The aim of this trial is to assess the MTD of BI 6727 administered at escalating doses using a toxicity-guided approach.

3.3 SELECTION OF TRIAL POPULATION

Patients with advanced solid tumours will be eligible for this trial.

A log of all patients screened will be maintained in the ISF at the investigational site.

3.3.1 Inclusion criteria

1) Patients with confirmed diagnosis of advanced, non resectable and / or metastatic solid tumours, who have failed conventional treatment, or for whom no therapy of proven efficacy exists, or who are not amenable to established forms of treatment
2) Age 18 years or older
3) Written informed consent consistent with ICH-GCP and local legislation
4) Eastern Cooperative Oncology Group (ECOG, R01-0787) performance score ≤ 2
5) Recovery from CTCAE Grade 2 - 4 therapy-related toxicities from previous chemo-, hormone-, immuno-, or radiotherapies (except alopecia)

The 18 additional patients recruited at the MTD must also meet the following criterion:

6) Measurable tumour deposits (RECIST) by one or more techniques (CT, MRI)

3.3.2 Exclusion criteria

1) Serious illness or concomitant non-oncological disease considered by the investigator to be incompatible with the protocol
2) Pregnancy or breastfeeding
3) Active infectious disease or known chronic Hepatitis B/Hepatitis C infection
4) Clinical evidence of active brain or leptomeningeal disease during the past 12 months

5) Second malignancy currently requiring active therapy
6) Absolute neutrophil count less than 1500 / mm^3
7) Platelet count less than 100 000 / mm^3
8) 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)
10) Serum creatinine greater than 1.5 mg / dl (> 132 µmol / L, SI unit equivalent)
11) Known history of relevant QT-prolongation, e.g. long QT-syndrome
12) Women and men who are sexually active and unwilling to use a medically acceptable method of contraception
13) Treatment with other investigational drugs or participation in another clinical trial within the past four weeks before start of therapy or concomitantly with this trial (except for present trial drug)
14) Chemo-, radio or immunotherapy within the past four weeks before start of therapy or concomitantly with this trial. This restriction does not apply to steroids and bisphosphonates.
15) Patients unable to comply with the protocol
16) Active alcohol or drug abuse

3.3.3 Retreatment criteria

Patients with a clinical benefit after a course of BI 6727 (clinical response, absence of progression or symptom improvement) and who have recovered from any clinically relevant drug-related AE are eligible for a further treatment course. In case of symptom improvement despite disease progression a repeated course may be allowed in agreement between the clinical monitor and the investigator.

Patients experiencing DLT are eligible for further treatment courses with BI 6727 at one dose tier below as soon as recovery from drug related toxicities allows further treatment. Patients eligible for a further (repeat) treatment course will not start treatment before 22 (± 2) days after start of the previous course. If an interruption of more than 6 weeks as counted from the start of the previous treatment course is necessary, the patient must be removed from this trial.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

4.1.1 Identity of investigational product(s)

Substance (INN):	BI 6727
Pharmaceutical form:	Solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	0,5 mg /mL (vials with 100 mL).
Daily dose:	See section 4.1.3
Duration of use:	Single dose
Route of administration:	intravenous
Posology:	Infusion over 60 min

4.1.2 Methods of assigning patients to treatment groups

Not applicable. This is a dose escalation trial.

4.1.3 Selection of doses in trial

4.1.3.1. First course of administration of BI 6727

The starting dose will be 12 mg. As long as no patient of an ongoing dose tier develops drug-related toxicity beyond Grade 1 according Common Terminology Criteria for adverse events (CTCAE) during the initial treatment course the dose will be escalated by up to 100% in new patients. As soon as any patient of an ongoing dose tier experienced drug-related toxicity Grade 2 or higher escalation steps of not more than 50% will be allowed thereafter. Should dose limiting toxicity (DLT) be observed in 1/6 patients treated in a cohort and escalation continues this will be in steps of not more than 35%. Before entering patients at a higher dose level it will be ensured that all patients at an ongoing dose level have completed the initial course of BI 6727 dosing. The decision regarding the incremental size of the dose escalation steps will only be taken after discussion between the sponsor and the clinical investigator considering toxicity data from each patient cohort. Prior to inclusion of a new patient the investigator has to confirm the respective dose with the clinical monitor of the sponsor.

4.1.3.2. Additional courses of BI 6727

The dose of BI 6727 will be the dose administered in the previous course, unless the patient experienced dose limiting toxicity. Patients experiencing DLT are eligible for further treatment courses at one dose tier below.

4.1.4 Selection and timing of doses for each patient

Each vial of BI 6727 contains 100 mL of a 0.5 mg/mL solution.

The procedure to prepare the infusion solution is the following:

Determine the amount of solution which needs to be added to the 500 mL infusion bags according to the dose level (e.g. dose of 12 mg = 24 mL Volume).

Withdraw the respective amount of NaCl 0.9% from the infusion bag.

Add the respective amount of BI 6727 solution to the infusion bag and mix

Take a 5 mL sample (corresponding to 1% total volume) out of the mixed prepared ready to use solution and store (the sample should not be cooled or frozen). The sample needs to be labelled with the right pre-printed, adhesive label.

Solution is ready to be infused to the patient by using an infusion pump (infusion duration 60 minutes).

4.1.5 Preparation of the infusion solution and of the sample for analysis.

Each vial of BI 6727 contains 100 mL of a 0.5 mg/mL solution.

The procedure to prepare the infusion solution is the following:

Determine the amount of solution which needs to be added to the 500 mL infusion bags according to the dose level (e.g. dose of 12 mg = 24 mL Volume).

Withdraw the respective amount of NaCl 0.9% from the infusion bag.

Add the respective amount of BI 6727 solution to the infusion bag and mix

Take a 5 mL sample (corresponding to 1% total volume) out of the mixed prepared ready to use solution and store (the sample should not be cooled or frozen). The sample needs to be labelled with the right pre-printed, adhesive label.

Solution is ready to be infused to the patient by using an infusion pump (infusion duration 60 minutes).

4.1.6 Selection and timing of doses for each subject

BI 6727 will be administered as a short infusion over 60 minutes using an infusion pump, on day 1 of each course (the start and end time of the infusion needs to be documented in the e-CRF). Immediately following the infusion of BI 6727 the infusion tubing will be washed with 100 mL physiological sodium chloride (0.9% NaCl) solution for a maximum duration of 10 minutes (The end time of the washing step needs to be documented in the e-CRF). BI 6727 should be administered strictly intravenously.

Initially, three patients will be treated per dose level. When at the ongoing dose level one patient experiences drug-related dose limiting toxicity (DLT; for definition, please refer to section 5.2.1) the number of patients treated at that dose level will be increased to a maximum of six evaluable patients. When no further patient experiences DLT the dose will be escalated to the next level. When two or more patients experience DLT in any dose cohort, other than the

expansion cohort at MTD level, enrolment into this dose cohort will be stopped. In order to define the maximum tolerated dose (MTD) three additional patients will be treated at one dose tier below unless six have already been treated at that dose tier. The MTD (see also section 5.2.1) is the highest dose at which not more than one patient out of six experiences DLT (R01-0028). Should safety data of patients treated at the next lower dose indicate a sufficient safety margin another escalation to an intermediate dose can be chosen after discussion between the investigator and the clinical monitor.

Once the MTD is determined patient enrolment at higher dose tiers will be suspended. Further patients will be included at the MTD level until a total of 24 patients will have been treated at the MTD.

4.1.7 Blinding

Not applicable, this is an open label trial.

4.1.8 Packaging, labelling and re-supply

BI 6727 will be supplied in 100 mL vials containing 50 mg BI 6727, respectively. Medication will be labelled with: trial number, medication number, contents, name and strength of product, pharmaceutical dosage form, route of administration, directions for use, storage conditions, term “for clinical trial use only”, use-by date, batch number and sponsor.

Examples of the labelling of the medication will be found in the investigator site file (ISF).

Medication will be delivered to the hospital's pharmacy where the total dose per patients will be prepared upon request from the investigator. The content of several vials may be needed for administration of the requested dose. For this purpose the medication will be filled in plastic bags prefilled with sodium chloride so that the trial drug can be administered as one single infusion to the patient. For details concerning the preparation of the infusion solution, please refer to section 4.1.4.

4.1.9 Storage conditions

BI 6727 will be stored in the hospital pharmacy in a limited access area at room temperature.

4.2 CONCOMITANT THERAPY

Concomitant medications, or therapy to provide adequate care, may be given as clinically necessary.

All concomitant (non-oncological) therapies starting or changing during the course of the study are allowed but should be recorded in the e-Case Report Form (eCRF) except for vitamins, appetisers or nutrient supplements. Trade name, indication, and dates of administration will be documented. If patients receive parenteral nutrition during the study, the components need not be specified in detail. It should just be indicated as 'parenteral nutrition' and the form be completed. If a patient needs anaesthesia, it will be sufficient to indicate 'anaesthesia' without specifying the details.

4.2.1 Rescue medication and additional treatment(s)

Rescue medication to reverse the action of BI 6727 is not available. Potential side effects of BI 6727 have to be treated symptomatically (see also section 5.2). Symptomatic treatments of side effects or tumour-associated symptoms are allowed.

4.2.2 Restrictions

Additional chemo-, immuno-, hormone - or radiotherapy is not allowed during the study. These restrictions do not apply for steroids and bisphosphonates. For symptom control palliative radiotherapy may be permitted after discussion with the BI Clinical Monitor.

For patients of the expansion cohort at MTD, the impact of any palliative radiotherapy administered on evaluable lesions has to be documented.

4.3 TREATMENT COMPLIANCE

The study medication will be administered as a single intravenous 60 minute infusion under supervision of the investigator or dedicated personnel.

5. OBSERVATIONS

Safety, pharmacokinetic and efficacy data will be collected and evaluated.

5.1 EFFICACY / CLINICAL PHARMACOLOGY

Efficacy as secondary endpoint will be assessed by analysing the tumour response to therapy and time to progression in all patients with measurable disease.

5.1.1 PRIMARY ENDPOINT

Not applicable since this study focuses on safety endpoints. The primary endpoint for safety is described in section 5.2.1.

5.1.2 SECONDARY ENDPOINTS

Response will be assessed by tumour measurements and will be evaluated according to the response evaluation criteria in solid tumours (RECIST, see ISF, R01-0754).

The investigator along with his / her radiologist will record the target and non-target lesions at baseline. One to ten target lesions should be identified at baseline and recorded in the eCRF. The same method of assessment and the same technique should be used to characterise each reported lesion at baseline and during follow-up. Lesions in previously irradiated areas may not be considered measurable at baseline. However, new lesions occurring in previously irradiated areas have to be considered for assessment of tumour response.

Response (complete response CR, partial response PR), stable disease (SD) and progression (progressive disease, PD) will be evaluated in this study using the international criteria proposed by the RECIST Committee. Changes in only the largest diameter (unidimensional measurement) of the tumour lesions are used in the RECIST criteria. For more details see also Appendix 10.4 "Tumour assessment according to RECIST".

5.2 SAFETY

5.2.1. Maximum tolerated dose (MTD) and dose limiting toxicity (DLT)

The maximum tolerated dose is defined as:

The dose of BI 6727 which is one dose tier below that dose at which two or more out of a maximum of six patients experienced DLT. At the maximum tolerated dose, no more than one patient out of six patients may experience DLT, i.e. MTD is defined as the highest dose studied for which the incidence of dose-limiting toxicity is no more than 17% (i.e. 1/6 patients) during the first course.

For definition of DLT, it is essential that patients are treated sufficiently according to supportive care standards. Patients with treatable adverse events that are not sufficiently treated need to be replaced.

Dose limiting toxicity is defined as:

drug related CTCAE grade 3 or 4 non haematological toxicity (except emesis or diarrhoea responding to supportive treatment), or

drug related CTCAE grade 4 neutropenia for seven or more days and / or complicated by infection, or

CTCAE Grade 4 thrombocytopenia .

The MTD will be defined on the basis of DLT observed during the first course of dose escalation cohorts. However, for those patients who receive a further infusion, unusual or unexpected toxicities will be considered for the purposes of confirming the MTD.

Patients with a clinical benefit after a course of BI 6727 (symptom improvement, clinical response or absence of progression) and who recovered from drug related adverse events are eligible for a further treatment course. In case of symptom improvement despite disease progression a repeated course may be allowed in agreement between the clinical monitor and the investigator. All DLT's occurring during the first or repeated treatment courses will be reported as significant adverse events.

5.2.2. Adverse Events

All patients will be monitored carefully during and after the treatment courses of BI 6727. During the trial, all adverse events (AE) will be recorded in the eCRF as described in section 8.4 of this protocol. The events will be graded according to the CTCAE v3.0 (attached to the ISF).

Adverse events with onset within 21 days after the previous administration of therapy with BI 6727 are considered as on treatment. Adverse events which are not yet recovered at the end of treatment (EOT) visit will be followed up until recovery or in case of persistence sufficient characterisation of the toxic effects has been achieved and the investigator and the clinical monitor agree to not further pursue them. Adverse events occurring during the follow-up period after the EOT visit will be reported in case they are serious or considered drug-related by the investigator.

Hospitalisations for administrative reasons or hospitalisations already planned prior to informed consent need not be reported as an SAE. Progressive disease (PD) will not be reported as an SAE if it is considered the natural course of the disease but will be recorded in the eCRF. Disease progression will be analyzed as part of the efficacy evaluation. Pre-existing conditions at baseline other than the disease will be not recorded as Adverse Events if they remain unchanged during the trial.

5.2.3. Physical examination, height, body weight, performance status and electrocardiogram

A general physical examination will be performed at screening and at the end of the treatment. The same investigator should perform this examination. Physical examination will include measurement of height and of body weight and the evaluation of the ECOG performance score. Height will be documented only once at screening of course 1. Weight and ECOG score will also be assessed when BI 6727 treatment is started and at the end of the treatment. ECOG will also be assessed at the last visit of each course.

12-lead resting electrocardiograms (ECG) will be performed at baseline, at visit 2 before and at the end of BI 6727 infusion and at the last visit of each course. In patients eligible for repeated courses of treatment ECGs should be done at visit 2 of the third course (second repeated course) before and at the end of infusion of BI 6727, at the last visit of that course and whenever the investigator deems necessary. In case of drug related ECG changes additional ECG monitoring will be performed in the respective and later courses of treatment. Except for the screening ECG all ECGs have to be digitally recorded using dedicated equipment provided by a CRO [redacted]. ECG recordings will be done at the following time points:

- One ECG during the screening examination (no digital monitoring needed)
- On day 1 a series of three consecutive ECGs prior to start of infusion of BI 6727 (approx. experimental time -0:15 min)
- On day 1 a series of three consecutive ECGs after end of infusion of BI 6727 (approx. experimental time 1h 15 min)
- On day 1 of course 3 a series of three consecutive ECGs prior to start of infusion of BI 6727 (approx. experimental time -0:15 min)
- On day 1 of course 3 a series of three consecutive ECGs after end of infusion of BI 6727 (approx. experimental time 1h 15 min)
- At the visit 8 of the first course and visit 5 of the third course a series of three consecutive ECGs

The recordings will be checked for pathological results (to be recorded as AEs) by the investigator. In addition a centralised evaluation of all 12-lead ECGs recorded during day 1 of courses 1 and 3, visit 8 of course 1 and visit 5 of course 3 will be performed by a CRO [redacted]. This analysis will include the determination RR-intervals, PR-intervals, QRS-intervals, QT-intervals. The CRO is also in charge of a safety overread of ECGs (one ECG out of every series of three) which will be done by a board-certified cardiologist. To allow for a heart rate correction of QT intervals according to Fridericia's formula ($QTcF = QT/RR^{-1/3}$) or other methods the QT intervals will be matched to the preceding RR intervals.

Physical examination will be performed prior to each course.

5.2.4. Vital signs

Vital signs (blood pressure (BP) and pulse rate after 2 minutes supine rest) will be recorded at the screening visit and at the following time points: pre-infusion and 20 (± 5), 65 (± 10), 120 (± 30) and 240 (± 30) minutes after start of infusion of BI 6727, at every visit of the observation phase and at EOT.

5.2.5. Laboratory examinations

Blood samples will be collected from venous blood at the times indicated in the flow chart.

Laboratory tests will include the following safety lab parameters:

- haematology

red blood cell count (RBC), haemoglobin, haematocrit, medium corpuscular volume (MCV), white blood cell count (WBC) and differential, platelets

- biochemistry

glucose, sodium, potassium, calcium, creatinine, aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphatase, lactate dehydrogenase (LDH), bilirubin, urea, serum protein electrophoresis (total protein, albumine, α1-globulines, α2-globulines, β-globulines, γ-globulines), uric acid, creatine phosphokinase (CPK). In case of pathological CPK further evaluation (e.g. by Troponin assays) should be performed and the findings documented.

- coagulation parameters

prothrombin time (PT), international normalised ratio (INR) where therapeutically indicated and partial thromboplastin time (PTT) (at day 1 before start of infusion and at day 2)

- tumour markers

in applicable tumour types markers will be taken at screening and at visit 8 (visit 5 of repeated courses) e.g.: PSA, AFP, β-HGG, CA 125, CEA, CA 19-9, NSE, TPA, CA 15.3, CYFRA 21-1, chromogranine, thyreoglobuline.

These parameters will be assessed as specified in the flow chart. In case of toxicity adequate and more frequent blood sampling is at the discretion of the investigator. In case of grade 4 neutropenia, blood has to be collected seven days after first occurrence of grade 4 neutropenia.

In case laboratory investigations have been performed within two weeks prior to screening, these values may be used for screening and no repeat laboratory examination is requested for the purpose of the trial.

- Urine (pH, glucose, erythrocytes, leukocytes, protein, nitrite) will be analysed by dipstick (semiquanitative measurements; -, +, ++, +++) during the screening visit, at visit 3 of initial

treatment course, at visit 1 and 2 of repeated treatment courses and at the end of treatment visit. In case of pathological findings, further evaluation should be performed and the findings documented. A pregnancy test will be performed at screening and immediately before any further administration of BI 6727 in women of childbearing potential.

5.2.6. Significant adverse events

Reaching DLT has to be recorded as a significant adverse event.

5.3 OTHER

5.3.1. Demographics and history

Demographics (sex, birth date, race), information on smoking and alcohol status, and baseline conditions will be collected during the screening visit and updated information will be collected at the first visit of additional courses.

History of cancer will also be obtained. The type of cancer, 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 Union Internationale Contre le Cancer (UICC) / 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 surgeries will be reported. Previously administered chemo-, immuno-, and hormone therapy will be reported including start and end dates (month and year may be sufficient), the therapy protocol with the number of courses (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. Concomitant diagnoses and/or therapies

Concomitant diagnoses and/or therapies present at study entry and/or during screening and relevant to the patient's safety during the trial as judged by the Investigator, will be recorded in the eCRF.

5.3.3. Genotyping for Pharmacokinetics

One blood sample will be collected for cytochrome P 450 (CYP2D6, CYP2C19, CYP2C9) and N-acetyltransferase (NAT2) genotyping to evaluate the possible influence of their polymorphism on the pharmacokinetic profile of BI 6727.

In order to analyse the pharmacokinetic data in more detail, an investigation should help to clarify if different interindividual areas under the concentration time curves at same dosages might be explained by the respective genotypes. These results could help to elucidate the maximal tolerable dose.

To perform such analysis, EDTA-anticoagulated blood samples for DNA isolation will be collected once at visit 2 after separate informed consent.

Only testing for genes involved in drug metabolism will take place and that no polymorphisms of genes which might predispose for different diseases will be analysed. Only frequent functional polymorphisms will be analyzed.

5.4 APPROPRIATENESS OF MEASUREMENTS

Not applicable.

5.5 DRUG CONCENTRATION MEASUREMENTS / PHARMACOKINETICS

Date and exact clock time of administration (start and end time of infusion) as well as of pharmacokinetic sampling times must be recorded. These actual sampling times will be used for determination of pharmacokinetic parameters.
The designation “before”/”predose” on study day 1 refers to the time period of 0:05 before drug administration (see Appendix 10.2), i.e. study measurements and assessments scheduled to occur “before”/”predose” have to be performed and completed 0:05 prior to drug administration/start of infusion.

5.5.1 Methods and timing of sample collection

5.5.1.1 Plasma sampling for pharmacokinetics

A total amount of 42 mL blood will be taken per subject during the initial treatment course of the study for pharmacokinetic purposes. Subsequent courses will require 12 mL of blood for pharmacokinetic sampling. The samples need to be taken in the opposite arm, not in the infusion arm. For patients having central venous access, BI 6727 may be administered using this device and PK samples obtained from either forearm.

For quantification of analyte plasma concentrations, 3 mL of blood will be taken in an EDTA (ethylendiaminetetraacetic acid)-anticoagulant blood drawing tube at the following time points:

During the initial treatment course:

At visit 2 – day 1: before drug administration and at 0:15, 0:30, 0:45, 1:00*, 1:30, 2:00, 4:00, 8:00 hours after start of infusion (*immediately prior to end of infusion of BI 6727).

At visit 3 – day 2: 24:00 hours after start of infusion

At visit 4 – day 3: 48:00 hours after start of infusion

At visit 5 – day 5 (±1 day): planned time 96:00 hours after start of infusion

At visit 6 – day 8 (±1 day): planned time 168:00 hours after start of infusion

At visit 7 – day 15 (±1 day): planned time 336:00 hours after start of infusion

During additional courses plasma samples will be taken at the following time points:

At visit R1 – day 1: prior to the end of infusion (1:00)

At visit R2 – day 2: 24:00 after start of infusion

At visit R3 – day 8 (±1 day): planned time 168:00 hours after start of infusion

At visit R4 – day 15 (±1 day): planned time 336:00 hours after start of infusion

Until shipment on dry ice to the analytical laboratory, the plasma samples will be stored at –20°C or below at the clinical site and stored at the analytical laboratory at –20°C or below until analysis.

Detailed handling instructions for plasma samples are provided in Appendix 10.3.

5.5.1.2 Urine sampling for pharmacokinetics (in course 1 only)

A blank urine sample will be collected prior to drug administration and two 2 mL aliquots retained to check for analytical interference. A protocol start time of -2:00 and a stop time of -2:00 will be used for database setup. All urine voided during the sampling intervals 0-24 and 24-48 hours after administration will be collected in containers. Patients have to empty their bladder at the end of each sampling interval. The urine weight/volume (weight will be set equal to volume, i.e. 1 kg = 1 L, without correction for specific gravity of urine) for each collection interval will be documented (the weight of the empty and the filled container needs to be documented) and two 2 mL aliquots will be stored for bioanalytical measurement.

Until shipment on dry ice to the analytical laboratory, the urine samples will be stored at –20°C or below at the clinical site and stored at the analytical laboratory at –20°C or below until analysis.

Detailed handling instructions for urine samples are provided in Appendix 10.3.

[redacted]

[redacted]

5.6 BIOMARKER / PHARMACODYNAMIC SAMPLING

5.6.1 Methods and timing of sample collection

In applicable tumour types markers will be taken at screening and at visit 8 (visit 5 of repeated courses) e.g.: PSA, AFP, β-HGG, CA 125, CEA, CA 19-9, NSE, TPA, CA 15.3, CYFRA 21-1, chromogranine, thyreoglobuline. (c.f. 5.2.6).

[redacted]

5.7 PHARMACOKINETIC / PHARMACODYNAMIC RELATIONSHIP

No analysis of pharmacokinetic/pharmacodynamic relationship is planned.

5.8 DATA QUALITY ASSURANCE

A quality assurance audit of this trial may be conducted by the sponsor or sponsor's designees. The quality assurance auditor will have access to all medical records, the investigator's trial related files and correspondence, and the informant consent documentation that is relevant to this clinical trial.

6. INVESTIGATIONAL PLAN

This is an open label, uncontrolled trial in patients with various solid tumours following the 3+3 design with dose escalation (R04-0569). The aim is to assess the MTD of BI 6727 administered at escalating doses.

Patients meeting the inclusion and exclusion criteria and who have given their written informed consent are eligible for participation in the trial.

Three to six patients each will be administered BI 6727 at a certain dose level. For exact dosing details refer to section 4.1.3.1. A total of 24 patients will be treated at the MTD.

6.1 VISIT SCHEDULE

6.1.1. Visit schedule in initial treatment course

6.1.1.1. Visit 1 – screening visit

The screening visit has to be performed within day -14 and the day before first administration of BI 6727.

6.1.1.2. Visit 2 – day 1

Visit 2 is the day of administration of BI 6727.

6.1.1.3. Visit 3 – day 2

Visit 3 is the day after the first administration of BI 6727.

6.1.1.4. Visit 4 – day 3, visit 5 – day 5 (±1), visit 6 – day 8 (±1) and visit 7 – day 15(±1)

Visits 4 through 7 should be performed on days 3, 5 (±1), 8 (± 1) and 15 (±1).

6.1.1.5. Visit 8 – day 22 (± 2)

Visit 8 should be performed on day 22 (±2).

6.1.2. Visit schedule in repeated treatment courses

6.1.2.1. Visit 1 – day 1

Visit 1 is the day of administration of BI 6727.

6.1.2.2. Visit 2 – day 2

Visit 2 is the day after the first administration of BI 6727.

6.1.2.3. Visit 3 – day 8 (±1), visit 4 – day 15 (±1) and visit 5 – day 22 (±2)

Visits 4 through 5 should be performed on days 8 (± 1); 15 (± 1) and 22 (± 2)

6.2 TRIAL PROCEDURES AT EACH VISIT

6.2.1 Screening phase

Visit 1 – Screening visit (day -14 to day 0)

- informed consent
- demographics (sex, birth date, race)
- history (oncological and relevant non oncological)
- patient eligibility (in- and exclusion criteria)
- physical examination including resting ECG, body weight, height, vital signs (blood pressure, pulse rate) and ECOG performance score
- pregnancy test in women of childbearing potential
- concomitant therapy
- Endosonography or ultrasound of primary or metastatic marker lesions (optional)
- tumour assessment. MRI and CT scans should not be older than 4 weeks
- tumour markers (in applicable tumour types of the underlying disease)
- laboratory examination including safety lab parameters (haematology including differential, biochemistry, coagulation parameters), urine dipstick

6.2.2 Treatment phase(s)

6.2.2.1. Treatment phase in course 1

Visit 2 – day 1

Visit 2 – day 1, day of BI 6727 administration

- patient eligibility (in- and exclusion criteria)
- final confirmation of dose tier
- changes in concomitant therapies

- occurrence of adverse events (AEs) since enrolment
- body weight
- ECOG performance score
- blood sampling for cytochrome P450 (CYP2D6, CYP2C19, CYP2C9) and NAT2 genotyping

immediately before administration of BI 6727:

- resting ECG (series of three consecutive ECGs using dedicated equipment)
- vital signs (blood pressure, pulse rate)
- safety lab parameters (haematology including differential, biochemistry)
- Pharmacokinetic blood sampling: obtain predose blood sample (-0:05) (refer section 10.3 for sample handling). The date and time of sampling must be recorded in the eCRF.
- Pharmacokinetic urine sampling: obtain predose urine sample (at least two 4 mL aliquots)

following administration of BI 6727 (start of infusion: 0:00) (the infusion rate needs to be constant during the whole infusion, deviations need to be documented in the eCRF. Duration (start and stop time of infusion) and actual dose administered need to be documented):

- vital signs (blood pressure, pulse rate) at 20 (± 5 minutes), 65 (± 10 minutes), 120 (2 hours; ± 30 minutes) and 240 minutes (4 hours; ± 30 minutes) after start of infusion
- Pharmacokinetic blood sampling: obtain blood samples at the following time points: 0:15, 0:30, 0:45, 1:00 (immediately prior to end of infusion of BI 6727), 1:30, 2:00, 4:00,
  8:00 h after start of infusion of BI 6727 (refer section 10.3 for sample handling). Blood samples have to be taken in the opposite arm of the infusion arm. For patients having central venous access, BI 6727 may be administered using this device and PK samples obtained from either forearm. The date and time of blood sampling must be recorded in the eCRF.
- Pharmacokinetic urine sampling: start urine sampling (0-24 h, only in first course)
- adverse events occurring during and after infusion
- changes in concomitant therapy
- resting ECG (series of three consecutive ECGs using dedicated equipment)

Visit 3 - day 2

- vital signs (blood pressure, pulse rate)
- Pharmacokinetic blood sampling: obtain blood sample 24:00 h after start of infusion of BI 6727 (refer section 10.3 for sample handling). The date and time of blood sampling must be recorded in the eCRF.
- Pharmacokinetic urine sampling: collect urine container from first interval and place new container for second interval to patients disposal (24-48 h, only in first course) (refer to section 10.3 for sample handling).
- adverse events
- changes in concomitant therapy
- safety lab including haematology, biochemistry, coagulation parameters
- urine dipstick

Visit 4 - day 3

- vital signs (blood pressure, pulse rate)
- adverse events
- changes in concomitant therapy
- safety lab including haematology, biochemistry
- Pharmacokinetic blood sampling: obtain blood sample 48:00 h after start of infusion of BI 6727 (refer to section 10.3 for sample handling). The date and time of blood sampling must be recorded in the eCRF.
- Pharmacokinetic urine sampling: collect urine container from second interval (24-48 h, only in first course) (refer section 10.3 for sample handling).

Visit 5 - day 5 (± 1)

- vital signs (blood pressure, pulse rate)
- adverse events
- changes in concomitant therapy
- safety lab including haematology, biochemistry

- Pharmacokinetic blood sampling: obtain blood sample 72:00, or 96:00, or 120:00 h after start of infusion of BI 6727 (respectively at day 4, or day 5, or day 6) (refer to section 10.3 for sample handling). The date and time of blood sampling must be recorded in the eCRF.

Visit 6 - day 8 (± 1) and Visit 7 - day 15 (± 1)

- vital signs (blood pressure, pulse rate)
- adverse events
- changes in concomitant therapy
- safety lab including haematology, biochemistry
- Pharmacokinetic blood sampling: obtain blood sample at visit 6 (planned time: 168:00 hours after start of infusion of BI 6727) and at visit 7 (planned time: 336:00 hours after start of infusion), respectively (refer to section 10.3 for sample handling). The date and time of blood sampling must be recorded in the eCRF.

Visit 8 - day 22 (±2)

Visit 8 is the last visit of the initial treatment course. This visit may coincide with day 1 of the following treatment course. Examinations which are due on both present visit and the day of
BI 6727 administration need to be documented only once (in the day 22 visit).

- vital signs (blood pressure, pulse rate)
- ECOG performance score
- adverse events
- changes in concomitant therapy
- safety lab including haematology, biochemistry, coagulation parameters
- Endosonography or sonography (optional)
- resting ECG (series of three consecutive ECGs using dedicated equipment)

6.2.2.2. Treatment Phase in repeated treatment courses

Visit 1 – day 1

Visit 1 – day 1, day of BI 6727 administration

- patient eligibility (in- and exclusion criteria)
- update of medical history

- physical examination including body weight, height, vital signs (blood pressure, pulse rate). Data from last visit of preceding course may be used in case examinations were done within the past 4 weeks.

- ECOG performance score

- laboratory examination including safety lab parameters (haematology including differential, biochemistry, coagulation parameters). Data from last visit of preceding course may be used in case examinations were done within the past 4 weeks.

- urine dipstick. Data from last visit of preceding course may be used in case examinations were done within the past 4 weeks.

- pregnancy test in women of childbearing potential

- changes in concomitant therapies

- occurrence of adverse events (AEs) since last visit

immediately before administration of BI 6727:

- resting ECG (series of three consecutive ECGs in third treatment course using dedicated equipment) at -0:15 min

- vital signs (blood pressure, pulse rate)

following administration of BI 6727 (start of infusion: 0:00) (the infusion rate needs to be constant during the whole infusion, deviations need to be documented in the eCRF. Duration (start and stop time of infusion) and actual dose administered need to be documented):

- resting ECG (series of three consecutive ECGs using dedicated equipment directly after completion of BI 6727 infusion (1h 15 min)

- vital signs (blood pressure, pulse rate) at 20 (± 5 minutes), 65 (± 10 minutes), 120 (2 hours; ± 30 minutes) and 240 minutes (4 hours; ± 30 minutes) after start of infusion

- Pharmacokinetic blood sampling: obtain blood samples 1:00 h (immediately prior to end of infusion of BI 6727) after start of infusion of BI 6727 (refer section 10.3 for sample handling). Blood samples have to be taken in the opposite arm of the infusion arm. For patients having central venous access, BI 6727 may be administered using this device and PK samples obtained from either forearm. The date and time of blood sampling must be recorded in the eCRF.

- adverse events occurring during and after infusion

- changes in concomitant therapy

Visit 2 – day 2

- vital signs (blood pressure, pulse rate)
- Pharmacokinetic blood sampling: obtain blood sample 24:00 h after start of infusion of BI 6727 (refer section 10.3 for sample handling). The date and time of blood sampling must be recorded in the eCRF.
- adverse events
- changes in concomitant therapy
- safety lab including haematology, biochemistry, coagulation parameters
- urine dipstick

Visit 3 - day 8 (± 1) and Visit 4 - day 15 (± 1)

- vital signs (blood pressure, pulse rate)
- adverse events
- changes in concomitant therapy
- safety lab including haematology, biochemistry
- Pharmacokinetic blood sampling: obtain blood sample at visit 3 (planned time: 168:00 hours after start of infusion of BI 6727) and at visit 4 (planned time: 336:00 hours after start of infusion of BI 6727), respectively (refer section 10.3 for sample handling). The date and time of blood sampling must be recorded in the eCRF.

Visit 5 – day 22 (± 2)

- vital signs (blood pressure, pulse rate)
- ECOG performance score
- adverse events
- changes in concomitant therapy
- safety lab including haematology, biochemistry, coagulation parameters
- tumour assessment at the end of every other course:

  MRI or CT if in accordance with RECIST or otherwise clinically indicated
- Endosonography or sonography optional

- resting ECG (series of three consecutive ECGs using dedicated equipment) in third course of treatment

6.2.3 End of trial and follow-up

Termination of trial medication – End of trial

The following will be obtained and / or performed:

- physical examination including vital signs, body weight and ECOG performance score
- adverse events
- laboratory examinations: urine dipstick

The conclusion of patient participation should be completed for all patients together with their last visit. The conclusion of patient participation will be completed during the final visit (day 22) for patients treated per protocol. For patients, who were withdrawn or dropped out of the trial, the end of trial investigations should be completed at the last visit.
Imaging and tumour assessment need to be done only if not yet performed within the past three weeks.

Follow up visit

All patients who completed a treatment course (all visits performed including visit at day 22) and are not eligible for a further course will be followed up until progression, lost to follow up or treatment with another anti-cancer drug. The intervals for follow up are every six weeks for the first 3 months and then every three months, respectively. At each follow up visit adverse events will be reported in case they were not recovered at the end of treatment of the last course. Performance of physical examination and ECG as well as determination of safety lab parameters is optional. The ECOG performance score will be reported. No tumour assessment is requested if the patient has progressive disease and/or received another anti-cancer therapy. CT or MRI examinations will be handled according to the RECIST guideline.

6.2.4. Missed visits

If a visit is missed and the patient reports to the investigator between this visit and the next one, the missed visit should be done with the actual date and the reason should be given for the delayed visit. The next visit, however, should take place at the scheduled time after administration of the trial drug.

6.3 REMOVAL OF PATIENTS FROM THERAPY ASSESSMENT

A patient has to be withdrawn from the trial if:

- the patient withdraws consent

- the patient is no longer able to participate in the trial (e.g. adverse events, surgery, concomitant diagnoses, concomitant therapies or administrative reasons); in such case the Investigator's reason for a patient removal must be recorded in the appropriate page of the eCRF.

- eligibility criteria are violated

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

The patients are free to discontinue their participation in this study at any time. The investigator may also stop patient's participation, if the patient is no longer able to attend study visits e.g. due to worsening of disease. A patient can be withdrawn after discussion between the sponsor and the investigator if eligibility criteria are violated or the patient fails to comply with the protocol (e.g. non-compliance to study visits, see 6.3.1).

6.3.1 Replacement of patients

Patients withdrawn or patients who miss more than one visit during their first treatment course will be replaced. Patients who miss one visit may be replaced after discussion between the sponsor and the investigator.

Patients who withdraw due to DLT will not be replaced.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN / MODEL

This phase I trial will be performed to determine the safety, tolerability, MTD, pharmacokinetics and preliminary therapeutic effects of BI 6727 (cf. 2.2. and 2.3. for definition of endpoints) in patients with various advanced and/or metastatic solid tumours for whom no established antitumour treatment options are available.

The dose escalation procedure is described in 4.1.3. Cohorts of patients will be entered sequentially into escalating dosage tiers with the aim to identify the maximum tolerated dose of BI 6727.

This study is open-label, which allows the safety of each dosage of BI 6727 to be assessed before treating additional patients with higher doses. Patients will not be randomized; they will be assigned to the cohort that is being filled at the time the patient is ready to enter the trial.

7.1.1. Safety and tolerability evaluation

Safety and tolerability of BI 6727 will be assessed in terms of changes in laboratory parameters, vital signs, the incidence and severity and causality of adverse events and of toxicities according to CTCAE criteria version 3.0. The results will be reported for each dose level separately as well as in terms of overall means, if appropriate.

The results will be displayed for the first course and overall courses separately.

7.1.2. Pharmacokinetic evaluation

If feasible, the following PK parameters will be calculated:

C_{max} (maximum concentration of the analyte in plasma)

t_{max} (time from dosing to maximum concentration)

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

AUC_{0-tz} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable time point tz)

$\%AUC_{0-tz}$ (the percentage of the $AUC_{0-\infty}$ that is obtained by extrapolation)

λ_z (terminal rate constant in plasma), $t_{1/2}$ (terminal half-life of the analyte in plasma)

MRT (mean residence time of the analyte in the body after intravenous administration)

CL (total clearance of the analyte in the plasma after intravascular administration)

V_z (apparent volume of distribution during the terminal phase λ_z following an intravascular dose)

V_{ss} (apparent volume of distribution at steady state following intravascular administration)

$Ae_{0\text{-}24/48}$ (amount of analyte that is eliminated in urine from the time point 0 to time point 24 and 48 h respectively)

$fe_{0\text{-}24/48}$ (fraction of analyte eliminated in urine from time point 0 to time point 24 and 48 h respectively)

$CL_{R,0\text{-}24/48}$ (renal clearance of the analyte from the time point 0 to time point 24 and 48 h respectively)

The pharmacokinetic parameters C_{max}, $AUC_{0\text{-}\infty}$ and $AUC_{0\text{-}tz}$ will be descriptively explored concerning dose proportionality.

7.1.3. Therapeutic efficacy evaluation

Tumour response will be the parameter for therapeutic efficacy. Tumour response will be evaluated according to the RECIST guidelines (see ISF). Tumour response will be assessed by the amount of patients with complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD), respectively. The number of patients with objective response (i.e. CR or PR) will be provided per dose level.

7.2 NULL AND ALTERNATIVE HYPOTHESES

All analyses in this trial are descriptive and exploratory by nature. Any statistical tests are performed only to provide a statistical framework from which to view the results and providing aid for planning further studies. No formal statistical inferences are foreseen.

7.3 PLANNED ANALYSES

Only one analysis population (the treated set) will be considered for efficacy and safety analyses. No Per protocol population will be used for analyses, however protocol violations will be described.

Treated Set consists of all patients who received at least one application of BI 6727

7.3.1 Primary analyses

Non evaluable patients will be replaced. The total number of study patients depends on the toxicity encountered. Patients who are evaluable for toxicity but not for efficacy need not be replaced.

The primary endpoint for this study is the tolerability and safety of BI 6727 as reflected by the Maximum Tolerated Dose (MTD) of BI 6727

Determination of MTD will be done using data from patients receiving the first course of BI 6727. Depending on the drug related toxicity observed in this study, up to six patients will be treated in each dose cohort. To increase the safety database at the presumed Phase II dose, a total of 24 patients will be enrolled at MTD.

MTD will be defined as the dose of BI 6727 that is one dose cohort below that dose at which two or more out of a maximum of six patients experienced DLT. At the maximum tolerated dose, no more than one patient out of six patients may experience Dose Limiting Toxicity (DLT, for definition, see section 5.2.1).

MTD will be defined on the basis of DLT observed during the first course. However, for those patients who receive a further infusion, unusual or unexpected toxicities will be considered for the purposes of confirming the MTD

To assess safety of BI 6727, all DLT's occurring during the first or repeated treatment courses will be reported as significant adverse events.

7.3.2 Secondary analyses

The secondary analysis will evaluate safety, pharmacokinetics and tumour response.

- Pharmacokinetic analyses

All evaluable subjects 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.

A subject is considered to be not evaluable if the subject has an important protocol violation relevant to the evaluation of pharmacokinetics or has insufficient data.

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, geometric coefficient of variation (refer also to 10.1).

Refer to Appendix 10.1 for details concerning handling and derivation of pharmacokinetic parameters.

If sufficient patients are entered into the study, covariates such as gender, age, and weight may be exploratively investigated for their potential influence on pharmacokinetic parameters. Exploratory analyses will compare the area under the plasma concentration-time profile and the maximum plasma concentration with considered relevant safety, efficacy, and pharmacodynamic endpoints.

- Efficacy analyses

Tumour response, objective response (CR, PR), and best overall response will be analysed descriptively according to the RECIST criteria (see section 5.1.2 and Appendix 10.4) at the end of every other treatment course.

For patients with no measurable lesion the overall response will be assessed as NEV (compare Table 10.4.4: 2). If data allow the assessment of the non-target lesion will be described in a explorative subgroup analysis.

The time to tumour progression will be defined as the time from first treatment administration to cancer progression or death due to the cancer under study.

7.3.3 Safety analyses

Key measures of safety will include:

- the incidence and intensity (according to CTCAE criteria version 3.0) of adverse events
- time course and distribution of patients by maximum CTCAE grade; and
- time course of laboratory changes

The type, number and intensity of adverse events will indicate how well BI 6727 is tolerated. Haematological toxicity such as thrombocytopenia, neutropenia and leukopenia as well as non-haematological toxicity will be evaluated continuously by using the CTCAE scheme.

Specific AE expected to be associated with BI 6727 may be described more accurately.

Frequency distributions and other descriptive statistical measures will be used to examine these variables. The time course of the changes and the reversibility will be displayed.

Descriptive statistics for ECG, in addition to abnormalities and other notable findings will also be analysed.

All data will be presented in the following segments:

- 1. First course of BI 6727
- 2. Data collected overall courses of BI 6727

7.3.4 Interim analyses

A pharmacokinetic interim analysis will be performed as soon as pharmacokinetic data of a sufficient number of patients are available and clean. A repeat pharmacokinetic interim analysis will be performed if requested. In contrast to the final pharmacokinetic calculations, the interim analysis will be based on planned sampling times rather than on actual times. Therefore, minor deviations of interim and final results may occur. The interim analysis will provide mean concentration-time profiles and summary statistics of pharmacokinetic

parameters/individual values without trial subject identification. The interim results will be distributed to the Investigator/trial team

7.4 HANDLING OF MISSING DATA

Every effort will be made to obtain complete information on all adverse events, with particular emphasis on potential dose limiting toxicities.

If not stated otherwise, missing data will not be imputed and remain missing. Potential outliers will be reported and analysed as observed.

Tumour evaluation : see RECIST criteria (see ISF, R01-0754) and Appendix 10.4.5 "Handling of missing tumour lesion measurement".

Time to progression:

Patients for whom no tumour assessments are available within the six weeks prior to discontinuation from treatment will be examined on a case by case basis. In case of early stop not related to the disease, patients will be censored at time of EOT.

Pharmacokinetic evaluation: For details refer to Appendix 10.1.

7.5 RANDOMISATION

In this open label, phase I, dose-escalating study, randomisation is not applicable.

Patients will be assigned, not randomized, into escalating dosage groups by order of admission into the trial. Differences in patient characteristics among dosage tiers will be examined carefully for any possible effects on the assessment of the maximum tolerated dose or tumour response.

7.6 DETERMINATION OF SAMPLE SIZE

In oncology trials six patients at the MTD are regarded sufficient to determine DLT. TABLE 7.6: 1 exhibits the probabilities of two or more out of six patients to be observed with DLT for some assumed underlying rates of DLT in the population of all patients. With the escalation scheme in this trial, there will be a probability of at least 80 % for two or more patients to exhibit DLT, if the underlying individual probability for a patient to reach DLT is 42 % or larger.

TABLE 7.6: 1 Assumed population rates of dose limiting toxicity

Individual probability of observing DLT	0.40	0.42	0.45
Probability of observing DLT in two or more out of six patients	0.77	0.80	0.84

Source: Probabilities calculated from the cumulative distribution function of the binomial distribution with n=6 and varying p's

8. ADMINISTRATIVE MATTERS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, version as of October 1996, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP)

Insurance Cover:

The Sponsor (Boehringer Ingelheim) will take out no-fault insurance cover for all subjects included in the study. The conditions of this insurance cover are available to the Investigator and the subjects in the ISF (Investigator Site File)

8.1 ETHICS

8.1.1 Institutional Review Board or Independent Ethics Committee

The trial will not be initiated before the protocol and informed consent and subject information form have been reviewed and received approval / favourable opinion from the Independent Ethics Committee (IEC) and implicit approval by the Competent Authority. Should a CTP Amendment be made that needs IEC approval and authority notification, the changes in the CTP will not be instituted until the Amendment and revised informed consent (if appropriate) have been reviewed and received approval / favourable opinion from the local IEC. A CTP Amendment intended to eliminate an apparent immediate hazard to subjects may be implemented immediately providing that the appropriate regulatory authorities and IEC are notified as soon as possible and an approval is requested. CTP Amendments only for logistical or administrative changes may be implemented with notification to the IEC only.

The constitution of the IEC must meet the requirements of the participating country / countries. A list of the IEC members, with names and qualifications, needs to be provided. The Sponsor must provide the name and address of the IEC along with a statement from the IEC that it is organised according to GCP and the applicable laws and regulations. The IEC must also perform all duties outlined by the requirements of the participating country / countries. For trials performed under an US IND: The US IND requirements outlined in the US Code of Federal Regulations must also be met.

8.1.2 Informed Consent and Patient Information

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

The subject 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 subject.

The subject 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 IEC members, and by inspectors from regulatory authorities.

Should a CTP Amendment become necessary, the subject consent form and subject information form may need to be revised to reflect the changes to the CTP. It is the responsibility of the Sponsor to ensure that an amended consent form is reviewed and received approval / favourable opinion from the IEC, and that it is signed by all subjects subsequently entered in the trial and those currently in the trial, if affected by the Amendment.

8.2 RECORDS

8.2.1 Drug accountability

Drug supplies, which will be provided by the Sponsor (or a CRO appointed by the Sponsor), must be kept in a secure, limited access storage area under the storage conditions defined by the Sponsor. Where necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature.

The Investigator / Pharmacist / Investigational Drug Storage Manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the Sponsor or alternative disposition of unused product(s). These records will include dates, quantities, batch/serial numbers, expiry dates, and the unique code numbers assigned to the investigational product(s) and trial subjects. The Investigator / Pharmacist / Investigational Drug Storage Manager will maintain records that document adequately that the subjects 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 Sponsor (or appointed CRO), the Investigator / Pharmacist / Investigational Drug Storage Manager must verify that all unused or partially used drug supplies have been returned by the clinical trial subject and that no remaining supplies are in the Investigator's possession.

8.2.2 Emergency code break

Not applicable in this open label trial.

8.2.3 Case Report Forms (CRFs)

All of the clinical data will be captured via electronic data capture (EDC) using the Oracle Clinical Remote Data Capture system, a web-based tool. The investigator site staff will enter and edit the data via a secure network, with secure access features (username, password and secure identification – an electronic password system). A complete electronic audit trail will be maintained. The investigator will approve the data using an electronic signature (Ref: 21 CFR Part 11), and this approval is used to confirm the accuracy of the data recorded.

Electronic CRFs (eCRFs) will be used for all patients. The investigator's data will be accessible from the investigator's site throughout the trial. Relevant medical history prior to enrolment will be documented at the baseline visit. Thereafter during the trial, narrative statements relative to the patient's progress during the trial will be maintained. The electronic

CRFs must be kept current to reflect patient status at each phase during the course of the trial. The patients must not be identified on the electronic CRF by name. Appropriate coded identification (i.e. Patient Number) must be used. The investigator must make a separate confidential record of these details (patient identification code list) to permit identification of all patients enrolled in a clinical trial in case follow-up is required. While a trial is ongoing and until the access to the database has been terminated, there will be no Documentation of Changes (DOCs). All changes will be requested from the investigator through the EDC system. If a change is necessary once the investigator has no further access to the database, a DOC will be sent to the investigator for confirmation of the change. The investigator's signature <for Japan> or seal is requested to show he/she agrees with the change that was made. The original DOC is kept by the investigator.

Copies of the electronic CRF together with all data changes made will be supplied to the investigator at the end of the trial. The investigator will be responsible for retaining all records pertaining to the trial as specified in the appropriate contract.

8.2.4 Source documents

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

Data reported on the eCRFs (electronic CRFs) 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 study; also current medical records must be available.

The following data to be reported on the eCRF need to be included and derived from the source documents:

Subject identification (gender, date of birth)

Subject participation in the study (substance, study number, subject number)

Dates of Subject's visits

Medical history (including trial indication and concomitant diseases, if applicable)

Medication history

Adverse Events (onset date)

Serious Adverse Events (onset date)

Concomitant therapy (onset date, changes)

Originals or copies of laboratory results (in validated electronic format if available)

Originals or copies of X-rays and Ultrasound findings, ECG results, EEG results, pneumological findings, endoscopic findings and other results based on hard copies of medical equipment

Conclusion of Subject's Participation in the study

All data that has been documented in the eCRF must be documented in the source data

8.2.5 Direct access to source data / documents

The investigator / institution will permit trial-related monitoring, audits, IRB / IEC 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 and inspection by health authorities (e.g. FDA). The Clinical Research Associate (CRA) / on site monitor may review all eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.2.4.

8.3 QUALITY ASSURANCE AUDIT

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

8.4 PROCEDURES

8.4.1 Adverse events

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.

All adverse events occurring during the course of the clinical trial (i.e., from signing the informed consent onwards through the observational phase) will be collected, documented and reported to the sponsor by the investigator according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the Investigator Site File.

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 representing a significant hazard, which is comparable to the aforementioned criteria.

All adverse events, serious and non-serious, will be fully documented on the appropriate CRF(s) / eCRFs. For each adverse event, the investigator will provide the onset, end, intensity, treatment required, outcome, seriousness and action taken with the investigational drug. The

investigator will determine the relationship of the investigational drug to all AE as defined in the 'Adverse Event Reporting' Section of the Investigator Site File.

The basis for judging the intensity of the AE as well as the causal relationship between the investigational product and the AE is described below.

Intensity of event

According to CTCAE criteria version 3.0 (see ISF)

Causal relationship

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. <For Japan> *The reason for the decision on causal relationship needs to be provided in the CRF.*

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

If a SAE is reported from a still blinded trial, the causal relationship must be provided by the investigator for all potential trial drugs, i.e. the BI trial drug and for all other trial drugs (i.e. any active comparator or placebo according to the trial design).

The investigator has the obligation to report AEs during the specified observational phase. If defined in the CTP, the investigator also has the responsibility to report AEs occurring in a certain period after a patient completes the trial. Any AEs reported to the sponsor during this phase must be documented in the safety database.

If not stipulated differently in the ISF, SAEs are to be reported to the sponsor using the BI Serious Adverse Event Report Form including a documented causal relationship assessment and providing as much detail regarding the SAE as possible. With receipt of follow-up information, all remaining fields on the SAE form are to be completed or updated.

Any serious or significant AE, whether or not considered related to the investigational product, and whether or not the investigational product has been administered, must be reported immediately by telephone / fax to the sponsor. Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs), will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the ISF.

Following every such telephone / fax reports, the Clinical Monitor must provide a written report of the serious or significant AE and any sequelae to Corporate Drug Safety according to the appropriate Corporate SOP(s). These narratives, which confirm the information collected by telephone, may give additional information not available at the time of the initial report.

8.4.2 Emergency procedures

Not applicable.

8.5 RULES FOR AMENDING PROTOCOL

All CTP amendments must be documented, dated and signed by all signatories (or their successors) of the original protocol. This also applies to any local amendment that may become necessary. Amendments need to be submitted to the IEC for review/approval and to the competent authority (CA) for approval.

8.6 DISCONTINUATION OF THE TRIAL BY THE SPONSOR

Boehringer Ingelheim reserves the right to discontinue the trial at any time for the following reasons:

1.) Failure to meet expected enrolment goals,
2.) emergence of any efficacy/safety information that could significantly affect continuation of the trial <if applicable>, *or any other administrative reasons, i.e.* <add pre-specified reasons>,
3.) violation of GCP, the CTP, or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial.

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

8.7 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 IEC and the regulatory authorities, i.e. the CA.

8.8 PUBLICATION POLICY

Boehringer Ingelheim is as much as possible dedicated to support process of free exchange of relevant scientific information. Any publication of the result of this trial must be consistent with the Boehringer Ingelheim publication policy. 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 finalization of the Clinical Trial Report (CTR).

8.9 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/patient out, unless specified differently in Section 6.2.3 of the CTP) or early termination of the trial.

9. REFERENCES

9.1 PUBLISHED REFERENCES

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R04-0423 Spaenkuch-Schmitt B, Bereiter-Hahn J, Kaufmann M, Strebhardt K. Effect of RNA silencing of polo-like kinase-1 (PLK1) on apoptosis and spindle formation in human cancer cells. J Natl Cancer Inst 2002;94(24):1863-1877.

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9.2 UNPUBLISHED REFERENCES

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10. APPENDICES

10.1 HANDLING OF PLASMA AND URINE DATA AND DERIVATION OF PHARMACOKINETICS PARAMETERS

Analyte plasma concentrations will be plotted graphically versus time for all subjects as listed in the analyte plasma concentration-time tables. For the presentation of the mean profiles, the arithmetic/geometric mean and the planned blood sampling times will be used.

Concentrations will be used for calculations in the format that is reported in the bioanalytical report. The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. For the calculation of pharmacokinetic parameters, only concentrations within the validated concentration range will be used. 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. The actual sampling times will be used. For predose samples, the actual sampling time will be set to zero.

Concentration data identified with NOS (no sample available), 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 including the pre-dose value). 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).

Non-compartmental pharmacokinetic parameters will be determined using WinNonlin or another validated program.

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 and/or NOP values of the profile will be ignored.

If the predose concentration before the first dose is less than or equal to 5% of C_{max} value in that subject, the subject's data without any adjustments can be included in all pharmacokinetic measurements and calculations (i.e., the predose value will not be changed to zero). If the predose value is greater than 5% of C_{max}, the subject should be dropped from all statistical evaluations. The individual pharmacokinetic parameters can be calculated and listed separately.
Every effort will be made to include all concentration data in an analysis. If not possible, a case to 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 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. Pharmacokinetic parameters which cannot be determined will be identified by "not calculated" (NC).

C_{max} and t_{max}: Individual C_{max} and t_{max} values will be directly determined from the plasma concentration time profiles of each subject. If the same C_{max} concentration occurs at different time points, t_{max} is assigned to the first occurrence of C_{max}.

Estimation of λ_z: The apparent terminal rate constant λ_z will be estimated from a regression of ln(C) versus time over the terminal log-linear disposition portion of the concentration-time profiles. The log-linear profiles, which include the regression line through the terminal points, will be checked via visual inspection, and it will be determined whether the regression appropriately represents the terminal slope. A minimum of three points will be used in the determination of λ_z. If the last concentration-time point increases, this time point may be included if the $t_{1/2}$ estimate is reasonable. If λ_z is not determinable then consequently only parameters not requiring λ_z will be reported. In addition, the lower ($t_{\lambda z,start}$) and upper ($t_{\lambda z,end}$) limit on time for values to be included in the calculation of λ_z will be listed.

$t_{1/2}$: The terminal half-life will be calculated from the terminal rate constant using the equation

$$t_{1/2} = \frac{\ln 2}{\lambda_z}$$

AUC: The area under the curve will be calculated using the linear up/log down algorithm. If an analyte concentration is equal to or higher than the preceding concentration, the linear trapezoidal method will be used. If the analyte concentration is smaller than the preceding concentration, the logarithmic method will be used.

Linear trapezoidal rule ($t_2 > t_1$ and $C_{t2} \geq C_{t1}$):

The area of the trapezoid between the two data points (t_1, C_{t1}) and (t_2, C_{t2}) will be computed by:

$$AUC_{t1\text{-}t2} = 0.5 \times (t_2 - t_1) \times (C_{t1} + C_{t2})$$

Logarithmic trapezoid rule ($t_2 > t_1$ and $C_{t2} < C_{t1}$):

The area of the trapezoid between the two data points (t_1, C_{t1}) and (t_2, C_{t2}) will be computed by:

$$AUC_{t1-t2} = \frac{(t_2 - t_1) \times (C_{t2} - C_{t1})}{\ln(C_{t2}/C_{t1})}$$

$AUC_{0\text{-}\infty}$: The area under the plasma concentration-time curve over the time interval from 0 extrapolated to infinity will be calculated according to the following equation

$$AUC_{0\text{-}\infty} = AUC_{0\text{-}tz} + \frac{C'_{tz}}{\lambda_z}$$

where C'_{tz} is the concentration predicted by the regression line for the time t_z (time of last measurable concentration of the analyte in plasma). The area under the concentration-time curve over the time interval from 0 to the last quantifiable plasma concentration ($AUC_{0\text{-}tz}$) will be calculated by the linear up/log down method as described above.

$\%AUC_{tz\text{-}\infty}$: The percentage of the $AUC_{0\text{-}\infty}$ will be obtained by extrapolation according to the following equation:

$$\%\,AUC_{tz-\infty} = \frac{AUC_{0\text{-}\infty} - AUC_{0\text{-}tz}}{AUC_{0\text{-}\infty}} \times 100$$

MRT: The mean residence time after intravenous bolus injection will be calculated as follows:

$$MRT = \frac{AUMC_{0-\infty}}{AUC_{0-\infty}}$$

In order to compare the mean residence time after intravenous bolus administration (MRT) and intravenous infusion (MRT_{inf}), the following equation will be used in addition, where T represents the infusion time.

$$MRT = MRT_{inf} - (T \times 0.5)$$

The area under the first moment curve from time 0 to infinity ($AUMC_{0-\infty}$) is calculated according to:

$$AUMC_{0-\infty} = AUMC_{0-tz} + \frac{C'_{tz} \times tz}{\lambda_z} + \frac{C'_{tz}}{\lambda_z^2}$$

CL: The total clearance after intravenous administration will be determined according to the following equation:

$$CL = \frac{Dose}{AUC_{0-\infty}}$$

(F = absolute bioavailability factor)

V_z: The apparent volume of distribution during the terminal phase after intravascular administration will be determined according to the following equation:

$$V_z = \frac{CL}{\lambda_z}$$

V_{ss}: After single intravenous bolus administration or intravenous infusion when the mean residence time has been adapted as described above, the distribution volume in the steady state will be calculated according:

$$V_{ss} = CL_{ss} \times MRT_{ss}$$

fe_{t1-t2}: The fraction excreted is calculated according to

$$fe_{t1-t2} = \frac{Ae_{t1-t2}}{Dose} \times 100$$

where **Ae_{t1-t2}** is the total quantity of the analyte that is excreted in urine over the time interval t_1 to t_2. This may represent the product of urine volume and urine analyte concentration for one time interval, as well as the cumulative amounts excreted calculated as the sum of the excreted amounts of subsequent time intervals.

$CL_{R,t1-t2}$: The renal clearance (CL_R) will be calculated as the quotient of the quantity of the analyte that is excreted in urine from the time point t_1 until the time point t_2 (Ae_{t1-t2}) and the area under the concentration-time curve within the same time interval (AUC_{t1-t2}).

$$CL_{R,t1-t2} = \frac{Ae_{t1-t2}}{AUC_{t1-t2}}$$

gMean, gCV: The geometric mean (gMean) and coefficient of variation, gCV (given in %), will be calculated by the formulae:

$$gMean = \exp\left[\frac{1}{n}\sum_{i=1}^{n}\ln(x_i)\right] = \exp\left[\overline{\ln(x_i)}\right]$$

$$gCV(\%) = 100 \cdot \sqrt{\exp\left[Var(\ln(x_i))\right] - 1}$$

where

$$Var(\ln(x_i)) = \frac{1}{n-1}\sum_{i=1}^{n}\left[\ln(x_i) - \overline{\ln(x_i)}\right]^2 .$$

10.2 BLOOD SAMPLING TIME SCHEDULE

Visit	Day	Course	Time Point [hh:min]	CRF Time/ planned time	Sample No	Repeated course
2	1	1	-0:05	-0:05	1	
			0:00 Start of infusion	0:00		
			0:15	0:15	2	
			0:30	0:30	3	
			0:45	0:45	4	
			1:00 Immediately prior to end of infusion of BI 6727	1:00	5	CnR1
			1:30	1:30	6	
			2:00	2:00	7	
			4:00	4:00	8	
			8:00	8:00	9	
3	2	1	24:00	24:00	10	CnR2
4	3	1	48:00	48:00	11	
5	5	1	96:00	96:00	12	
6	8	1	168:00	168:00	13	CnR3
7	15	1	336:00	336:00	14	CnR4

Cn = number of course ($n \geq 2$)

For repeated courses blood sampling will be performed 1:00 h after start of infusion (immediately prior to end of infusion) and 24:00, 168:00 and 336:00 h after drug administration.

Please note: Blood samples during infusion have to be taken in the opposite arm of the infusion arm.

[redacted]

[redacted]

[redacted]

10.4. TUMOUR ASSESSMENT ACCORDING TO RECIST

10.4.1 Tumour assessment

Measurable disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques (CT, MRI) or as ≥10 mm with spiral CT scan. All tumour measurements must be recorded in millimetres (or decimal fractions of centimetres).

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by colour photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.

Ultrasound. Ultrasound should not be used to measure tumour lesions. The same holds true for endoscopy or laparoscopy.

Non-measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not confirmed or followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions

All measurable lesions up to a maximum of five lesions per organ and ten lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum longest diameter. The baseline sum longest diameter will be used as reference by which to characterize the objective tumour response.

Non-target lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

10.4.2 Evaluation of target lesions

Complete Response (CR): disappearance of all target lesions

Partial Response (PR): at least a 30 % decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter

Progressive Disease (PD): at least a 20 % increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions

Stable Disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum longest diameter since the treatment started

10.4.3 Evaluation of non-target lesions

Complete Response (CR):	disappearance of all non-target lesions
Incomplete Response/ Stable Disease (SD):	persistence of one or more non-target lesion(s)
Progressive Disease (PD):	appearance of one or more new lesions and / or unequivocal progression of existing non-target lesions

10.4.4 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression / recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement (overall response, Table 10.4.4: 1).

The overall responses for all combination of tumour response (target and non-target lesions) with and without appearance of new lesion is given in Table 10.4.4: 1

Table 10.4.4: 1 Overall responses for target and non-target lesions with and without appearance of new lesion

Target lesions	non-target lesions	new lesions	overall response
CR	CR	no	CR
CR	incomplete response / SD	no	PR
PR	non-PD	no	PR
SD	non-PD	no	SD
PD	any	yes or no	PD
any	PD	yes or no	PD
any	any	yes	PD

The examinations should be performed at screening and in line with RECIST after every second course of treatment if the patient qualifies for further courses. Tumour measurements at earlier time points after start of study treatment may be performed if clinically indicated as assessed by the investigator. Tumour measurements during the follow-up period after discontinuation of the study treatment are optional. Imaging results can be used at screening if they were done within the previous four weeks, i.e. no repeat investigation is requested for the purpose of the study.

To be assigned a status of CR, PR, or SD, changes in tumour measurements should be confirmed by repeat assessments that should be performed according to RECIST.

In the case that an assessment of the target and non-target lesion of a patient could not be made by the investigator the category "non-evaluable" (NEV) should be used. In case of absence of non-target lesion at baseline the category of NEV has to be used. The overall responses for all combination of tumour response (target and non-target lesions) with and without appearance of new lesion and non-evaluable lesion measurements is given in Table 10.4.4: 2

Table 10.4.4: 2 Overall responses for target and non-target lesions with and without appearance of new lesion and non-evaluable lesion measurements

Target lesions	non-target lesions	new lesions	overall response
NEV	Any, except of PD	no	NEV
NEV	PD	yes or no	PD
Any, except of PD	NEV	no	response criteria of target lesion
PD	NEV	yes or no	PD
any	any	yes	PD

If the overall response is NEV the additional categories (NEVCP and NEVCNP) will be used. Description see Table 10.4.4: 3. In the case that a tumour measurement was not performed please see handling of missing value (section 10.4.5).

Table 10.4.4: 3 Tumour response criteria in the case of no assessment of the tumour by the investigator

Label of tumour response	Shortcut	Tumour Response
Non-evaluable, clinically not progressive	NEVCNP	No assessment of the tumour is possible, but the investigator rated the patient's disease status as clinically not progressive
Non-evaluable, clinically progressive	NEVCP	No assessment of the tumour is possible, but the investigator rated the patient's disease status as clinically progressive

10.4.5 Handling of missing tumour lesion measurements

One to ten target lesions (not exceeding 5 lesions per organ) should be identified at screening. These lesions should be followed up with the same method(s) used at screening and their size will be recorded in millimetres.

If target lesions selected at baseline become non-evaluable (i.e. different technique used or missing of tumour lesion measurement, etc), the following rules will be applied

- Analysing strategies:

missing imaging at one time point: if there are lesion measurements during the next course then the non-evaluable tumour evaluation will be reassessed as follows - in case of objective response and stable disease the previous tumour evaluation will be assessed as non-evaluable but no progressive disease (NEVNPD censored with reassessment REASS), the time point of the following non-evaluable measurement will be used for tumour response duration. In the case of progressive disease the previously non-evaluable measurement will be reassigned with non-evaluable but progressive disease (NEVPD censored with reassessment REASS).

- one of the tumour lesions was missed but tumour imaging will be performed within one week of the scheduled time point - this new imaging will be used
- for determination of time of tumour response - the latest time point will be used except in the case of progressive disease when the earliest time point will be used.