CLINICAL TRIAL PROTOCOL

	Document Number:	c02441868-07
EudraCT No.:	2014-005395-28	
BI Trial No.:	1336.1	
BI Investigational Product(s):	BI 836880	
Title:	A First-in Human Phase I, non-randomized, open-label, multi-center dose escalation trial of BI 836880 administered by repeated intravenous infusions in patients with solid tumors.	
Brief Title:	Dose finding study of BI836880 in patients with solid tumors	
Clinical Phase:	Phase I	
Trial Clinical Monitor:	[redacted] Phone: [redacted] Fax : [redacted]	
Coordinating Investigator:	[redacted] Phone: [redacted] Fax: [redacted]	
Status:	Final Protocol (revised protocol based on global amendment 5)	
Version and Date:	**Version:**	**Date:**
	6.0	08 March 2019

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		not applicable	
Name of active ingredient:		BI 836880	
Protocol date: 11 May 2015	**Trial number:** 1336.1		**Revision date:** 08 March2019

Title of trial:	A First-in Human Phase I, non-randomized, open-label, multi-center dose escalation trial of BI 836880 administered by repeated intravenous infusions in patients with solid tumors.
Coordinating Investigator	[redacted]
Trial site(s):	Multi-centre trial conducted in 2 countries
Clinical phase:	Phase I; First In Human
Objective(s):	Objective of this trial is to determine the maximum tolerated dose (MTD) of BI 836880 and to provide preliminary safety data given as intravenous infusion and to determine recommended phase II dose. Further the PK-, immunogenicity and PD-profile, as well as primary signs of anti-tumor activity of BI 836880 should be assessed.
Methodology:	Non-randomized, uncontrolled, open-label, dose escalating study of BI 836880 administered intravenously
No. of patients:	About 80 patients will be entered, including at least 12 patients treated at MTD with tumour lesions evaluable for Dynamic contrast-enhanced (DCE)-MRI.
total entered:	80
each treatment:	80 (all patients will receive trial drug, but on different dose levels)

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Diagnosis :	Advanced or metastatic/refractory solid tumors
Main criteria for inclusion:	• Age ≥ 18 years • Histologically or cytologically confirmed malignancy which is locally advanced or metastatic solid tumor, and either refractory after standard therapy for the disease or for which standard therapy is not reliably effective, e.g. they do not tolerate or have contraindications to otherwise available standard therapy and tumour lesions evaluable for Dynamic contrast-enhanced (DCE)-MRI at MTD • ECOG performance status ≤ 2 • Adequate hepatic, renal and bone marrow functions • Signed written informed consent • Life expectancy ≥ 3 months in the opinion of the investigator • Recovery from all reversible adverse events of previous anti-cancer therapies to baseline or CTCAE grade 1, except for alopecia (any grade) sensory peripheral neuropathy CTCAE grade ≤ 2 or considered not clinically significant.
Test product(s):	BI 836880 and Diluent for BI 836880 drug product
dose:	Starting dose will be 40 mg every 3 weeks; the dose can be increased up to 1250 mg administered every 3 weeks.
mode of administration:	i.v.
Comparator products:	n/a
dose:	n/a
mode of administration:	n/a
Duration of treatment:	Administration of BI 836880 can be continued up to disease progression or until intolerable toxicities has been recorded.
Endpoints	1° endpoint: • assessment of the maximum tolerated dose (MTD) based on the number of patients presenting dose-limiting toxicities (DLTs) using CTCAE v4.03, started within 3 weeks after first administration of study treatment (i.e. within first

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	cycle of treatment) and judged to be related to the study medication . 2° endpoints: • Exposure measures (AUC0-tz) after the first dose ; • Disposition kinetic measures (t1/2) after the first dose; • Drug related AEs leading to dose reduction or discontinuation during treatment period		
Safety criteria:	Incidence and intensity of adverse events graded according to the common terminology criteria for adverse events (CTCAE, version 4.03), incidence of dose limiting toxicities; laboratory parameters, vital signs, ECG		
Statistical methods:	Dose escalation guided by a Bayesian logistic regression model with over dose control		

FLOW CHART

Trial Periods	**Screen**	**Treatment courses**										**EOT**	**EoR**	**FU / EoFU**
Course		1, 2, 3, 4						5, 6			7^{18} ongoing			
Week		w1			w2	w3	Imaging	w1	w2	Imaging	w1			
Visit	Screen	V1			V2	V3	V4	V1	V2	V3	V1			
Day; visit window [days]	-21 to -1	d1	d2	d3; +1d (1,2)*	d8; -1/+2d	d15; -1/+2d	d18; +/-3d (2,4)*	d1	d8; -1d/ +2d	d18; +/-3d (6)*	d1	EoT (when defined)	Last admin +42d; -2/+3d	every 6 weeks (+/-3d) until PD
Informed consent / IRT call	X													
Demographics	X													
Medical history	X													
Review of in-/ exclusion criteria[1]	X													
Height	X													
Weight	X	X						X			X	X		
ECOG performance status	X	X						X			X	X		
body temperature [2]	X	X			X (1,2)*			X			X	X		
Blood pressure, heart rate [3]	X	X (2x)**	X	X	X	X		X (2x)	X		X (2x)	X	X	
12-lead ECG [4]	X	X (2x)**	X (1,2)*					X (2x)			X (2x)	X		
Echocardiography [5]	X	if clinically indicated										X		
General safety laboratory parameters [6]	X	X		X	X	X		X	X		X	X		
Serum pregnancy test [7]	X	X						X			X	X		
Concomitant therapy	X	X	X	X	X	X		X	X		X	X	X	
Physical examination [8]	X	X	X	X	X	X		X	X		X	X	X	
Adverse events [9]	X	X	X	X	X	X		X	X		X	X	X	
Eligibility for treatment / IRT call [10]		X						X			X			
Administration of BI 836880 [11]		X						X			X			
[redacted]														
Pharmacokinetics [13]		X	X	X	X (1,2,4)*	X (1,2,4)*		X			X (7-12)*	X	X	X (FU1)*
[redacted]														

Trial Periods	**Screen**	**Treatment courses**										**EOT**	**EoR**	**FU / EoFU**
Course *		1, 2, 3, 4						5, 6			7[18] ongoing			
Week		w1			w2	w3	Imaging	w1	w2	Imaging	w1			
Visit	Screen	V1			V2	V3	V4	V1	V2	V3	V1			
Day; visit window [days]	-21 to -1	d1	d2	d3; +1d (1,2)*	d8; -1/+2d	d15; -1/+2d	d18; +/-3d (2,4)	d1	d8; -1/+2d	d18; +/-3d (6)	d1	EoT (when defined)	EoT +42d; -2/+3d	every 6 weeks (+/-3d) until PD
[redacted]														
Reason for treatment discontinuation												X		
Patients status													X	X
Next line of anti-cancer therapy													X	X

* number in brackets indicate the course this visit/assessment is applicable EoC = End of Course; FU1 = 1st Follow-up visit
** 2 timepoints to be evaluated at this visit; see detailed flowchart in Appendix 10.4

1 See section 3.3
2 See section 5.3.4
3 See section 5.3.4 and Appendix 10.2; for exact time points see detailed flowchart in Appendix 10.4
4 See section 5.3.6; for exact time points see detailed flowchart in Appendix 10.4
5 See section 5.3.7
6 See section 5.3.5
7 See section 5.3.5
8 See section 5.3.3
9 See section 5.3.8
10 See re-treatment criteria in section 4.1.4; for medication number allocation it's possible to conduct IRT call ahead of the planned visit (= day of administration).
11 See section 4.1.4 and "Instruction for Pharmacist" which is filed in Investigator Site File;
see section 6.1 for hospitalization requirements

[redacted]

13, See detailed flowchart in Appendix 10.4. No samples will be collected after data base lock and trial completion (see section 6.2.3.5)

[redacted]

18 For the 2 ongoing patients, minimum set of procedures is mandatory. This includes safety lab, vital signs including blood pressure, adverse events, and pregnancy test if applicable. However, other assessments as indicated in the flowchart of the protocol or single lab values can be omitted according to investigator's opinion.

TABLE OF CONTENTS

ABBREVIATIONS

[redacted]

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine amino transferase
ANC	Absolute neutrophil count
Ang2	Angiopoietin2
AST	Aspartate amino transferase
BI	Boehringer Ingelheim
BIRDS	Boehringer Ingelheim Regulatory Documents for Submission
BLQ	Below the limit of quantification
BP	Blood Pressure
CA	Competent Authority
CI	Confidence Interval
CML	Local Clinical Monitor
CPL	Clinical Program Leader
CPPL	Clinical Pharmacology Program Leader

[redacted]

CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
DCE-MRI	Dynamic Contrast-Enhanced Magnetic Resonance Imaging
DEDP	Drug Exposure During Pregnancy
DILI	Drug Induced Liver Injury
DL	Dose Level
DLT	Dose Limiting Toxicity
DSB	Data Safety Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDTA	Ethylendiaminetetraacetic Acid
EOT	End Of Treatment
EudraCT	European Clinical Trials Database
EWOC	Escalation with overdose control
FC	Flow Chart
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice

[redacted]

i.v.	intravenous
IB	Investigator's Brochure
IEC	Independent Ethics Committee
INR	International Normalized Ratio

IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
[redacted]	
LMWH	Low Molecular Weight Heparine
MedDRA	Medical Dictionary for Drug Regulatory Activities
MTD	Maximum Tolerated Dose
NC	Not calculated
NCA	Noncompartmental Analysis
NCI	National Cancer Institute
NOA	Not analysed
NOAEL	No Observed Adverse Effect Level
NOP	No peak detectable
NOR	No valid result
NOS	No sample
NSAID	Nonsteroidal Anti-Inflammaroty Drug
OPU	Operative Unit
p.o.	per os (oral)
PC	Patient Completion
PD	Pharmacodynamics
PD	Progressive Disease
PK	Pharmacokinetics
[redacted]	
RDC	Remote Data Capture
RECIST	Response Evaluation Criteria In Solid Tumors
REP	Residual Effect Period
SAE	Serious Adverse Event
SD	Stable Disease
SOP	Standard Operation Procedure
SUSARs	Suspected Unexpected Serious Adverse Reactions
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
Tie2	Receptor of the TIE Family
TME	Translational Medicine Expert
TMF	Trial Master File
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
[redacted]	
TSTAT	Trial Statistician
ULN	Upper Limit of Normal

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Cancer remains an important health problem with 14.1 million new cancer cases, 8.2 million cancer deaths and 32.6 million people living with cancer (within 5 years of diagnosis) in 2012 worldwide (R14-2220). Most patients with locally advanced and/or metastatic tumors are not curable and died due to their disease. There is therefore a substantial need for novel therapeutic strategies to improve the outcome of patients with advanced or metastatic malignancies who have failed conventional therapies, or for whom no therapy of proven efficacy exists. In the last decade, several novel compounds targeting specific cellular components or tumor environment, including tumor vasculature and angiogenesis have been developed based on increasing understanding of cancer biology and cell regulation.

Angiogenesis is considered as a key process in tumor growth (R12-2552). Once a certain tumor size is reached, these blood vessels are no longer sufficient and new blood vessels are required to continue growth. Acquisition of the angiogenic phenotype can result from genetic changes or local environmental changes that lead to the activation of endothelial cells. One way for a tumor to activate endothelial cells is through the secretion of pro-angiogenic growth factors (e.g. vascular endothelial growth factor, angiopoietin2, etc.) which then bind to receptors on nearby dormant endothelial cells that line the interior of vessels.

Vascular endothelial growth factor plays a major role in angiogenesis. Blockade of VEGF axis has proven to represent an efficacious treatment for patients with advanced malignancies when given in combination with cytotoxic “backbone” therapy.

Angiopoietin2 (Ang2), a ligand of the Tie2 receptor, plays an important role in angiogenesis and it’s *in vivo* inhibition results in tumor growth inhibition and vasculature changes (R12-3593).

Both pro-angiogenic pathways (VEGF/VEGF-R and Ang-2/Tie-e) have been reported to synergize and to crosstalk (R14-5320, R14-5323). The anticipated clinical benefit of VEGFxAng2 dual inhibition would be the modulation of tumor angiogenesis and reduced tumor growth rate.

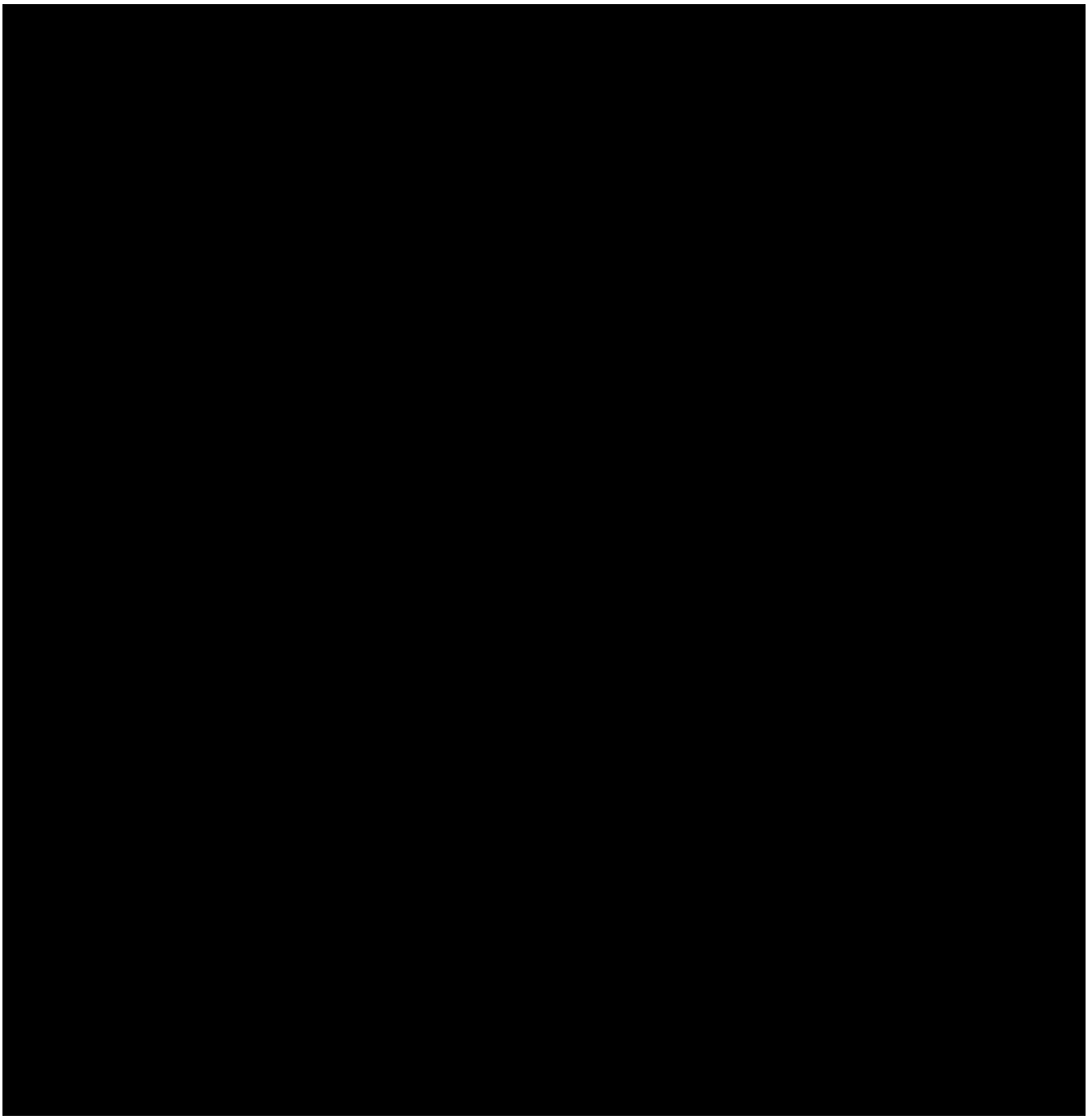
Developement of anti-angiogenic agents targeting pro-angiogenic factors is a valid concept which showed clinical efficacy in monotherapy (mainly with tyrosine kinase inhibitors: TKI) and/or in combination with standard treatment (chemotherapies) ((R05-2504, R09-5764, R12-5190, R14-5143, R14-5142, R14-3261, R13-5295, R14-5374, R12-0021, R14-5318)).

1.2 DRUG PROFILE

The Nanobody® technology was originally developed following the discovery that camelidae (camels and llamas) possess fully functional antibodies that lack light chains. These heavy-chain antibodies contain a single variable domain (V_{HH}) and two constant domains (CH2 and CH3). The cloned and isolated V_{HH} domain is a stable polypeptide harbouring the full

antigen-binding capacity of the original heavy-chain antibody. These newly discovered V_{HH} domains form the basis of a new generation of therapeutic antibodies named Nanobodies. (R15-1719)

BI 836880 is a genetic fusion protein of one VEGF-A-binding and one Ang2-binding single domain antibodies (V_{HH}, Nanobody®). The two single domain antibody moieties are linked via a human serum albumin-binding Alb11 domain, serving as half-life extension, and glycine-serine linkers between the domains. The protein has a molecular mass of 40.7 kDa (c02353882-01)



No clinical experience has been gained in humans so far.

For a more detailed description of the drug profile refer to the current Investigator's Brochure (IB) which is included in the Investigator Site File (ISF).

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Angiogenesis is the formation of new blood vessels from pre-existing vasculature and is a key process in tumor growth. The Ang2/Tie2 and the VEGF/VEGFR2 pathways have been identified as key pathways mediating tumor angiogenesis (R13-0448). Multiple studies have described increased VEGF levels in a variety of human cancers and the VEGF expression levels have been correlated with poor survival (R15-1720). The VEGF neutralizing monoclonal antibody bevacizumab has demonstrated anti-tumor activity in clinical trials and is currently approved for several indications and setting, mainly in combination with standard chemotherapy regimens (R15-1222).

Studies in mice have shown that Ang2, a ligand of the Tie2 receptor, controls vascular remodeling by enabling the functions of other angiogenic factors, such as VEGF (R12-3593). Ang2 is primarily expressed by endothelial cells, strongly induced by hypoxia and other angiogenic factors and has been demonstrated to regulate tumor vessel plasticity, allowing vessels to respond to VEGF and FGF2 (R12-3834).
The inhibition of Ang2 is currently being tested in Phase II/III trials of the peptibody Trebaninib in ovarian cancer. In a randomized Phase III trial in patient with recurrent ovarian cancer Trebaninib was tested in combination with paclitaxel compared to chemotherapy alone and demonstrated improvement in PFS (7.2 month vs 5.4 months, HR 0.66 95% CI 0.57-0.77, p< 0.0001) (R14-5440).

Unfortunately, the anti-tumor activity of VEGF blokers and Ang2 blockers is not durable and only a limited number of patient benefit from such therapies. New therapeutic strategies are needed to improve outcome of metastatic/advanced cancer patients.

Pre-clinical data demonstrate that improved efficacy can be achieved by combined inhibition of VEGF and Ang2 (R14-5320, R14-5323). This observation was confirmed by internal data (Investigator's Brochure).

This supports testing BI 836880 in human with the objective to improve patients' outcome. First step for this clinical development is to define the safety profile of BI 836880 and the recommended dose for further development.

2.2 TRIAL OBJECTIVES

Primary objective:
- To determine the maximum tolerated dose (MTD) of BI 836880 given as intravenous infusion and to determine recommended phase II dose.

Secondary objective:
- To provide preliminary safety data

[redacted]

2.3 BENEFIT - RISK ASSESSMENT

BI 836880 has not been tested in human so far. In the 13 weeks toxicology study in cynomolgus monkeys BI 836880 was well tolerated up to the highest tested dose of 60 mg/kg.

Anti-VEGF or anti-VEGF-R antibodies have been largely tested in clinic with a well-defined safety profile. Most commonly reported adverse events with such compounds are fatigue, hypertension, proteinuria, diarrhea and bleeding (epistaxis). Severe adverse events include gastrointestinal perforations, tumor haemorrhage and arterial thromboembolism (R14-3588, R14-3261).

There is less clinical experience with anti-Ang2 compared to VEGF pathway blockade clinical experience. The most advanced anti-angiopoietin compound (Trebaninib) in development is in Phase III in combination with chemotherapyR14-5440. Other anti-Ang2 compounds are currently in early stage of clinical development (R15-1645, R15-1646, R15-1648). From this clinical experience the most commonly reported side effects are fatigue and gastro-intestinal symptoms (diarrhea, nausea and vomiting). No bleeding or thromboembolic events were reported with this class of compound. Of note, almost all tested anti-Ang2 molecules failed to define a MTD (R15-1646, R15-1648).

Limited clinical experience of dual blockade is available. Recently, Phase I data of the bispecific human anti-Ang2/anti VEGF-A antibody (RG7221) were reported. MTD was not reached with only one dose limiting toxicity (DLT) reported (fatal pulmonary hemorrhage). Hypertension was the most common observed adverse event (R15-1644).

Based on this clinical available data it is expected that blockade of both targets will result in similar side effects as anti-VEGF and anti-Ang2 blockade. Based on the phase I trial results of RG7221 no increase in side effect severity is anticipated with BI 836880. It is anticipated that the safety profile of BI 836880 will most likely includes fatigue, hypertension, proteinuria, gastro-intestinal side effects and bleeding.

Previous clinical experience with nanobodies in different disease showed acceptable safety profile with no specific side effect related to this technology (R13-2303).

Because additional adverse event not previously observed with anti-VEGF and anti-Ang2 may also occur in humans, and taking in consideration BI 836880 toxicology study results, patients will be closely monitored for the development of adverse events that may results from BI 836880 administration, with a special attention to renal function and immunogenic side effect.

Although rare, a potential for drug-induced liver injury is under constant surveillance by sponsors and regulators. Therefore, this study requires timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to ensure patients´ safety see also section 5.3.8.1.

Because of the early stage of development of BI 836880 no reproduction toxicity or genotoxicity studies were performed. Because of the advanced stage of disease of phase I studies populations, women of childbearing potential can be included into the trials. To minimize the risk of unintentional exposure of an embryo or fetus to the investigational drug, women of childbearing potential must agree to the requirements for pregnancy testing and contraceptive methods described in this protocol.

Overall, BI 836880 is expected to have an acceptable safety profile and an adequate risk/benefit in patients with locally advanced or metastatic solid tumor who are either refractory after standard therapy for the disease or for which standard therapy is not reliably effective.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a Phase I, non-randomized, uncontrolled, open-label, dose escalating study of BI 836880 administered intravenously. The eligible patient population will be patients with advanced solid tumors. Dose escalation will be guided by a Bayesian logistic regression model with over dose control (details refer to Section 7), restricted to a maximum of 200% dose increment for dose up to 120 mg and a maximum of 100% dose increment for dose >120 mg. At any time during the trial, it will not be permitted to escalate to a dose which does not fulfil the escalation with overdose control (EWOC) criterion (refer to Section 7).

For any dose-escalation cohort, at least 2 patients will be required. At first dose level, first patient will be treated and observed for at least 2 weeks before allowing the second patient to receive BI 836880 infusion. Subsequent enrollment at all dose levels within dose escalation, each patient in a given cohort (dose level) will be observed for a minimum of 48 hours after first BI 836880 application before allowing treatment for subsequent patient in the same cohort. In case only 2 patients are evaluable and neither has experienced a DLT within the first cycle, then dose-escalation can occur based on these 2 patients. However, should one of these 2 patients experience a DLT in the first cycle, a third patient will be enrolled on the same dose level. After all patients in a cohort have either experienced a DLT or have been observed for at least one cycle (=3 weeks) without a DLT, the Bayesian model will be updated with the newly accumulated data. The overdose risk will then be calculated for each dose, and escalation will be permitted to all doses which fulfil the EWOC criterion and dose escalation rules according to section 4.1.3. Decision on further recruitment (dose escalation, de-escalation or cohort expansion will be made by a Data Safety Board (DSB) based on the collected safety data as well as other data (e.g. PK/PD data) when available.

If DLTs are observed in the first two consecutive patients of a previously untested dose level, subsequent enrolment to that cohort will be stopped. The Bayesian logistic regression model will be re-run to confirm that the dose-level still fulfils the EWOC criterion. Decision will be made whether the next patients will be enrolled on the same dose level, or if they will be enrolled to a lower dose level. Figure 3.1: 1 shows how the decision of dose escalation is made.

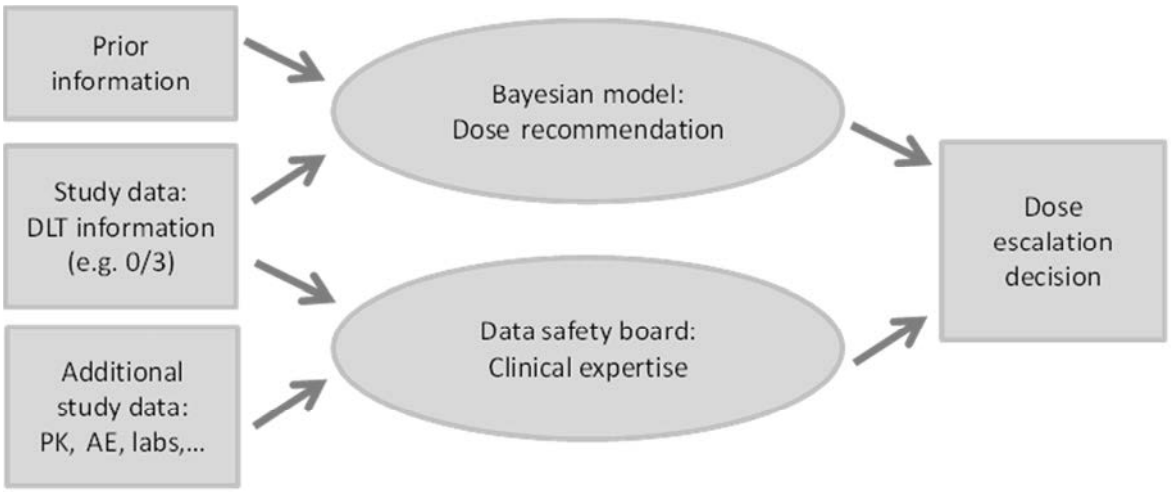


Figure 3.1: 1: Escalation Decision – Combination of clinical and statistical expertise

BI 836880 infusion will be repeated every 3 weeks. In the case the patient shows a stable disease or even a response, the administration of BI 836880 can be continued up to disease progression or until intolerable toxicity has been recorded. In specific cases an intra-patient dose escalation can be granted (see section 4.1.3).

Once a MTD has been reached it is foreseen to enroll up to 12 patients on this dose level to enlarge the group of patients treated on proposed RP2D. A minimum of 12 patients must have tumour lesions evaluable for Dynamic contrast-enhanced (DCE)-MRI to allow a better interpretation of a pharmacodynamics (vascular) effect of BI 836880. Confirmation of the RP2D will be made based on all available safety, PK and Pharmacodynamics (PD) data at all treatment cycles and all dose levels.

In case of anti-tumor activity signals in a given tumor type, DSB can take the decision for a trial expansion to recruit patients with the same tumor type with the aim to generate safety and preliminary efficacy data specific to such disease. 2-3 tumor type expansion cohorts are planned. Up to a total of 20 patients may be recruited in each tumor type expansion cohort and will be treated according to same Flow Chart as patient in previous cohorts. This is to confirm RP2D in patient with specific tumor type according to study objective and to prepare further Phase II studies. This change will be implemented with a further amendment to this protocol.

3.1.1 Administrative structure of the trial

The coordinating investigator is an investigator participating in the trial that has experience of this type of trial and investigations. The coordinating investigator has been designated by Boehringer Ingelheim and will sign the clinical trial report.

A DSB will be appointed to evaluate DLT, overall safety and other available data (e.g. PK data) and confirm dose escalation steps. DSB will also evaluate all available data to confirm recommended Phase II dose as well as the decision for a tumor type expansion cohort. Members of this DSB will be investigators of participating trial sites, Trial Statistician

(TSTAT), Clinical Program Leader (CPL) and Trial Clinical Monitor (TCM); Clinical Pharmacology Program Leader (CPPL) and Translational Medicine Expert (TME) can be invited as needed, especially for discussion of PK/PD data and discussion of biomarker. Minimum needed data for dose escalation decision is explained in the DSB charter.

On-site monitoring will be performed by BI or a CRO authorized by Boehringer Ingelheim. Pharmacokinetic analyses will be performed by Boehringer Ingelheim or a CRO authorized by Boehringer Ingelheim.

[redacted]

Routine safety laboratory exams will be performed by local laboratories.
All trial relevant documentation will be stored in the Trial Master File (TMF) at BI. In addition each site will have an ISF containing all trial documents relevant for the site.

Boehringer Ingelheim has appointed a TCM, responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal Standard Operating Procedures (SOPs),
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- order the materials as needed for the trial,
- ensure appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and Investigators of participating countries.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

An IRT system from an external vendor will be used for trial medication supply and re-supplies.

Tasks and functions assigned in order to organise, manage, and evaluate the trial will be defined according to BI SOPs. A list of responsible persons and relevant local information (as protocol reference, if applicable) can be found in the ISF and BIRDS.

A Coordinating Investigator will be nominated and will be responsible to coordinate Investigators at different centres participating in this multicentre trial. Tasks and responsibilities will be defined in a contract. Relevant documentation on the participating (Principal) Investigators and other important participants, including their curricula vitae, will be filed in BIRDS.

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

This open label, single arm, dose-escalation trial is designed to determine the MTD and recommended phase II dose of BI 836880 monotherapy. No control group is planned. Dose escalation and cohort size will be determined based on a Bayesian logistic regression model

with overdose control. An escalation with overdose control design will increase the chance of treating patients at efficacious doses while reducing the risk of overdosing. This design is based on practical experience and is a preferable algorithmic method due to its superior ability to identify the dose with the desired toxicity rate and its allocation of a greater proportion of patients to doses at, or close to, that dose (R13-4802, R13-4804, R13-4805).

The trial can be expanded for early evaluation of anti-tumor effect of the drug in a specific tumor type and setting if signal of antitumor activity is observed during the dose escalation phase and/or RP2D confirmation phase.

3.3 SELECTION OF TRIAL POPULATION

Patients with advanced/metastatic solid malignant tumors who are either refractory after standard therapy for the disease or for which standard therapy is not reliably effective will be eligible. This study is planned to be conducted in at least 2 sites in Germany and France. Approximately 80 patients will be enrolled.

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

3.3.1 Main diagnosis for trial entry

All patients who will be included into the trial must have been diagnosed with histologically or cytologically confirmed advanced or metastatic solid tumor, and either refractory after standard therapy for the disease or for which standard therapy is not reliably effective.

Please refer to section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

1. Age ≥18 years

2. Histologically or cytologically confirmed malignancy which is locally advanced or metastatic solid tumor, and either refractory after standard therapy for the disease or for which standard therapy is not reliably effective, e.g. they do not tolerate or have contraindications to otherwise available standard therapy and tumour lesions evaluable for Dynamic contrast-enhanced (DCE)-MRI at MTD
3. ECOG performance status ≤ 2

4. Adequate hepatic, renal and bone marrow functions:
   a. Total bilirubin within normal limits
      (≤ 1.5x ULN for patient with Gilberts syndrome) and
   b. ALT and AST ≤ 1.5x ULN
      (<5x ULN for patients with known liver metastases) and
   c. Serum creatinine < 1.5x ULN and

d. INR 0,8-1,2 or PTT < 1.5x ULN;
e. ANC > 1,5x 10^9/L and
f. Platelets > 100x10^9/ L.
g. Hb > 10 g/dl (without transfusion within previous week)

5. Signed written informed consent.

6. Life expectancy ≥ 3 months in the opinion of the investigator

7. Recovery from all reversible adverse events of previous anti-cancer therapies to baseline or CTCAE grade 1, except for alopecia (any grade), sensory peripheral neuropathy CTCAE grade <=2 or considered not clinically significant.

8. Male or female patients:
   Women of childbearing potential* must be ready and able to use highly effective methods of birth control per ICH M3(R2) in combination with male condom as “double barrier”, during the trial and for at least 6 months after the end of treatment with BI 836880, that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information.
   Male patient must always use condoms when sexually active during the trial and for at least 6 months after the end of treatment with BI 836880.

*Women of childbearing potential are defined as:
Any female who has experienced menarche and does not meet the criteria for "women not of childbearing potential" as described below.

Women not of childbearing potential are defined as:
Women who are postmenopausal (12 months with no menses without an alternative medical cause) or who are permanently sterilized (e.g., , hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

3.3.3 Exclusion criteria

1. Known hypersensitivity to the trial drugs or their excipients or risk of allergic of anaphylactic reaction to drug product according to Investigator judgement (e.g. patient with history of anaphylactic reaction or autoimmune disease that is not controlled by nonsteroidal anti-inflammatory drugs (NSAIDs), inhaled corticosteroids, or the equivalent of </= 10 mg/day prednisone)

2. Current or prior treatment with any systemic anti-cancer therapy either within 28 days or a minimum of 5 half-lives, whichever is shorter before start of treatment.

3. Serious concomitant disease, especially those affecting compliance with trial requirements or which are considered relevant for the evaluation of the endpoints of the trial drug, such as neurologic, psychiatric, infectious disease or active ulcers (gastro-intestinal tract, skin) or laboratory abnormality that may increase the risk associated with

trial participation or trial drug administration, and in the judgment of the investigator would make the patient inappropriate for entry into the trial.

4. Major injuries and/or surgery or bone fracture within 4 weeks of start of treatment, or planned surgical procedures during the trial period.

5. Patients with personal or family history of QT prolongation and/or long QT syndrome, or prolonged QTcF at baseline (> 470 ms). QTcF will be calculated by Investigator as the mean of the 3 ECGs taken at screening.

6. Significant cardiovascular/cerebrovascular diseases (i.e. uncontrolled hypertension, unstable angina, history of infarction within past 6 months, congestive heart failure > NYHA II).
uncontrolled hypertension defined as: Blood pressure in rested and relaxed condition >= 140 mmHg, systolic or >= 90 mmHg diastolic (with or without medication), measured according to section 5.3.4 and Appendix 10.2.

7. History of severe haemorrhagic or thromboembolic event in the past 12 months (excluding central venous catheter thrombosis and peripheral deep vein thrombosis).

8. Known inherited predisposition to bleeding or to thrombosis in the opinion of the investigator.

9. Patient with brain metastases that are symptomatic and/or require therapy.

10. Patients who require full-dose anticoagulation (according to local guidelines).
No Vitamin K antagonist and other anticoagulation allowed;
LMWH allowed only for prevention not for curative treatment

11. Active alcohol or drug abuse in the opinion of the investigator.

12. Patients who are under judicial protection and patients who are legally institutionalized

13. Patients unable or unwilling to comply with protocol

14. Women who are pregnant, breast-feeding, or who plan to become pregnant while in the trial

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

An individual patient is to be withdrawn from trial treatment if:
- The patient withdraws consent, without the need to justify the decision.
- The patient needs to take drugs that interfere with the investigational product or other trial medication (see also section 4.2.2) or patient require concomitant drugs, which in the opinion of the Investigator may interfere with the investigational drug.

- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases or pregnancy).
- The Investigator may also stop a patient's participation if the patient is no longer able to complete trial visits or trial-required procedures.

A patient can be withdrawn from the trial after discussion between the Investigator and the Sponsor if eligibility criteria are violated and/or the patient fails to comply with the protocol.

All withdrawals will be documented and the reason for withdrawal recorded and discussed, as necessary, in the final report of the trial. As soon as a patient is withdrawn from the trial treatment, the end of treatment visit (EoT) has to be performed if feasible. Every effort should be made to follow-up with patients in case an adverse event is still ongoing at the time of withdrawal. If a patient is withdrawn from the trial due to consent withdrawal, no further visit will be completed.

A patient has to discontinue trial drug administration in case:
- A DLT occurs which does not recover to a degree that allows continuation of treatment (see section 4.1.4 for re-treatment criteria and dose reduction guidelines)
- Progressive disease (PD; except in cases with intra-patient dose escalation, see section 4.1.3) or start of any new anti-cancer therapy.

Patients who have not completed one cycle of BI 836880 treatment (3 weeks) will be replaced. Patient who terminated treatment due to DLT will not be replaced.
Patient who discontinue study drug for above mentioned reasons or any other reason prematurely should continue Follow up visits until study end (e.g. progressive disease). Study assessments may be omitted if a patient is willing to return to the pre-defined study visits and may stay on treatment, with the exception of following assessments which are considered mandatory for each Follow up visit: collection of adverse events, patient status, concomitant therapy, safety lab tests including pregnancy test (if applicable), vital signs.

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow up as outlined in the FC and section 6.2.3
For all patients the reason for withdrawal (e.g. adverse events) must be recorded in the Electronic Case Report Form (eCRF). These data will be included in the trial database and reported.

3.3.4.2 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial
3. Violation of Good Clinical Practice (GCP), the Clinical Trial Protocol (CTP), or the contract 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).

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

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

In this trial, the IMP BI836880 will be switched to a new pharmaceutical formulation which is to be diluted in a standard 5% Glucose/dextrose solution. The New formulation will be made available in this trial at the latest before expiry of the old formulation prepared with a drug specific diluent. Details of the trial medication BI836880 and respective diluent are presented in the table below, in the IB's for BI836880 as well as in the instructions for the pharmacist (filed in ISF)

Table 4.1.1: 1 Test product 1

Substance:	BI 836880
Pharmaceutical formulation:	Solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	10 mg/ml (vials with 10ml)
Posology	rate controlled infusion
Route of administration:	i.v.
Duration of use:	until progression or unacceptable toxicity

4.1.2 Method of assigning patients to treatment groups

No randomiation, all patient will receive investigational product.

Allocation to dose cohorts or expansion groups will be done according to subjects' temporal availability and depending on dose cohort open for recruitment.
Medication will be assigned via Interactive Response Technology (IRT) for each treatment course. Each medication box does have a unique medication number. To facilitate the use of the IRT, the Investigator will receive all necessary instructions.

4.1.3 Selection of doses in the trial

Starting Dose
Maximum safe starting dose was estimated using different methods taking in account all available nonclinical information, including PK/PD and toxicity data. The starting doses from these calculations were compared. The lowest dose derived from these calculations is recommended for the maximum safe starting dose (see Investigator's Brochure for more details (c02353882-01)).

The recommended starting dose is 0.67 mg/kg, correlates to a total dose of 40 mg.

Dose escalation Scheme
Furthermore, the PK/PD modelling provided information on the number of doses needed to reach a steady state the targeted concentration that allow a continuous high level target coverage (≥ 90%). In an every 3 weeks schedule, C_{trough} plasma concentrations at steady state above the targeted C_{min} are expected be achieved after 3 infusions of BI 836880 at dose of 6 mg/kg (360 mg) and1 infusion of BI 836880 at dose of 12 mg/kg (720 mg).

To minimize the number of patients to be treated at a non-therapeutic dose (below targeted concentration) within an acceptable time to steady state, a maximum of 200% dose increment will be applied for dose levels up to 120 mg. Dose escalation ≥120mg will not exceed 100% dose increment. No dose adaptation to body weight or body surface will be made. All patients

at the same dose level (DL) will be treated with the same total dose. Table 4.1.3: 1 shows potential dose levels to be tested.

Table 4.1.3: 1 Potential dose levels

Dose level	Total dose (mg)	Maximum dose increment
DL 1	40	200%
DL 2	120	200%
DL3	360	100%
DL4	720	100%
DL5	1000	100%
DL6	1440 Limited to 1250*	

Intermediate dose levels can be tested based on DSB decision.
*Maximum dose that can be tested due to excipient limitation

Whenever a dose escalation step is to be performed (or: a new cohort will be opened for recruitment), the data of previous dose cohorts with priority on DLTs will be reviewed and discussed within the DSB. DSB can decide to increase the dose, expand the tested cohort or to test an intermediate dose level.

Patients, who received at least two treatment cycles, deeming to have clinical benefit from treatment and tolerated the drug BI 836880 well (i.e. do not show any DLT) could be allowed to receive increased dose. Such decision will be taken in a case by case manner on request by Investigator and confirmation by DSB based on actual patient profile. Intra-patient dose escalation can be repeated; however the dose can only be increased to highest tested safe dose.

For patients with an intra-patient dose escalation(s) all assessments will be done according to instructions for the first cycle at start of treatment with BI 836880 and intensive PK-sampling, [redacted] will be conducted (see Flow Chart and Appendix 10.4) and patients have to be closely followed for any adverse events. Therefore patients have to come to the clinic during the first course of intra-patient dose escalation every week. Additional visits are needed at day 2 and at day 3 of the 1st cycle of dose escalation.
The above-mentioned procedures will be followed also in case of further intra-patient dose escalations.

4.1.4 Drug assignment and administration of doses for each patient

The study drug will be prepared and handled according to “Instruction for Pharmacists” which will be filed in ISF. Upon notification a patient entered the study; the pharmacy will prepare the study drug in the assigned dosage for administration to the patient.

BI 836880 will be given as 3 weekly intra-venous infusion by authorised site staff in a specialized unit where emergency care can be provided (e.g. intensive care unit available, medical personal trained in advanced live support) according to "Instruction for Pharmacists". The expected infusion time is 90 minutes. In case no relevant infusion reactions are observed, this can be shorten to about 30 minutes but should not be prolonged to more than 6 hours, also in case of technical issues. Appropriate drugs and medical equipment to treat anaphylactic reactions must be immediately available and study personal must be trained to recognize and treat anaphylaxis.

If symptoms of an infusion-related reaction CTCAE grade 2 or higher, but not qualifying as DLT according to section 5.3.1 occur, the infusion should be temporarily stopped. Upon recovery, it should be infused at 50% of the rate at which the reaction occurred. Depending on the time of occurrence and the severity of the reaction, the investigator may consider administering additional supportive medication, e.g. corticosteroids for re-introduction. Infusion rate and premedication for further treatment courses should be adapted according to Investigator decision, but adaption of application scheme need to be agreed with sponsor. An every 2 week application scheme with comparable visit schedule to every 3 week application is optional in case there are no concerns from every 3 week schedule and can only be started with approval by DSB.

Premedication: No premedication will be required for BI 836880 IV infusion. If a patient expressed sign of infusion reaction at any BI 836880 treatment, a premedication will be **considered** for all subsequent treatment infusions (dosage and schedule according investigator's decision) comparable to following scheme:

- Acetaminophen/Paracetamol 650 mg - 1000 mg p.o., or equivalent
- Antihistamine p.o. or i.v., equivalent to Diphenhydramine 50 mg i.v.
- Glucocorticoid i.v., equivalent to prednisolone 100 mg

If infusion reaction and/or hypersensitivity reaction occurred in a substantial amount of patient (about 30%) of treated patients without premedication, premedication (as described above) prior to BI 836880 infusion will be given to all patients to be treated in the study. Such decision will be confirmed by the DSB; dosage and schedule should be aligned, but also should reflect local clinical standards.

Re-treatment criteria:
Before initiating a new treatment course the actual health status will be assessed according to Flow Chart and described in section 5.3. To continue treatment with further courses, **all** of the following criteria must be met:

- No uncontrolled hypertension (according to Exclusion-Criterion #6)

- QTcF <=470 ms (according to Exclusion-Criterion #5)

- Acceptable tolerability (in case of an adverse event at the planned start of a treatment course patients may continue therapy only after recovery to a level which would allow further therapy; i.e. CTCAE grade 1 or pre-treatment value or considered not clinically significant)

In case one of the above mentioned criteria is not fulfilled the patient should be re-evaluated for up to 2 weeks. Any case of a delay in treatment course should be communicated to the Clinical Monitor at Boehringer Ingelheim. The investigator in agreement with the Clinical Monitor will decide about further treatment of individual patient, based on known risk/benefit of BI 836880.

Dose reduction guidelines
Administration of trial drug has to be stopped temporarily in case of a DLT (see section 5.3.1). Patients may continue therapy only after recovery from DLT to at least fulfil re-treatment criteria. The future dose of BI 836880 must be finally agreed on between the sponsor and the investigator. A reduction of the dose will be allowed only once for an individual patient during the whole trial. Treatment has to be discontinued in case the DLT is not reversible.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Not applicable, as this is an open-label single arm study.

The trial will be handled in an open fashion, i.e. also for the purpose of data cleaning and preparation of the analysis.

4.1.5.2 Unblinding and breaking the code

Not applicable.

4.1.6 Packaging, labelling, and re-supply

BI 836880 will be supplied in 10ml 10R vial containing 100mg BI 836880 [10mg/ml] solution for infusion. The BI 836880 vials will be packed in one vial per box.

Boxes and vials will be labelled according to local regulations. Re-supply to sites will be triggered by IRT, depending on available medication, recruitment and current dose level.

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

4.1.7 Storage conditions

BI 836880 vials must be stored in their original packaging. The study product must be stored according to the instructions on the label. The Investigator, the Pharmacist, or other personnel is allowed to store and dispense investigational product. They will be responsible for ensuring

that the investigational product used in the study is securely maintained as specified by the sponsor and in accordance with the applicable regulatory requirements.

A temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature.

In-use-stability of ready to use solution refers to “Instructions for Pharmacists” as described in section 4.1.4.

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation

If the storage conditions are found to be outside the specified range, the CML (as provided in the list of contacts) must be contacted immediately.

4.1.8 Drug accountability

The Investigator or pharmacist or investigational drug storage manager will receive the investigational drugs delivered by the Sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the IRB / ethics committee,
- Availability of a signed and dated clinical trial contract between the Sponsor and the head of the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the principal Investigator,
- Availability of a signed and dated clinical trial protocol
- Availability of the proof of a medical license for the principal Investigator

The Investigator or pharmacist or 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 patient, and the return to the Sponsor or alternative disposal of unused products.

These records will include dates, quantities, batch/serial numbers, expiry (‘use- by’) dates, and the unique code numbers assigned to the investigational product and trial patients. The Investigator / pharmacist / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the Sponsor. All remaining drug supplies received at a respective study site will be destroyed at site. Partially used vials will be destroyed after preparation infusion; unused medication and diluent will be destroyed after expiry or at the end of study before closing the site.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

Concomitant (non-oncological) therapies starting or changing during the course of the trial should be recorded in the electronic case report form (eCRF).

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

Potential side effects of BI 836880 have to be treated symptomatically. Symptomatic treatments of side effects or tumor-associated symptoms are allowed.

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

There are no special emergency procedures to be followed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Previous anti-cancer therapy must have been discontinued before first administration of trial drug and the patient must have recovered from all clinically relevant reversible toxicities (see Exclusion Criteria section 3.3.3 for further details).

Concomitant anti-cancer therapy is not allowed.

Radiotherapy for local symptom control of non-target lesions can be allowed after consulting the investigator and sponsor.

Full-dose anticoagulation (according to local guidelines) with Vitamin K antagonist and other anticoagulation is not allowed during the trial conduct; LMWH is allowed only for prevention not for curative treatment.

Any planned surgeries are not allowed (see Exclusion Criteria section 3.3.3 for further details). Unplanned surgeries should be postponed whenever possible four weeks after stop of treatment. For urgent interventions patients should not be further treated and should be intensely monitored regarding wound healing and post-operative complications.

4.2.2.2 Restrictions on diet and life style

No restriction.

4.3 TREATMENT COMPLIANCE

BI 836880 will be administered as an intravenous infusion under supervision of the Investigator or dedicated clinical personnel. Compliance may also be verified by pharmacokinetic assessment. Any discrepancies will be documented in the eCRF by the Investigator or designee.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

5.1.1 Primary Endpoint(s)

The primary endpoint to assess the maximum tolerated dose (MTD) is based on the number of patients presenting dose-limiting toxicities (DLTs) using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)v4.03, started within 3 weeks after first administration of study treatment (i.e. within first cycle of treatment) and judged to be related to the study medication .

5.1.2 Secondary Endpoint(s)

- Exposure measures (AUC_{0-tz}) after the first dose ;
- Disposition kinetic measures ($t_{1/2}$) after the first dose;
- Drug related AEs leading to dose reduction or discontinuation during treatment period;

[redacted]

[redacted]

5.3 ASSESSMENT OF SAFETY

5.3.1 Dose limiting Toxicity (DLT)

The DLT is defined as follows:

- Drug related CTCAE grade ≥ 3 non hematological toxicity with the following exceptions:
  - Vomiting or diarrhea responding to supportive treatment
  - Fatigue shorter than 4 days
  - Transient Grade 3 infusion reaction; i.e. if infusion-related reaction IRR can be controlled by appropriate medication according to Investigator's decision and next infusion will not be delayed for more than two weeks.
  - Any laboratory abnormality, which is considered not clinically relevant by the Investigator or resolves spontaneously or can be recovered with appropriate treatment (e.g.: ALK-P, GGT, Amylase, Lipase)
    Clinically relevant abnormalities have to be documented as AE (see section 5.3.8)
- CTCAE grade 4 neutropenia > 7 days or complicated by infection (please note, that in case of grade 4 neutropenia a more frequent follow up of patient is necessary as planned according to Flow Chart), or
- febrile neutropenia CTCAE grade ≥3 or
- CTCAE Grade 4 thrombocytopenia or CTCAE Grade thrombocytopenia ≥3 with bleeding
- Treatment delay for > 2 weeks due to unresolved drug-related adverse events, started within 3 weeks after first treatment.
- Hypertension: increase of diastolic blood pressure (BP) by 15mmHg confirmed by a second measurement or by ambulatory blood pressure measurement (when indicated; e.g. white coat effect) which can't be controlled by hypertensive medication and requests a dose reduction of BI 836880 for further treatment cycle.
- Proteinuria: urinary protein >= 3.5 g/day (CTCAE grade 3)

5.3.2 Maximum Tolerated Dose (MTD)

The MTD may be considered reached if the probability that the true DLT rate is in target interval (16% - 33%) is sufficiently large. For detailed definition see statistical part (section 7). The DSB may recommend stopping the dose finding phase after the criterion for MTD is fulfilled. Further patients may be included to confirm the MTD.

If next dose level is recommended by the statistical model; however, the efficacy is considered sufficient at current dose level, the DSB may decide to include additional number of patients at this dose level, declare this dose as RP2D and no further dose escalation will happen.
Decision on next steps (dose escalation, de-escalation or cohort expansion) will be made by a Data Safety Board (DSB) based on all available safety data, including DLT information from

last cohort as described above but also findings from subsequent courses as well as other data (e.g. PK/PD data) when available.

Based on the overall data after all patients on proposed RP2D have been treated for at least 1 cycle, the DSB will make a final determination of RP2D.

Before the conclusion of the dose escalation phase and prior to the start of the expansion cohort, up to 12 patients should have been treated on the proposed RP2D.

After determination of RP2D, 2-3 expansion cohorts could be started to treat a specified patient population based on preliminary efficacy data and according to DSB decision.

All DSB decisions of dose escalation, and to open a new cohort for recruitment will be communicated to Investigators. Once MTD and RP2D is defined this information will be send to authorities.

5.3.3 Physical examination

A complete physical examination (including cardiac, neurological, dermatological, pulmological etc.), record of height, weight and ECOG performance score will be performed at screening and before start of treatment and EoT and EoR. At further time points specified in the FC not a complete PE must be done, but at minimum the actual health status of the patient should be assessed (incl. evaluation of BP, ECG, lab values, AE, CT, ECOG as applicable). During the physical examination, the patient should be assessed for possible AEs.

5.3.4 Vital Signs

Vital signs (blood pressure, heart rate and body temperature) will be recorded at every visit indicated in the FC.
At days of administration blood pressure and heart rate will be evaluated at two time points:

1. pre-dose (-60 min. to -5 min.),
2. shortly before the end of the infusion.

In case of an infusion-related reaction, the Investigator should decide whether to intensify or prolong monitoring of vital signs of the patient.

Blood pressure
Systolic and diastolic blood pressure as well as pulse rate (electronically or by palpation, count for 1 minute) will be measured after 5 minutes of rest in the seated position. The blood pressure measurement should be performed three times at each time point and the values of these measurements will be entered in the eCRF. Further details on the procedure for blood pressure measurements are given in Appendix 10.2.

Body temperature
Whenever possible the same method should be used for body temperature measurement in one patient. All methods used should deliver valid and reproducible results according to

common clinical practice. Acceptable methods could be, but are not limited to: oral, rectal measurement with thermometer (digital, mercury or other fluid). Not acceptable/preferred methods include: IR-measurement in ear, forehead or temple.

Body temperature measurements >= 38°C must be re-assesed after 1 hour, especially in cases suspective for febrile neutropenia (see CTCAE v. 4.03).

5.3.5 Safety laboratory parameters

Blood and urine samples for assessment of general safety laboratory examinations have to be collected at the time points specified in the Flow Chart, but should be more frequent in case of relevant findings, e.g. in case of grade 4 neutropenia, as any non-proven recovery within 7 days will be counted as DLT or proteinurea, for which determination of CTCAE grade 2 vs. grade 3 need to be done by quantitative measurement. Laboratory values planned for V1d1 (=day of administration) must be available before start of infusion in order to evaluate eligibility of patient to receive treatment. Therefore it's possible to take blood sample a valuable time ahead (usually the day before treatment). Safety laboratory examinations will include hematology, biochemistry, coagulation and urine analysis:

Hematology	Hemoglobin, white blood cell count (WBC) with differential, platelets (PLT)
Biochemistry	Glucose, sodium, potassium, calcium, magnesium, inorganic phosphate, creatinine, AST, ALT, alkaline phosphatase (AP), lactate dehydrogenase (LDH), bilirubin, urea, total protein, albumin, uric acid, CK, CK-MB Serum immunoglobulin levels (IgG, IgM, IgA; IgE) and direct antiglobulin test have to be measured at Screening and at occurrence of infusion related reactions.
Coagulation	Activated partial thromboplastin time (aPTT), prothrombin time (PT) or international normalised ratio (INR) where indicated (e.g. treatment with vitamin K antagonists)
Urine	pH, glucose, erythrocytes, leukocytes, protein, nitrite will be analysed primarily qualitatively by dipstick.. In case of clinically relevant findings, further evaluation should be performed and the findings documented. A positive urine dipstick for protein of $\geq$ 2+ (CTCAE gr 2) has to be followed by a determination of the ratio of urine protein to creatinine (UPCR) in a morning spot urine sample. In case of a ratio $\geq$ 0.5, a 24 hour urine collection for protein loss has to be performed. The 24 hour urine collection will be repeated every time the UPCR ratio is $\geq$ 0.5 as often as clinically indicated.
Pregnancy test	A serum pregnancy test needs to be obtained at the time

points indicated in the Flow Chart in patients of childbearing potential.

In case an administration is delayed due to an AE, the patient should visit the site at least once a week for assessment of safety laboratory and AEs. More frequent visits may be appropriate as assessed by the Investigator.

5.3.6 Electrocardiogram (ECG)

Triplicate 12-lead ECGs (3 ECGs taken approximately 2-3 minutes apart) will be performed in all patients at various time points according to Study Flow:

- At Screening, visits between administration and at EoT:
  only one time point will be evaluated.
- At days of administration two time points will be evaluated:
  1. pre-dose (-60 min. to -5 min.),
  2. shortly before the end of the infusion.

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

In order not to confuse ECG recording, PK samples should be taken after performing the ECG. The ECG recordings will be analysed and checked for pathological results by the investigator; QTcF for each time point will be calculated as the mean of the 3 ECGs. Decision on patients' eligibility will be taken based on Investigator analysis of QTcF, based on same recordings. Pathological ECG results will be recorded as AEs by the investigator.

5.3.7 Echocardiography

Echocardiography have to be conducted at screening (not older than 7 days) and at EoT-visit. During treatment phase it has only to be done when clinically indicated.

5.3.8 Assessment of adverse events

5.3.8.1 Definitions of AEs

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Serious adverse event
A serious adverse event (SAE) is defined as any AE which:

- results in death,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
  or
- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Life-threatening in this context refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.

AEs considered "Always Serious"
In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as given above.

The latest list of "Always Serious AEs" can be found in the Remote Data Capture (RDC) system. These events should always be reported as SAEs as described in section 5.3.9.

Adverse events of special interest (AESIs)
The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESI need to be reported to the Sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, see section 5.3.9.

The following are considered as AESIs:

Hepatic injury
A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- For patients with normal liver function at baseline:
  an elevation of AST and/or ALT ≥ 3 fold ULN combined with an elevation of total bilirubin ≥ 2 fold ULN measured in the same blood draw sample and/or.
  Marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

- For patients with impaired function tests at baseline:
  an elevation of AST and/or ALT ≥ 5 fold ULN combined with an elevation of bilirubin ≥ 2 fold ULN measured in the same blood draw sample.

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" via the RDC-system.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Dose Limiting Toxicities:
Any medical event fulfilling the criteria of DLT (see section 5.3.1) should be reported by Investigator as AESI.

Intensity of AEs
The intensity of the AE should be judged based on the following:

The intensity of adverse events should be classified and recorded in the (e)CRF according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (v4.03: June 14, 2010) (R12-2532).

Causal relationship of AEs
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.

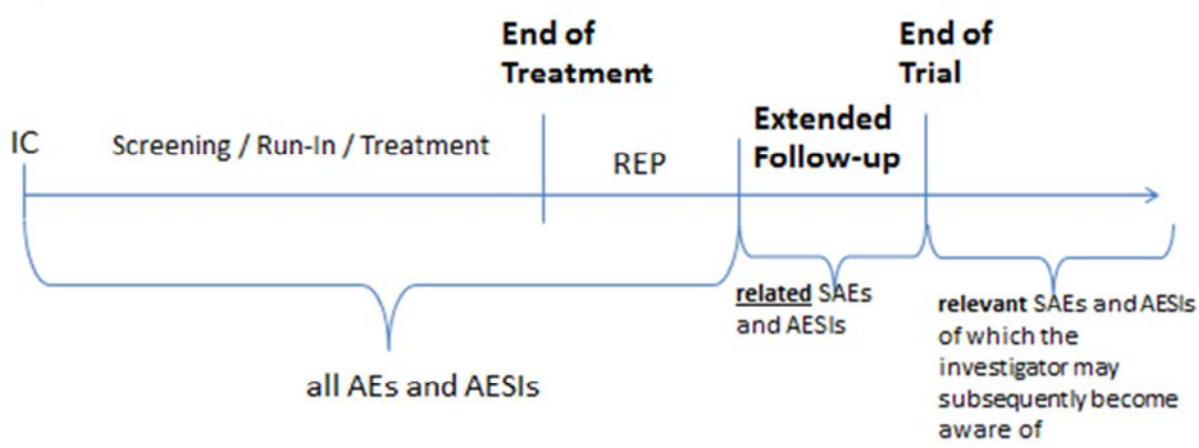
Yes: There is a reasonable causal relationship between the investigational product administered and the AE.
No: There is no reasonable causal relationship between the investigational product administered and the AE.

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 (such as any active comparator or placebo). The reason for the decision on causal relationship needs to be provided in the (e)CRF and on the SAE form (if applicable).

5.3.9 Adverse event collection and reporting

AE Collection
The following must be collected and documented on the appropriate / eCRF by the Investigator:

- From signing the informed consent onwards until the end of the REP all AEs (non-serious and serious), and AESIs.
- After the end of the REP until trial completion, all related SAEs and related AESIs.
- If in an individual patient only vital status information is collected from a certain time point on, no further AEs or AESIs will be reported for this patient.



The REP is defined as 42 days (6 weeks) after the last trial medication application. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment please see section 7.3.4. Events which occurred after the REP will be considered as post treatment events.

After the last per protocol contact the Investigator does not need to actively monitor patients for AEs. However, if the Investigator becomes aware of SAEs or AESIs that occurred after the last per protocol contact, the SAEs and AESIs should be reported by the Investigator to the Sponsor if considered relevant by the Investigator.

AE reporting to sponsor and timelines
The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) to the Sponsor's unique entry point (country specific contact details will be provided in the ISF). In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

Information required
For each AE, the Investigator should provide the information requested on the appropriate (e)CRF pages and the BI SAE form, e.g. onset, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug(s). The Investigator should determine the causal relationship to the trial medication.

The following should also be recorded as an (S)AE in the (e)CRF and SAE form (if applicable):

- Worsening of the underlying disease (if not recorded as study endpoint, see exemption below) or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the Investigator.

If such abnormalities already pre-exist prior trial inclusion they will be considered as baseline conditions.
All (S)AEs, including those persisting after trial completion must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

Pregnancy
In the rare case that a female subject participating in this clinical trial becomes pregnant after having taken trial medication, the Investigator must report immediately (within 24 hours) the drug exposure during pregnancy (DEDP) to the Sponsor's unique entry point (country-specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the Sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE associated with the pregnancy then the SAE has to be reported on the SAE form in addition.

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B).

Exemptions to (S)AE Reporting
Disease Progression in oncology trials is a study endpoint for analysis of efficacy and as such is exempted from reporting as an (S)AE. Progression of the subject's underlying malignancy will be recorded on the appropriate pages of the (e)CRF as part of efficacy data collection only and will not be reported on the SAE Form. It will therefore not be entered in the safety database (ARISg) and hence not get expeditiously reported. Death due to disease progression is also to be recorded on the appropriate (e)CRF page and not on the SAE Form.

Examples of exempted events of PD may be:

- Progression of underlying malignancy (Progressive disease [PD]): if PD is clearly consistent with the suspected progression of the underlying malignancy as defined by the respective response criteria.
- Hospitalization/Procedures due solely to the progression of underlying malignancy (PD)
- Clinical symptoms and/or signs of progression (without confirmation by objective criteria e.g. imaging, clinical measurement): if the symptom can exclusively be determined to be due to the progression of the underlying malignancy and does meet the expected pattern of progression for the disease under study.

However, when there is evidence suggesting a causal relationship between the study drug(s) and the progression of the underlying malignancy, the event must be reported as an (S)AE on the SAE Form and on the (e)CRF.

Exempted events are collected and tracked following a protocol-specified monitoring plan. Exempted events are monitored at appropriate intervals preferably by an independent committee such as a Data Safety Board.

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.4.1 Assessment of Pharmacokinetics

Pharmacokinetic profiles of BI 836880 in plasma will be investigated after the first and after repeated doses. Standard plasma PK parameters as listed in Appendix 10.3 will be calculated.

Pharmacokinetic data may additionally be analysed using population pharmacokinetic approach. For this purpose data may also be combined with data from other trials. Modelling activities will be planned and documented separately according to internal and external guidelines and SOP.

Exploratory pharmacokinetic interim analyses can be performed as necessary for DSB decisions, but are not expected to be done more frequently than every other DSB and do require sufficient lead time to collect samples, measure BI 836880 plasma concentrations, analyse data and prepare meaningful outputs. The final exploratory interim analysis will be performed after the cohort at MTD in the dose finding phase completed the first treatment course.
For the purpose of these exploratory interim analyses, PK plasma samples obtained up to at least 24 hours after drug administration will be used. A scientifically sound subset of the PK parameters listed in Appendix 10.2 will be calculated which may include C_{max}, AUC and $t_{1/2}$, if these parameters can be reliably determined from the available samples and plasma concentration time profiles. In contrast to the final PK analysis, the interim analyses will be based on planned sampling times rather than on actual times; no supplementary subject information, e.g. on adverse events or concomitant medication, will be used in these interim analyses, and the outputs will not be validated. Minor discrepancies between interim and final results may therefore occur.

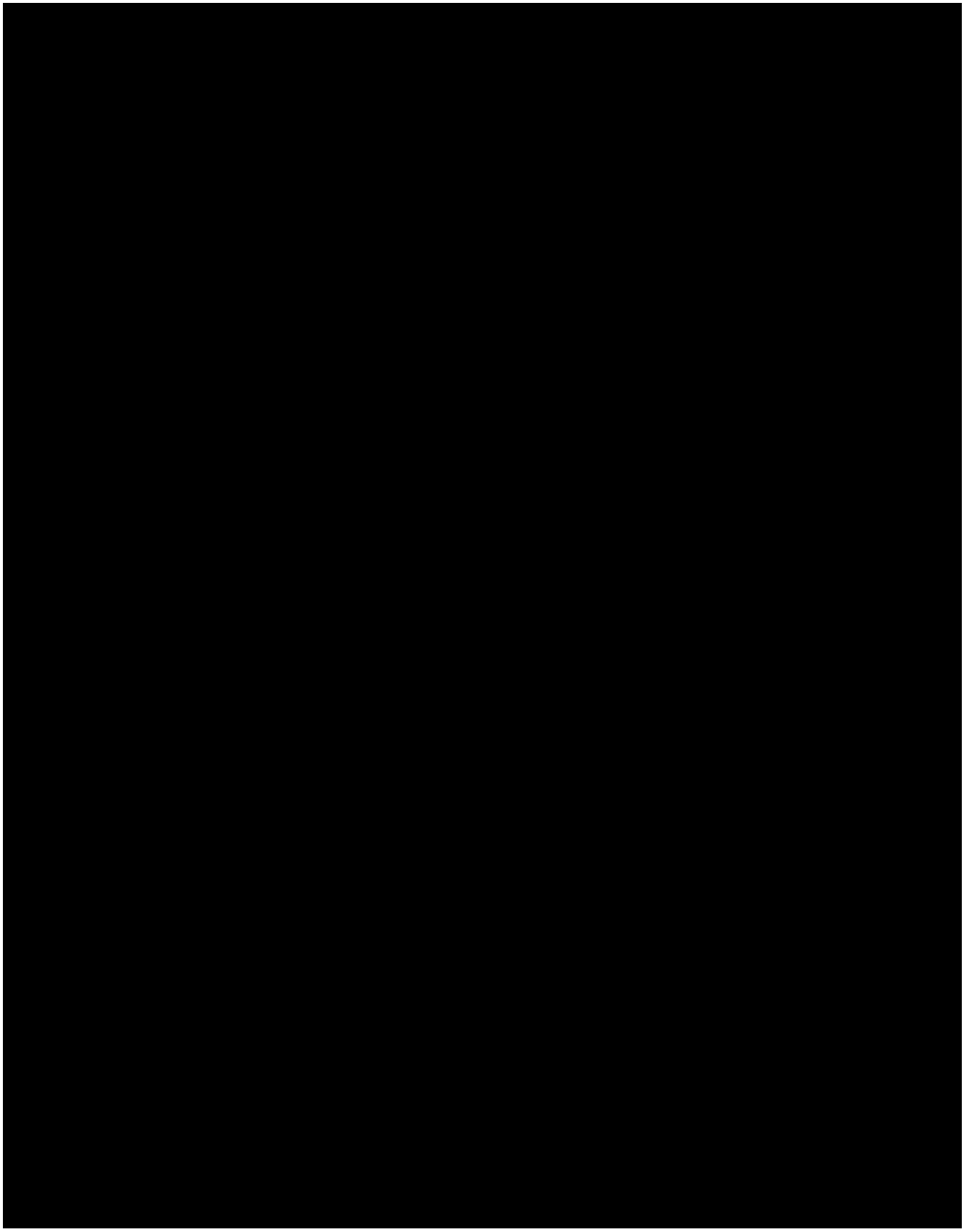
5.4.2 Methods of sample collection

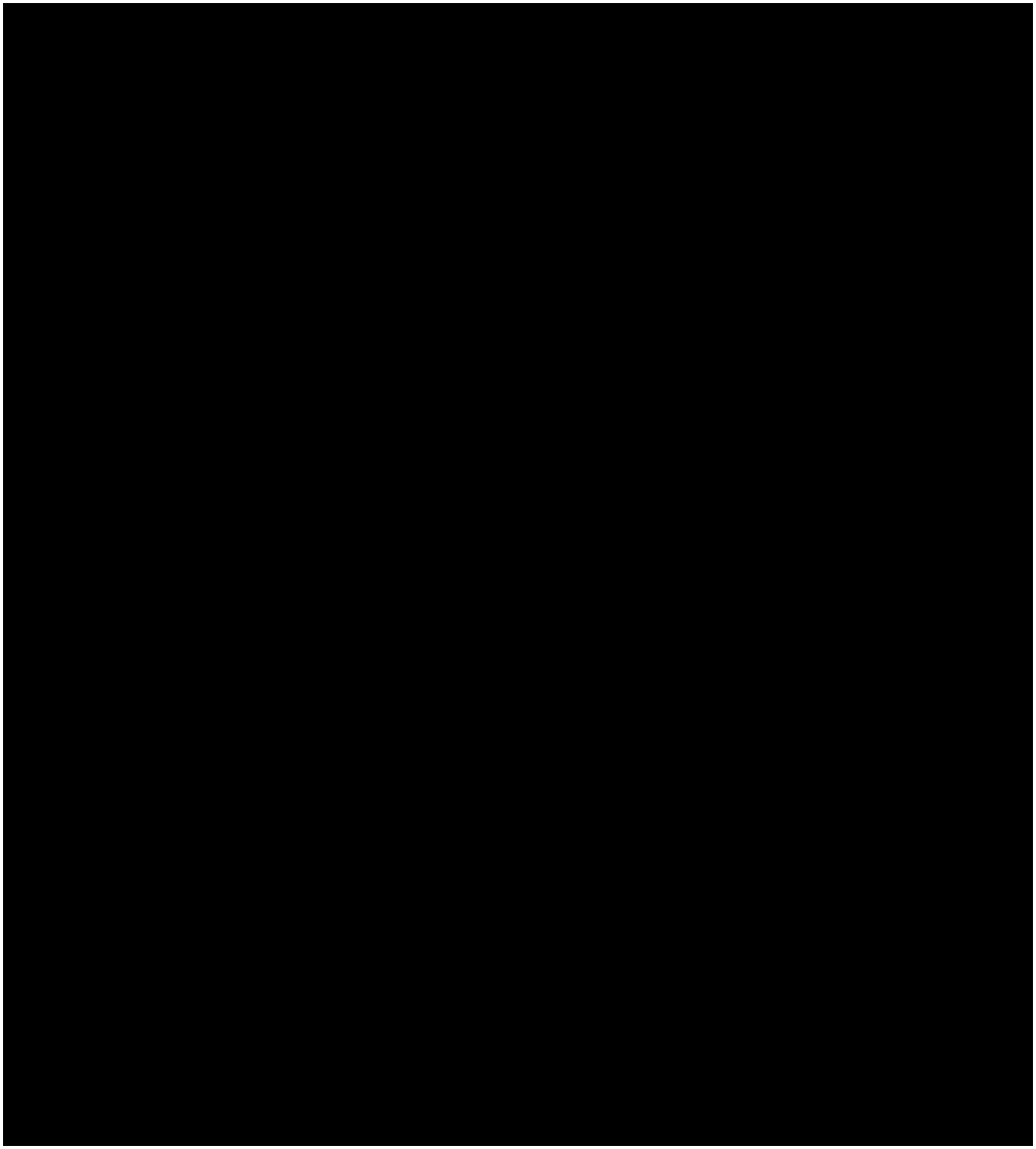
For the quantification of BI 836880 plasma concentrations, at least 2 mL blood will be taken from a forearm vein in an EDTA (ethylenediaminetetraacetic acid) anticoagulant blood drawing tube at time points specified in the Flow Chart and in Appendix 10.4. Plasma will be divided into duplicate aliquots and stored frozen at about -70°C at the participating sites or logistics CRO until shipment on dry ice to the bioanalytical laboratory of Boehringer Ingelheim or a Boehringer Ingelheim selected and authorized CRO.

Details about sample collection, EDTA plasma preparation, required tubes, labelling of tubes, storage and shipment (frequency and addresses) will be provided in a separate laboratory manual.

After completion of the study the plasma samples may be used for further methodological investigations, e.g., for stability testing. However, only data related to the analyte will be generated by these additional investigations, and such data will be reported separately.

The study samples will be discarded no later than 3 years after the final study report has been generated.

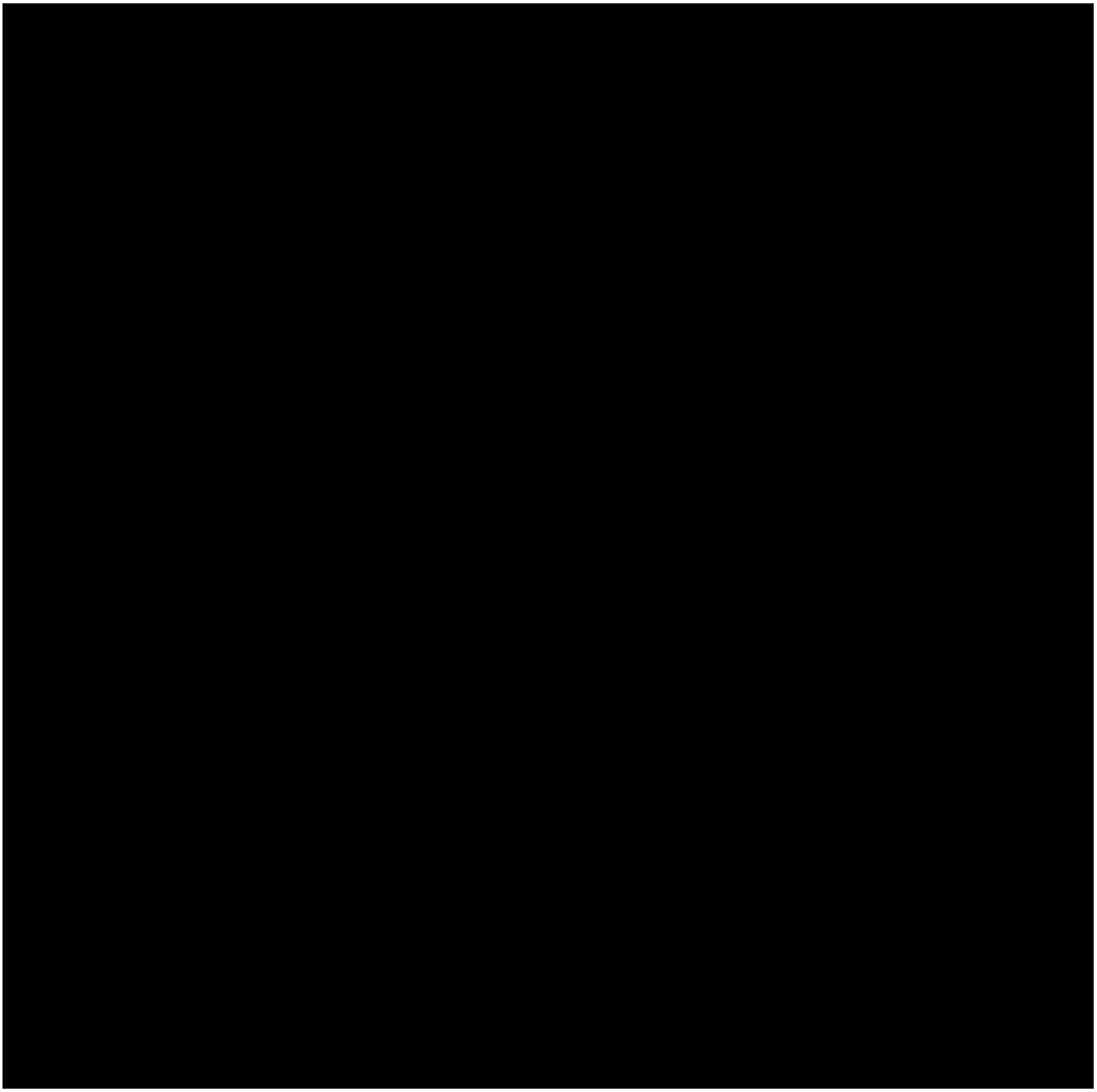




5.6 OTHER ASSESSMENTS

5.6.1 Demographics and history

Demographics including gender, year of birth and race/ethnicity, as well as detailed oncologic disease history will be obtained, which include date of first diagnosis of malignancy, history of previous treatment lines, as well as staging and grading information.



5.7 APPROPRIATENESS OF MEASUREMENTS

Determination of MTD is based on toxicities graded according to CTCAE version 4.03 (R12-2532). The CTCAE criteria are commonly used in the assessment of AEs in cancer patients. These criteria are well established and scientifically accepted.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Patients must comply with all inclusion and exclusion criteria prior to the patient enters the study (see Section 3.3).

All patients should adhere to the visit schedule as specified in the Flow Chart. In case a patient misses a visit within one treatment course and the patient belatedly reports to the investigator between the missed and the next scheduled visit, the delayed visit should be scheduled as soon as possible and documented with the actual date and the reason for the delayed visit. The next visit, should still take place at the time it was originally scheduled in this treatment course. Some flexibility is allowed in scheduling the visits according to the time window specified in the Flow Chart.

However, in case the day of treatment administration (visit 1 day 1 of a course) is delayed, all subsequent visits of a course will be recalculated based on the actual date of treatment of the delayed course.

During the treatment phase, after administration of BI 836880, patients are required to be hospitalized under close surveillance with access to intensive care for at least 48 hours after administration of BI 836880 to allow close monitoring for infusion-related reactions or other adverse events and availability of patients for PK visits. After good tolerability of the first two courses of BI 836880 the investigator may evaluate the risk for an infusion-related reaction and other adverse events in view of relevant comorbidities or disease related symptoms, and as a result, shorten the duration of surveillance to 8 hours for courses 3 and 4 (PK samples included) and at investigator's discretion for further cycles.
If pathological laboratory values or other issues require an additional unscheduled visit, a new eCRF page will be created for the unscheduled visit. At the unscheduled visit, it is sufficient to record only the clinical relevant labs/examinations performed.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

The investigations as outlined in the Flow Chart will be performed at the respective visits. A more detailed overview of collection of blood samples for PK, [redacted] as well as ECG assessment and BP measurements are given in Appendix 10.4.

Specific details to conduct of physical examination, collection of vital signs (incl blood pressure measurement), laboratory investigations, assessment of ECG and echocardiography can be found in section 5.3.

Procedure for collection of blood samples for PK, [redacted] are given in section 5.4 and 5.5.

[redacted]

6.2.1 Screening and run-in period(s)

Screening Period
The examinations required for the screening visit may be conducted within a time interval of 21 days prior to the first study drug administration. Prior to any other study related procedure, written informed consent must be obtained from the patient.

CT/MRI images obtained prior to study participation can be used within the study as long as they are not older than 28 days at day of first treatment.

Echocardiography must be obtained within 7 days before start of treatment.

If for administrative or medical reasons, the patient is not entered within the defined screening period, it is allowed to re screen a patient. There is no maximum time period defined for re-screening. The same Pat-ID will be used for the patient throughout the re-screening as assigned during first screening.

If the patient has been determined eligible by the investigator to enter the trial (refer to Section 3.3), the investigator will assign one or more medication number(s) to the patient through the IRT system at Visit 1 (Section 4.1.3). First dose of BI 836880 will be administered at the beginning of Visit 1 at the trial site (Day 1, cycle 1).

6.2.2 Treatment period(s)

A treatment cycle is defined as 3 weeks of duration. If initiation of a subsequent cycle is delayed due to medical reasons, additional visits beyond Day 21 may be necessary and may be performed at investigator's discretion, and should be recorded in the eCRF.

Patients may continue treatment as long as they have clinical benefit (no PD, no toxicities, no new anti-cancer treatment started) and patient is willing to continue.

During cycle 1, 2 and 4 intensive PK-sampling will be conducted and patients have to be observed closely for any adverse events. Therefore patients have to come to the clinic during the first four courses every week to the clinic. Additional visits are needed at day 2 for cycles 1, 2 and 4 and at day 3 for cycle 1. In course 5 and 6 the patient is requested to come to the clinic on day 8 after administration of study drug. From cycle 7 onwards no additional visits, beside day 1 including drug administration, are requested by protocol.
For the 2 ongoing patients, minimum set of procedures is mandatory. This includes safety lab, vital signs including blood pressure, adverse events, and pregnancy test if applicable. However, other assessments as indicated in the flowchart of the protocol or single lab values can be omitted according to investigator's opinion.

[redacted]

6.2.3 Follow Up Period and Trial Completion

6.2.3.1 End of treatment visit (EOT)

The EOT visit will be performed after permanent discontinuation of trial medication for any reason as soon as possible but no later than 3 weeks after permanent discontinuation of the trial medication or when the investigator decided with the patient to permanently discontinue the trial medication or became aware that the trial medication had been terminated.

6.2.3.2 Residual effect period (REP)

The REP is defined in Section 5.3.9 (6 weeks). The End of REP (EoR) visit should not be performed earlier than 42 days after permanent discontinuation of the trial medication. The information collected at this visit should include all new AEs that occurred after EOT and a follow-up of adverse events ongoing at EOT. Any subsequent anti-cancer therapy administered between EoT and EoR should be reported

6.2.3.3 Extended follow-up period

6.2.3.3.1 Follow-up for progression

For patients who did not progress, additional follow-up visits after the EoR visit will be performed every 6 weeks plus/minus 3 days.

[redacted]

The follow-up for progression period will end at the earliest of the following events:

- Lost to follow-up
- Disease progression
- Start of a new anti–cancer therapy
- Death
- End of whole trial as specified in Section 8.6

At the end of the follow-up period, the EoFU (End of Follow-Up) visit has to be performed. The following will be obtained and / or performed during the follow-up visits and the EoFU visit.

- Record all related SAEs and all related AESI and a follow-up of adverse events ongoing since End of REP to EoFU as entered in source data
- Concomitant medications for treatment of an adverse event reported in the (e)CRF including trade name, indication and dates of administration
- Perform tumour assessment and imaging
- Treatment and date with any other anti-cancer drug including the name and type of the anti-cancer drug and/or best supportive care
- Outcome (date of and reason for death, in case the patient had PD the actual date of PD shall be recorded)
- Samples for PK, [redacted] at first Follw-up (FU1)

6.2.3.3.2 Follow-up for Overall Survival

Not applicable.

6.2.3.4 Trial completion for an individual patient

A patient is considered to have completed the trial in case any of the following applies:
- Completion of planned follow-up period
- Lost to follow-up
- Withdrawal to be followed-up
- Death

At the earliest of the above criteria, the Patient Completion (PC) information should be entered in the CRF.

6.2.3.5 Trial completion

The end of the trial will occur when the last patient completes his/her REP. In case patients would be still on treatment when data base is locked and the Clinical Trial Report (CTR) is being drafted, these patients will be maintained in the trial and may continue treatment as long as they have clinical benefit (no PD, no drug-related adverse events requiring discontinuation, no new anti-cancer treatment started) and patient is willing to continue. For these patients, no blood sample will be collected for PK [redacted] analysis. After the discontinuation of these patients, the data collected after the database lock (DBL) will be provided as separate listings and will not lead to any further updating of tables produced for section 15 of the CTR unless deemed necessary. These listings will be included in a revised CTR.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

This is phase I, open-label, dose-escalating trial to determine the MTD and RP2D for BI 836880 in patients with solid tumor. The MTD may be considered reached if the probability that the true DLT rate is in target interval (16% - 33%) is sufficiently large. Dose escalation and determination of MTD will be guided by a Bayesion 2-parameter logistic regression model with overdose control (R13-4803; R13-4806). These designs have been shown to be superior regarding the precision of MTD determination compared to 3+3 designs and have been particularly endorsed by the FDA (R13-4881).

The model is formulated as follows:

$\text{logit}(p(d)) = \log(\alpha) + \beta * \log(d/d^*)$,

where $\text{logit}(p) = \log(p/(1-p))$.

p(d) represents the probability of having a DLT in the first cycle at dose d, d* = 720mg is the reference dose, allowing for the interpretation of α as the odds of a DLT at dose d*, and $\theta = (\log(\alpha), \log(\beta))$ with $\alpha, \beta > 0$ is the parameter vector of the model.

Since a Bayesian approach is applied, a prior distribution $\pi(\theta)$ for the unknown parameter vector θ needs to be specified. This prior distribution will be specified as a mixture of three multivariate normal distributions, i.e.

$\pi(\theta) = \varphi_1\pi_1(\theta) + \varphi_2\pi_2(\theta) + \varphi_3\pi_3(\theta)$

with

φ_i, i = 1, 2, 3 the prior mixture weights ($\varphi_1 + \varphi_2 + \varphi_3 = 1$)

and

$\pi_i(\theta) = \text{MVN}(\mu_i, \Sigma_i)$

the multivariate normal distribution of the i-th component with mean vector μ_i and covariance matrix Σ_i, with

$$\Sigma_i = \begin{pmatrix} \sigma_{i,11}^2 & \sigma_{i,11}\sigma_{i,22}\rho_i \\ \sigma_{i,11}\sigma_{i,22}\rho_i & \sigma_{i,22}^2 \end{pmatrix}$$

Mixture prior distributions have the advantage that they allow for specification of different logistic dose-toxicity curves, therefore making the prior more robust.

Prior derivation

For the current study, no relevant information in the form of human data was available, since no study in a comparable population has been conducted. Therefore, the three mixture components were established as follows:

1. A weakly informative prior was derived to reflect a priori assumption that the median DLT rate at the starting dose of 40mg would equal 0.1%, and the median DLT rate at the anticipated MTD of 720mg would equal 20%. This yields $\mu_1 = (-0.333, 0.647)$. The standard deviations were set such that large uncertainty about the parameter means is reflected, and the correlation was set to 0, thus yielding $\sigma_{1,11} = 2$, $\sigma_{1,22} = 1$ and $\rho_1 = 0$, respectively. The prior weight φ_1 for the first component was chosen as 0.9.
2. A high-toxicity weakly informative prior was derived to reflect the case that the compound would be much more toxic than expected. For this prior component, it was assumed that the median DLT rate at the starting dose of 40mg would equal 10%, and the median DLT at the anticipated MTD of 720mg would equal 50%. These assumptions yield $\mu_2 = (0.419, -0.274)$. The standard deviations and correlations were set identical to the weakly informative prior, i.e. $\sigma_{2,11} = 2$, $\sigma_{2,22} = 1$ and $\rho_2 = 0$, respectively. The prior weight φ_2 for the second component was chosen as 0.05.
3. A low-toxicity weakly informative prior was derived to reflect the case that the compound would be much less toxic than expected. For this prior component, it was assumed that the median DLT rate at the starting dose of 40mg would equal 0.1%, and the median DLT at the anticipated MTD of 720mg would equal 2%. These assumptions yield $\mu_3 = (-3.316, 0.042)$, i.e. basically a flat curve. The standard deviations and correlations were set to $\sigma_{3,11} = 5$, $\sigma_{3,22} = 0.01$, therefore almost fixing the slope parameter to its mean. The correlation was set to 0, i.e. $\rho_3 = 0$. The prior weight φ_3 for the third component was chosen as 0.05.

A summary of the prior distribution is provided in Table 7.1:1. Additionally, the prior probabilities of DLT at different doses, as well as the corresponding probability of under-, targeted and overdosing, are shown in Table 7.1: 2. Graphically, the prior medians with accompanying 95% credible intervals are shown in Figure 7.1: 1. As can be seen from both, the Table and the Figure, the prior medians of the DLT probabilities are in-line with the prior medians derived from the weakly informative prior, and the uncertainty around the medians is large, showing the low amount of information this prior provides. This is also supported by the prior sample size, i.e. the information contained in the prior. This is approximately equal to 1.2 patients, i.e. less than or around half of the weight the first cohort in the study will have.

Table 7.1: 1 Summary of prior distribution

Prior Component	Mixture Weight	Mean vector	SD vector	Correlation
1: Weakly inf.	0.900	-0.333 0.647	2.000, 1.000	0.000
2: High Tox	0.050	0.419 -0.274	2.000, 1.000	0.000
3: Low Tox	0.050	-3.316 0.042	5.000, 0.010	0.000

Table 7.1: 2 Prior probabilities of DLT at selected doses

Dose	Probability of true DLT rate in					Quantiles		
	[0–0.16)	**[0.16–0.33)**	**[0.33–1]**	**Mean**	**SD**	**2.5%**	**50%**	**97.5%**
40	0.877	0.049	0.074	0.069	0.172	<.001	0.001	0.703
120	0.813	0.071	0.116	0.104	0.208	<.001	0.006	0.812
360	0.685	0.110	0.205	0.176	0.258	<.001	0.043	0.899
720	0.515	0.153	0.332	0.274	0.295	<.001	0.148	0.944
1250	0.269	0.164	0.566	0.444	0.318	0.005	0.410	0.975

Doses printed in bold face meet the overdose criterion (P(overdose) < 0.25))

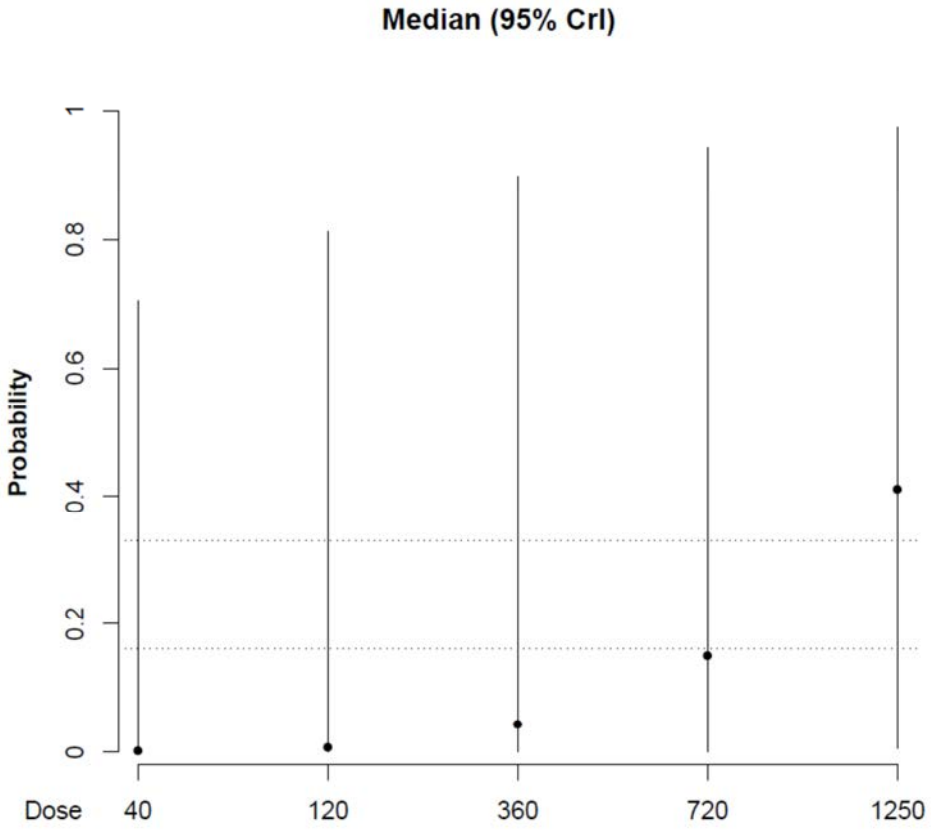


Figure 7.1: 1 Prior medians and 95% credible intervals

The MTD may be considered reached if the following criteria is fulfilled
1. At least 1 DLT on the trial and either
2. At least 6 patients haven been treated at the MTD and the posterior probability of the true DLT rate in the target interval (16%-33%) is above 50%, OR
3. At least 18 patients in the trial with 6 patients have been treated at MTD.

Statistical model assessment

The model was assessed using two different metrics:
1. Hypothetical data scenarios: for various potential data constellations as they could occur in the actual trial, the maximal next doses as allowed by the model and by the 100% escalation limit are investigated. Data scenarios thus provide a way to assess the “on-study” behaviour of the model.
2. Simulated operating characteristics: these illustrate for different assumed true dose-toxicity relationships, how often a correct dose would be declared as MTD by the model. They are a way to assess the “long-run” behaviour of the model.

In summary, the model showed very good behaviour as assessed by these metrics. More details can be found in Appendix 10.6.

Based upon these design considerations, the trial will be analysed using general linear models which will include terms for centre and disease severity as covariates.

7.2 NULL AND ALTERNATIVE HYPOTHESES

No formal hypothesis testing is planned in this trial. All analyses in this trial are descriptive and exploratory by nature.

7.3 PLANNED ANALYSES

Only one analysis population will be considered for efficacy and safety analyses: the treated set. The treated set (TS) will consist of all patients who were treated with at least one single dose of BI 836880.

The primary analysis will be based on the treated set population excluding patients that have to be replaced for analysis of the MTD, see section 3.3.4.1 for further details.

No per protocol population will be used for analyses; however protocol violations will be identified and listed.

7.3.1 Primary endpoint analyses

In order to determine the MTD the occurrence of a DLT in the first cycle will be assessed on an individual patient level. The MTD will be determined as described in section 7.1.

Based on the data observed in the trial other models might be considered either additionally or replacing the primary model. For feasibility or other reasons a different dose might be considered as the recommended dose for Phase II.

7.3.2 Secondary endpoint analyses

Please refer to section 7.3.4 for safety related secondary endpoints and section 7.3.5 for PK related endpoints.

7.3.4 Safety analyses

All patients of the treated set will be included in the safety analyses. Two analyses will be performed. The first analysis of safety will be performed for the first part of the trial

(determination of the MTD, first cycle only, treatment regimen = initial dose at the start of the treatment, treated set). This descriptive analysis will evaluate the MTD for the monotherapy of BI 836880. The second analysis will be performed with respect to all cycles and will act as a support for the determination of the MTD (treated set).

Events that started between the first administration of the treatment until 6 weeks (42 days) after the last administration of treatment will be considered as having occurred on treatment. In general, later events will be attributed to the post-study period and will be presented separately. However, post-study events will be examined to determine whether they need to be combined with on-treatment events in an additional table.

Adverse events will be graded according to CTCAE Version 4.03 (R12-2532) and reported according to BI standards. *Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA).*

Serious adverse events will be tabulated. In addition, events leading to dose reduction or treatment discontinuation will be examined, but may not be reported as individual tables, depending upon the extent of overlap. Descriptive statistics will be used to describe changes in laboratory tests over time. In addition, all abnormalities of potential clinical significance will be reported. In general, potential clinical significance is defined as at least CTCAE Grade 2 and an increase in CTCAE classification from baseline. The incidence and intensity of the more important adverse events (as determined from the analyses above) will be correlated descriptively with pharmacokinetic data, if possible.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the residual effect period (REP), a period of 42 days after the last dose of trial medication, will be assigned to the treatment period for evaluation.
All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

7.3.5 Pharmacokinetic analyses

Refer to section 5.4.1 for pharmacokinetic parameters to be calculated using non-compartmental analysis (NCA). [redacted]

All evaluable subjects who received at least one dose of BI 836880 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.

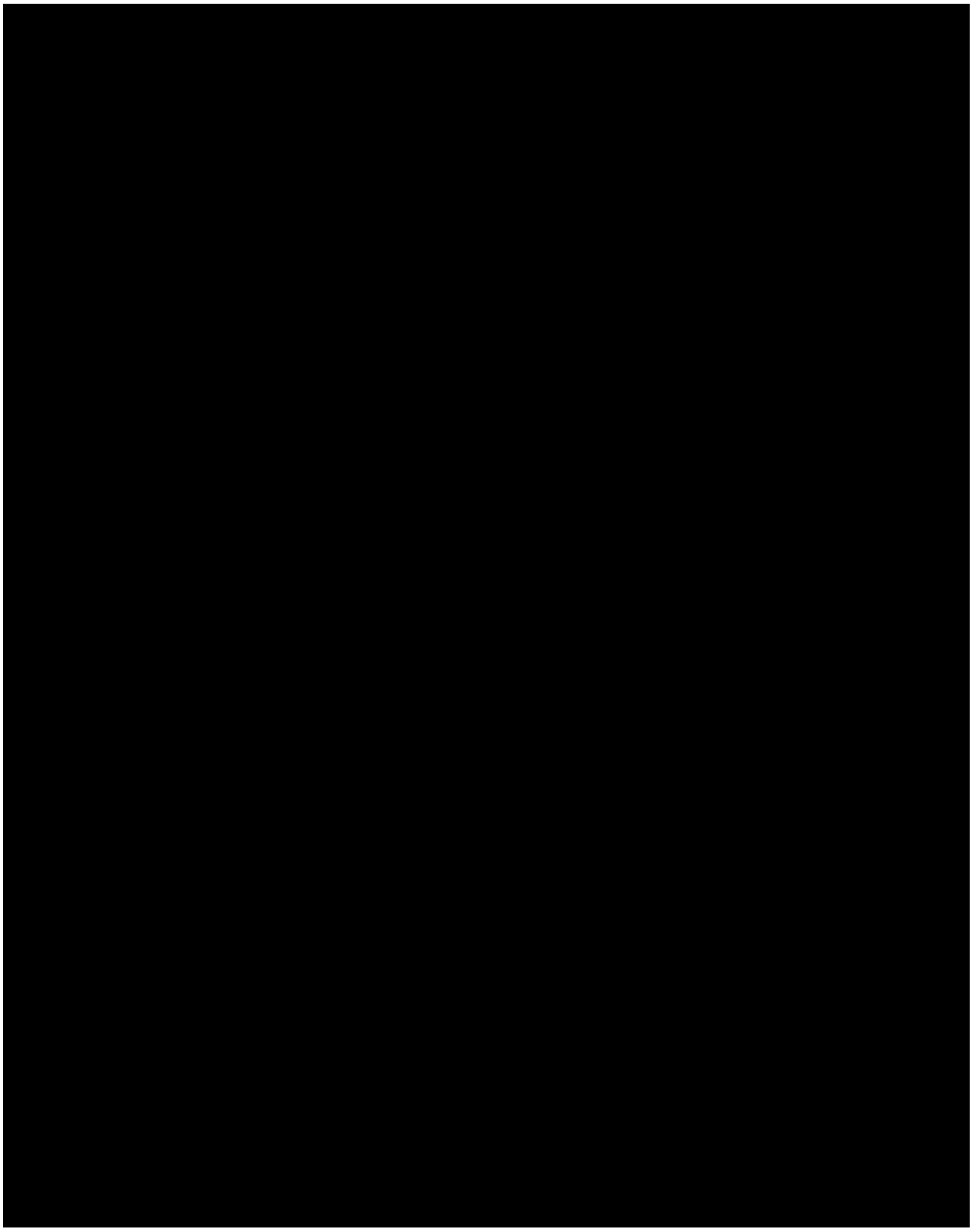
Every effort will be made to include all concentration data in an analysis. If not possible, a case to case decision is required whether the value should only be excluded from half-life estimation or the complete analysis.

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

Concentrations will be used for graphs and calculations in the format that is reported in the bioanalytical report. Noncompartmental pharmacokinetic analyses of the plasma concentration-time data will be performed using a validated software program, e.g. Phoenix WinNonlin. Only concentrations within the validated concentration range will be used for the calculation of pharmacokinetic parameters. For pre-dose samples, the actual sampling time will be set to zero.
Plasma concentrations will be plotted graphically versus time for all evaluable subjects as listed in the drug plasma concentration-time tables. For the presentation of the mean profiles, the geometric and arithmetic mean and the planned blood sampling times will be used. If the actual sampling time deviates significantly from the planned time, the corresponding plasma concentration will be excluded from the calculation of descriptive statistics.

The following descriptive statistics will be calculated for analyte concentrations as well as for all pharmacokinetic parameters: N, arithmetic mean, standard deviation, minimum, median, maximum, P10, Q1, Q3, P90, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of pharmacokinetic parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual

values as well as the descriptive statistics will be reported with three significant digits in the clinical trial report.



7.4 INTERIM ANALYSES

Interim safety evaluations will be performed as considered necessary. In particular safety evaluations will be performed after each dose cohort by the DSB consisting of the investigators and representatives of the sponsor (refer to section 3.1.1). Based on this the DSB will recommend the next dose level as well as the corresponding cohort size. DSB meeting minutes and outputs provided for these DSB meetings will be documented and archived in the clinical trial master file (CTMF).

If considered necessary, as soon as the MTD is determined an evaluation of the safety aspects will be performed. Results of this evaluation will be documented and archived. If applicable such an analysis will be defined in more detail in the TSAP.

7.5 HANDLING OF MISSING DATA

No imputation will be performed on missing efficacy data.

Missing baseline laboratory values will be imputed by the respective values from the screening visit. No other imputations will be performed on missing data although every effort will be made to obtain complete information on all adverse events and to follow-up the patients for efficacy data.

Pharmacokinetics:
Drug concentration-time profiles: Concentration data identified with NOS (no sample), NOR (no valid result), NOA (not analyzed), BLQ (below the limit of quantification) and NOP (no peak detectable) will be ignored and not replaced by zero at any time point (including the lag phase). Descriptive statistics of concentrations at specific time points will be calculated only when at least 2/3 of the individuals have concentrations within the validated concentration range.

Pharmacokinetic parameters: In the non-compartmental analysis, concentration data identified with NOS, NOR and NOA will not be considered. BLQ and NOP values in the lag phase will be set to zero. The lag phase is defined as the period between time 0 and the first time point with a concentration above the quantification limit. All other BLQ and NOP values of the profile will be ignored. Descriptive statistics of parameters will be calculated only when at least 2/3 of the individual parameter estimates of a certain parameter are available. Pharmacokinetic parameters which cannot be determined will be identified by "not calculated" (NC).

7.6 RANDOMISATION

Patients will be assigned, not randomised, into escalating dosage cohorts by order of admission into the trial. Doses will be assigned based on the decision made by the DSB (see section 7.4.).

7.7 DETERMINATION OF SAMPLE SIZE

About 40 patients will be expected for the dose finding part and confirmation of RP2D. Fewer patients might be needed based on the recommendation of the DSB and the criteria specified (see section 7.1). Additional 40 patients will be included in the expansion cohorts, in case two (or three) tumor types will be selected for further evaluation.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

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

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

The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report unless there is public interest to publish before the end of the trial. In this event the Sponsor and the investigator(s) will agree on the publication strategy

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI Standard Operating Procedures (SOPs).

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The Investigator will inform the Sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP.

The certificate of insurance cover is made available to the Investigator and the patients, and is stored in the ISF (Investigator Site File)."

8.1 TRIAL APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

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

Prior to patient participation in the trial, written informed consent must be obtained from each patient according to ICH GCP and to the regulatory and legal requirements of the

participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

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

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

8.2 DATA QUALITY ASSURANCE

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

8.3 RECORDS

Case Report Forms (e)CRF for individual patients will be provided by the Sponsor. See section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to section 4.1.8.

8.3.1 Source documents

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

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

For eCRFs all data must be derived from source documents.

8.3.2 Direct access to source data and documents

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

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore a unique reference document for the evaluation of listedness needs to be provided. For the BI 836880 this is the current version of the Investigator's Brochure (c02353882-01). The current version of this reference document is to be provided in the ISF. No AEs are classified as listed for study design, or invasive procedures.

8.4.2 Expedited reporting to health authorities and IEC / IRB

Expedited safety reporting (7/15 days reports) at a site will end 30 days after the trial drug was permanently discontinued for the last patient at that site.

8.5 STATEMENT OF CONFIDENTIALITY

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

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

8.6 END OF TRIAL

The trial will end when the last patient has completed the EoR visit as specified in Section 6.2.3.4 and 6.2.3.5. The IEC / competent authority in each participating EU member state needs to be notified about the end of the trial or early termination of the trial.

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10. APPENDICES

10.1 INSTRUCTIONS FOR USE

10.1.1 Instructions for Pharmacists

Available in ISF.

10.2 BLOOD PRESSURE MEASUREMENT PROCEDURE

The preferred method of blood pressure measurement is by a standard mercury sphygmomanometer. If a standard mercury sphygmomanometer is not available, alternative devices according to website dableducational.org may be used. At screening, blood pressure should be taken in both arms. If the pressures differ by more than 10 mmHg (as in the presence of a subclavian steal syndrome), the arm with the higher pressure (either systolic or - if needed to decide - diastolic) should be used for subsequent measurements. Blood pressure measurements should be performed on the same arm and, if possible, by the same person. The same method and device must be used throughout the trial for a patient i.e. if a patient receives the first blood pressure measurement for example with an electronic device, the same method and device should be used throughout the study for this patient (without switching to manual blood pressure measurement). On the other hand, inter-patient variability is acceptable, i.e. a study site is allowed to consistently use an electronic device to measure the blood pressure in a given patient throughout the study and a manual technique in another patient. After patients have rested quietly, in the seated position for five minutes, three blood pressure measurements will be taken two minutes apart and all three results have to be entered in the eCRF. The seated pulse rate will be taken during the two-minute interval between the second and third blood pressure reading. Blood pressure measurements should be recorded to the nearest 2 mmHg only when measured with a manual sphygmomanometer; when digital devices are used the value from the device should be rounded to the nearest 1 mmHg. For calculation of mean values, decimal places should be rounded to integers (e.g. a DBP of 94.5 would be rounded to 95 mmHg and a DBP of 109.4 would be rounded to 109 mmHg). The above mentioned procedure is considered as standardised conventional blood pressure measurement (CBPM).

In case of a suspected “white coat effect” it is recommended to repeat the measurement in an pleasant condition after sufficient rest. Ambulatory blood pressure measurement (ABPM) can be an option in specific cases to observe BP profiles over a longer period (e.g. during infusion and thereafter) and even outside the hospital in private surrounding. However treatment decisions should be based whenever possible on CBPM as decribed above and ABPM should be used for observation only. In case BP values from ABPM should be used for treatment related decisions, this has to be taken from appropriate timepoints and validated ABPM devices according to website dableducational.org should be used. Values from self blood pressure measurement (SBPM) communicated from patient to investigator is not considered valuable for study related decisions.

10.3 PHARMACOKINETIC ANALYSES

If data allow, the following pharmacokinetic parameters of BI 836880 will be evaluated using noncompartmental analysis methods according to the internal BI [redacted]

After the first dose:

[redacted]

- AUC_{0-168} (area under the plasma concentration-time curve over the time interval from 0 to 168h).

[redacted]

- $t_{1/2}$ (terminal half-life).

[redacted]

Pharmacokinetic parameters will be calculated using noncompartmental analyis (NCA). The derivation of pharmacokinetic parameters is described in detail in

10.4 BLOOD SAMPLING TIME POINTS FOR PK, [redacted] AND ECG RECORDING IN THE PHASE I PART OF THE STUDY (DOSE ESCALATION PHASE)

Table 10.4: 1 Blood sampling scheme for PK, [redacted] in courses 1, 2, 3 and from course 4 onwards

Course	Visit	Day	Time Point (hh:min)	CRF Time / planned time	PK: BI 836880	[redacted]	ECG	BP
1***	V1	1	Before start of BI 836880 infusion	-0:05	x		X (3x)	X (3x)
			Start of BI 836880 infusion	0:00				
			Before end of infusion	1:30**			X (3x)	X (3x)
			Immediately after end of infusion*	1:30**	x			
			0.5h after the end of infusion	2:00	x			
			1.5h after the end of infusion	3:00	x			
			3.5h after the end of infusion	5:00	x			
			6.5h after the end of infusion	8:00	x			
		2		24:00	x		X (3x)	X (3x)
		3	48h after the end of infusion	48:00	x			X (3x)
	V2	8		168:00	x			X (3x)
	V3	15		336:00	x			X (3x)

Table 10.4: 1(cont'd) Blood sampling scheme for PK, [redacted] in courses 1, 2, 3 and from course 4 onwards (cont.)

Course	Visit	Day	Time Point (hh:min)	CRF Time / planned time	PK: BI 836880	[redacted]	ECG	BP
2	V1	1	Before start of BI 836880 infusion	-0:05	x		X (3x)	X (3x)
			Start of BI 836880 infusion	0:00				
			Before end of infusion	1:30**			X (3x)	X (3x)
			Immediately after end of infusion*	1:30**	x			
			0.5h after the end of infusion	2:00	x			
			1.5h after the end of infusion	3:00	x			
			3.5h after the end of infusion	5:00	x			
			6.5h after the end of infusion	8:00	x			
		2		24:00	x		X (3x)	X (3x)
		3	48h after the end of infusion	48:00	x			X (3x)
	V2	8		168:00	x			X (3x)
	V3	15		336:00	x			X (3x)
3	V1	1	Before start of BI 836880 infusion	-0:05	x		X (3x)	X (3x)
			Start of BI 836880 infusion	0:00				
			Before end of infusion	1:30**			X (3x)	X (3x)
			Immediately after end of infusion*	1:30**	x			
		2		24:00	x			X (3x)

Table 10.4: 1(cont'd) Blood sampling scheme for PK, [redacted] in courses 1, 2, 3 and from course 4 onwards (cont.)

Course	Visit	Day	Time Point (hh:min)	CRF Time / planned time	PK: BI 836880	[redacted]	ECG	BP
4	V1	1	Before start of BI 836880 infusion	-0:05	x		X (3x)	X (3x)
			Start of BI 836880 infusion	0:00				
			Before end of infusion	1:30**			X (3x)	X (3x)
			Immediately after end of infusion*	1:30**	x			
			0.5h after the end of infusion	2:00	x			
			1.5h after the end of infusion	3:00	x			
			3.5h after the end of infusion	5:00	x			
			6.5h after the end of infusion	8:00	x			
		2		24:00	x			X (3x)
	V2	8		168:00	x			X (3x)
	V3	15		336:00	x			X (3x)
5-12	V1	1	Before start of BI 836880 infusion	-0:05	x		X (3x)	X (3x)
			Start of BI 836880 infusion	0:00				
			Before end of infusion	1:30**			X (3x)	X (3x)
EOT****					x		X (3x)	X (3x)
EoR****					x			X (3x)
FU1****					x			

* within 5 min after the end of infusion

** PTM of 1:30 according to an infusion duration of 90 min. If the infusion duration should be shorter (or longer), the PK sample has to be taken in any case immediately after the end of the infusion/ the ECG has to be conducted shortly before end of infusion and the actual sampling time needs to be recorded in the eCRF. Subsequent PK samples (in C1, C2 and C4) have to be taken 0.5h, 1.5h, 3.5h and 6.5h after the end of the infusion.

*** in case of an intra-patient dose escalation the 1st cycle with the higher dose will follow cycle one at the start of treatment with BI 836880 with regards to sampling, (PK, [redacted]

**** No samples will be collected after data base lock and the trial is completed (see Section 6.2.3.5)

[redacted]

10.6 STATISTICAL APPENDIX INCLUDING MODEL PERFORMANCE AND DATA SCENARIOS

The model was assessed by two different metrics: hypothetical on-study data scenarios and long-run operating characteristics.

Hypothetical data scenarios
Hypothetical data scenarios are shown in Table 10.6: 1. These scenarios reflect potential on-study data constellations and related escalation as allowed by the model and the 200% escalation limit or doses of interest. For each scenario, the probability of overdose for the current dose, as well as the next potential dose and related probabilities of under-dosing, target dose and over-dosing are shown. A new cohort will be open for enrolment after the review on data from the previous cohort is completed by DSB.

For example, scenario 1 represents the case that no DLT is observed in two patients at the starting dose of 40mg. In this case, the next dose permitted by the model and by the 200% escalation rule is 120mg. Scenario 4 represents the case that no DLTs are observed in the first cohort of two patients at 40mg, and 1 DLT is observed in the second cohort of three patients at 120mg. In this case, the model requires to re-enroll at the current dose level of 120mg. Scenario 5 shows the case that 2 DLTs are observed in the second cohort of three patients at 120mg. The model then allows a de-escalation.

Finally, scenario 6 and 7 illustrate the case where no DLTs are seen in the first three cohorts. In scenario 6, no DLT is observed at 720mg, either. However, the model does not allow the escalation to 1250mg for safety concerns despite the fact that no DLTs are observed in the first four cohorts. On the other hand, scenario 7 presents the case that 1 DLT is seen at 720mg. In this case, no escalation to 1250mg is allowed as well. These two cases illustrate the adaptive behaviour of the model even in extreme situations.

Table 10.6: 1 Hypothetical data scenarios.

Scenario	Cohort	Dose (mg)	# DLT	# Pat	Current Dose: P(OD)	Next Dose	Next Dose		
							P(UD)	P(TD)	P(OD)
1	1	40	0	2	0.013	120	0.894	0.062	0.044
2	1	40	1	3	0.278	N/A	N/A	N/A	N/A
3	1 2	40 120	0 0	2 2	0.013	360	0.816	0.103	0.081
4	1 2	40 120	0 1	2 3	0.194	120	0.497	0.309	0.194
5	1 2	40 120	0 2	2 3	0.575	40	0.434	0.330	0.236
6	1 2 3 4	40 120 360 720	0 0 0 0	2 2 3 3	0.025	720	0.878	0.097	0.025
7	1 2 3 4	40 120 360 720	0 0 0 1	2 2 3 3	0.224	720	0.436	0.340	0.224

Operating characteristics

Operating characteristics are a way to assess the long-run behaviour of a model. Under an assumed true dose-toxicity curve, metrics such as the probability of recommending a dose with true DLT rate in the target interval can be approximated via simulation. Table 10.6: 2 describes 5 assumed true dose-toxicity scenarios which were used to assess the operating characteristics of the model. These scenarios reflect a wide range of possible cases as follows:

- - Scenario 1: aligned with prior medians
- - Scenario 2: high-toxicity scenario
- - Scenario 3: low-toxicity scenario
- - Scenario 4: low-tox followed by high-tox
- - Scenario 5: non-logistic dose-toxicity scenario

Table 10.6: 2 Assumed true dose-toxicity scenarios

Scenario		Dose (mg)				
		40	120	360	720	1250
1 (Prior)	P(DLT)	0.069	0.104	**0.176**	**0.274**	0.444
2 (High Tox)		0.100	**0.204**	0.371	0.500	0.603
3 (Low Tox)		0.001	0.006	0.039	**0.180**	**0.250**
4 (Non-Logistic)		0.040	**0.180**	**0.280**	0.360	0.380
5 (Low-High)		0.001	0.010	**0.180**	**0.317**	0.600

For each of these scenarios, 1000 trials were simulated. It was then assessed how often a dose was declared as MTD with true DLT rate in the under-, targeted or over-dose range. Furthermore, the average, minimum and maximum number of patients per trial and the average number of DLTs per trial are reported. Results are shown in Table 10.6: 3.

Table 10.6: 3 Simulated operating characteristics

Scenario	**% of trials declaring an MTD with true DLT rate in**				**# Patients**	**# DLT**
	underdose	**target dose**	**overdose**	**STOPPED**	**Mean (Min-Max)**	**Mean (Min- Max)**
1	22.7	61.6	0.2	15.5	17.05 (3 – 34)	2.896 (1 – 10)
2	9.5	52.0	14.8	23.7	15.38 (3 – 30)	3.642 (1 – 10)
3	26.2	73.8	0	0	19.77 (16 – 36)	2.236 (1 – 6)
4	5.5	79.2	5.7	9.6	17.78 (3 – 35)	3.664 (1 – 10)
5	14.4	85.4	0.2	0	19.60 (15 – 40)	3.303 (1- 8)

In scenario 1, which reflects the case that the true dose-toxicity is aligned with prior medians, 61.6% of the simulated trials declared a dose as MTD with true DLT rate in the targeted dose range. Note that 15.5% of the simulated trials stop because of high toxicity. This is mostly due to the cases that 1 DLT is observed out of 3 patients at the starting dose 40mg. In reality, this situation would rarely happen as the safety profile of starting dose is expected to be good. In addition, dose escalation could still happen after the discussion within DSB.

In scenario 2 (high-toxicity scenario), the starting dose has already >10% probability of observing at least 2 DLTs out of 3 patients or 1 DLT out of 2 patients in the first cohort. This contributes to the high percentage (23.7%) of all simulated trials for which the trial is stopped

since none of the doses is considered tolerable anymore. This is an expected situation for a high-toxicity scenario.

In scenarios 3, 4 and 5, more than 50% of the simulated trials declared a dose as MTD with true DLT rate in the targeted dose range.

The mean patient numbers range from 15.4 patients (high-toxicity scenario) to 19.8 patients (low-toxicity scenario) and the maximum number of patients was 40. Therefore, the patient numbers are as expected and increase when moving away from the high-toxicity scenario. In summary, the considered data scenarios show a reasonable behavior of the model and the operating characteristics demonstrate a good precision of MTD determination.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		19 Oct 2015
EudraCT number		2014-005395-28
BI Trial number		1336.1
BI Investigational Product(s)		BI 836880
Title of protocol		A First-in Human Phase I, non-randomized, open-label, multi-center dose escalation trial of BI 836880 administered by repeated intravenous infusions in patients with solid tumors.
To be implemented only after approval of the IRB / IEC / Competent Authorities	X	
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		Synopsis
Description of change		Change of one of the main inclusion criteria
Rationale for change		Adapted in synopsis according to change in section 3.3.2
Section to be changed		Flow Chart
Description of change		a) BP measurement added whenever AE assessment foreseen b) IRT call can be made ahead of study visit
Rationale for change		a) To have complete assessment of AESI at each visit b) Clarification for logistical reasons
Section to be changed		Section 3.1
Description of change		Sequential start of treatment added; 1. 2 weeks between 1st and 2nd patient in first dose cohort, 2. 48 hours between first administration to

		different subjects during dose escalation, 3. At least 3 week observation (=1 cycle) between subsequent cohorts Further description of extension of MTD cohort and objective of expansion cohort
Rationale for change		a) Added to CTP for safety reasons b) Further clarification
Section to be changed		Section 3.3.2
Description of change		a) Incl.-Crit. #2 reworded b) Incl.-Crit. #8: contraception period extended c) Excl.-Crit. #12 added
Rationale for change		a) More precise description of study population b) Safety reasons c) Added according to German drug law
Section to be changed		Section 4.1.3
Description of change		Added “clinical” benefit
Rationale for change		As continuation of treatment could be considered in best interest of patient even in case of objective progression according to RECIST. Any decision to continue treatment need to be confirmed by DSB.
Section to be changed		Section 4.1.4
Description of change		Added more detailed description of medical requirements at study site
Rationale for change		More detailed site description as pre-requisit according to CTP
Section to be changed		Section 5.3.5
Description of change		Added time window for blood drawing
Rationale for change		Blood drawing allowed ahead of study visit for logistical reasons
[redacted]		
Section to be changed		Section 6.1

Description of change		Prolonged hospitalization time after admin from 24 h to 48 h
Rationale for change		Increase of close observation time for safety reasons in first-in-human trial
Section to be changed		Section 8.1
Description of change		Deleted “patient’s legally accepted representative”
Rationale for change		According to ethics request
Section to be changed		Section 10.6
Description of change		Text and table of statistical appendix updated
Rationale for change		To better illustrate possible dose escalation scenarios according to Bayesian design

Number of global amendment		2
Date of CTP revision		14 February 2017
EudraCT number		2014-005395-28
BI Trial number		1336.1
BI Investigational Product(s)		BI 836880
Title of protocol		A First-in Human Phase I, non-randomized, open-label, multi-center dose escalation trial of BI 836880 administered by repeated intravenous infusions in patients with solid tumors.
To be implemented only after approval of the IRB / IEC / Competent Authorities	X	
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		Titel page
Description of change		Change of TCM Was changed to [redacted] Phone: [redacted] Fax: [redacted]
Rationale for change		Previous TCM has taken over another position
Section to be changed		Synopsis
Description of change		No. of patients: The following: About 80 patients will be entered Was changed to: About 80 patients will be entered, including at least 12 patients treated at MTD with tumour lesions evaluable for Dynamic contrast-enhanced (DCE)-

		MRI
Rationale for change		Change was implemented to make sure that a pharmacodynamics effect can be documented
Section to be changed		Synopsis
Description of change		Main criteria for inclusion The following: ….. • Histologically or cytologically confirmed malignancy which is locally advanced or metastatic solid tumor, and either refractory after standard therapy for the disease or for which standard therapy is not reliably effective, e.g. they do not tolerate or have contraindications to otherwise available standard Was changed to: • Histologically or cytologically confirmed malignancy which is locally advanced or metastatic solid tumor, and either refractory after standard therapy for the disease or for which standard therapy is not reliably effective, e.g. they do not tolerate or have contraindications to otherwise available standard therapy and tumour lesions evaluable for Dynamic contrast-enhanced (DCE)-MRI at MTD
Rationale for change		Change was implemented to make sure that a pharmacodynamics effect can be documented
Section to be changed		3.1 OVERALL TRIAL DESIGN AND PLAN
Description of change		The following: Once a MTD has been reached it is foreseen to enroll up to 12 patients Confirmation of the RP2D will be made based on all available safety, PK and Pharmacodynamics (PD) data at all treatment cycles and all dose levels. In case of anti-tumor activity signals in a given tumor type, DSB can take the decision for a trial expansion to recruit patients with the same tumor type with the aim to generate safety and preliminary efficacy data specific to such disease. 2-3 tumor type expansion cohorts are planned. Up to a total of 20 patients may be recruited in each tumor type expansion cohort and will be treated

		according to same Flow Chart as patient in previous cohorts. This is to confirm RP2D in patient with specific tumor type according to study objective and to prepare further Phase II studies. This change will be implemented with a further amendment to this protocol. Was changed to: Once a MTD has been reached it is foreseen to enroll up to 12 patients on this dose level to enlarge the group of patients treated on proposed RP2D. A minimum of 12 patients must have tumour lesions evaluable for Dynamic contrast-enhanced (DCE)-MRI to allow a better interpretation of a pharmacodynamics (vascular) effect of BI 836880. on this dose level to enlarge the group of patient treated on proposed RP2D. Confirmation of the RP2D will be made based on all available safety, PK and Pharmacodynamics (PD) data at all treatment cycles and all dose levels. In case of anti-tumor activity signals in a given tumor type, DSB can take the decision for a trial expansion to recruit patients with the same tumor type with the aim to generate safety and preliminary efficacy data specific to such disease. 2-3 tumor type expansion cohorts are planned. Up to a total of 20 patients may be recruited in each tumor type expansion cohort and will be treated according to same Flow Chart as patient in previous cohorts. This is to confirm RP2D in patient with specific tumor type according to study objective and to prepare further Phase II studies. This change will be implemented with a further amendment to this protocol.
Rationale for change		Change was implemented to make sure that a pharmacodynamics effect can be documented. Administrative change
Section to be changed		3.3.2 Inclusion criteria
Description of change		The following: ….. 2. Histologically or cytologically confirmed malignancy which is locally advanced or metastatic solid tumor, and either refractory after standard

		therapy for the disease or for which standard therapy is not reliably effective, e.g. they do not tolerate or have contraindications to otherwise available standard therapy Was changed to: 2. Histologically or cytologically confirmed malignancy which is locally advanced or metastatic solid tumor, and either refractory after standard therapy for the disease or for which standard therapy is not reliably effective, e.g. they do not tolerate or have contraindications to otherwise available standard therapy and tumour lesions evaluable for Dynamic contrast-enhanced (DCE)-MRI at MTD
Rationale for change		Change was implemented to make sure that a pharmacodynamics effect can be documented.
Section to be changed		3.3.2 Inclusion criteria
Description of change		The following: ….. Women not of childbearing potential are defined as: Women who are postmenopausal (12 months with no menses without an alternative medical cause) or who are permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral oophorectomy or bilateral salpingectomy). Was changed to: …… Women not of childbearing potential are defined as: Women who are postmenopausal (12 months with no menses without an alternative medical cause) or who are permanently sterilized (e.g., hysterectomy, bilateral oophorectomy or bilateral salpingectomy).
Rationale for change		Tubal occlusion is no longer defined as “not of childbearing potential”
Section to be changed		4.1.3 Selection of doses in the trial

Description of change		The following: Table 4.1.3: 1 Potential dose levels

		Dose level / Total dose (mg) / Maximum dose increment DL 1 / 40 / 200% DL 2 / 120 / 200% DL3 / 360 / 100% DL4 / 720 / 100% DL5 / 1440 Limited to 1250* / Was changed to: Dose level / Total dose (mg) / Maximum dose increment DL 1 / 40 / 200% DL 2 / 120 / 200% DL3 / 360 / 100% DL4 / 720 / 100% DL5 / 1000 / 100% DL6 / 1440 Limited to 1250* /
Rationale for change		Data Safety Board decided on introduction of this additional dose level
Section to be changed		4.1.3 Selection of doses in the trial
Description of change		The following was added: … For patients with an intra-patient dose escalation(s) all assessments will be done according to instructions for the first cycle at start of treatment with BI 836880 and intensive PK-sampling, [redacted] will be conducted (see flow chart and Appendix 10.4) and patients have to be closely followed for any adverse events. Therefore patients have to come to the clinic during the first course of intra-patient dose escalation every week. Additional visits are needed at day 2 and at day 3 of the 1st cycle of dose escalation. The above-mentioned procedures will be followed

		also in case of further intra-patient dose escalations.
Rationale for change		Specific guidance for patients with an intra-patient dose escalation is provided for assessments to be done within the first cycle with the escalated dose.

[redacted]

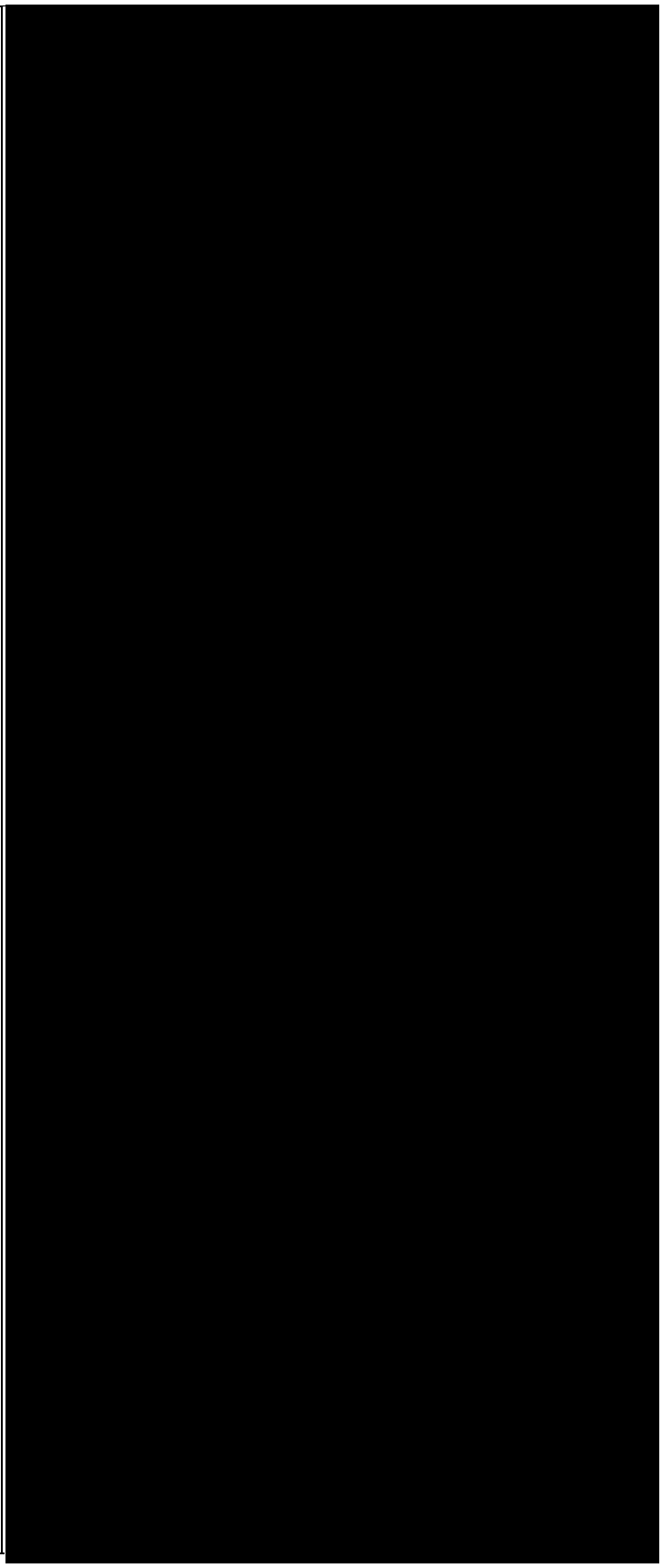
[redacted]

Section to be changed		10 APPENDICES 10.4 BLOOD SAMPLING TIME POINTS FOR PK, [redacted] AND ECG RECORDING IN THE PHASE I PART OF THE STUDY (DOSE ESCALATION PHASE) Table 10.4: 1 Blood sampling scheme for PK, [redacted] in courses 1, 2, 3 and from course 4 onwards
Description of change		The following footnote was added: .. *** in case of an intra-patient dose escalation

		the 1st cycle with the higher dose will follow cycle one at the start of treatment with BI 836880 with regards to sampling, (PK, [redacted]
Rationale for change		Specific guidance for patients with an intra-patient dose escalation is provided for assessments to be done within the first cycle with the escalated dose.
Section to be changed		Minor changes within the following sections: - Synopsis - Abbreviations - 3.3 SELECTION OF TRIAL POPULATION - 7.3.5 Pharmacokinetic analyses - Table 10.4: 1 Blood sampling scheme for PK, [redacted] in courses 1, 2, 3 and from course 4 onwards
Description of change		Typos as well as minor inconsistencies between sections have been corrected
Rationale for change		See above

Number of global amendment		3
Date of CTP revision		12 May 2017
EudraCT number		2014-005395-28
BI Trial number		1336.1
BI Investigational Product(s)		BI 836880
Title of protocol		A First-in Human Phase I, non-randomized, open-label, multi-center dose escalation trial of BI 836880 administered by repeated intravenous infusions in patients with solid tumors.
To be implemented only after approval of the IRB / IEC / Competent Authorities	X	
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		

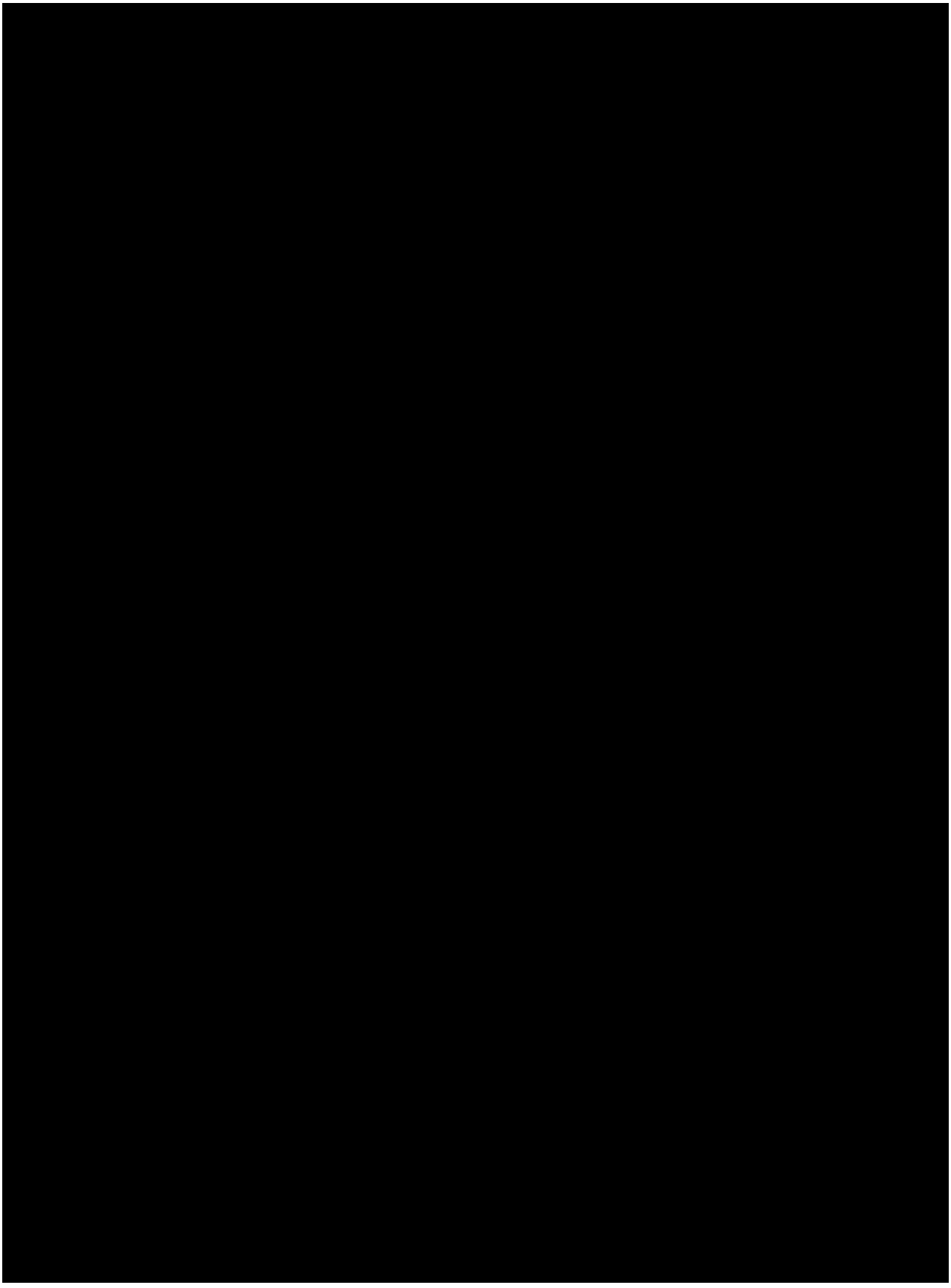
[redacted]



		[redacted]

Number of global amendment		4
Date of CTP revision		10 July 2018
EudraCT number		2014-005395-28
BI Trial number		1336.1
BI Investigational Product(s)		BI 836880
Title of protocol		A First-in Human Phase I, non-randomized, open-label, multi-center dose escalation trial of BI 836880 administered by repeated intravenous infusions in patients with solid tumors.
To be implemented only after approval of the IRB / IEC / Competent Authorities	X	
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		Synopsis
Description of change		Change of TCM Was changed to: [redacted] Phone: [redacted] Fax : [redacted]

[redacted]



[redacted]

Section to be changed		6.2.3 Follow Up Period and Trial Completion
Description of change		Section 6.2.3.3.1 was changed The following: For patients who did not progress, additional follow-up visits after the EoR visit will be performed every 6 weeks plus/minus 3 days. Was changed to: For patients who did not progress, additional follow-up visits after the EoR visit will be performed every 6 weeks plus/minus 3 days. [redacted] Section 6.2.3.5 was added : 6.2.3.5 Trial completion The end of the trial will occur when the last patient completes his/her REP. In case patients would be still on treatment when data base is locked and the Clinical Trial Report (CTR) is being drafted, these patients will be maintained in the trial and may continue treatment as long as they have clinical benefit (no PD, no drug-related adverse events requiring discontinuation, no new anti-cancer treatment started) and patient is willing to continue. For these patients, no blood sample will be collected for PK [redacted] analysis. After the discontinuation of these patients, the data collected after the database lock (DBL) will be provided as separate listings and will not lead to any further updating of tables produced for section 15 of the CTR unless deemed necessary. These listings will be included in a revised CTR.
Rationale for change		[redacted]

		[redacted] ▪ Clarification about trial completion and planned procedures about ongoing patients at DBL and additional data collected after DBL.
Section to be changed		Appendix 10.4 Table 10.4 : 1(cont'd) Blood sampling scheme for PK, [redacted] in courses 1, 2, 3 and from course 4 onwards (cont.)
Description of change		This footnote was added: **** No samples will be collected after data base lock and the trial is completed (see Section 6.2.3.5)
Rationale for change		footnote added to be in line with section 6.2.3.5

Number of global amendment		5
Date of CTP revision		08 March 2019
EudraCT number		2014-005395-28
BI Trial number		1336.1
BI Investigational Product(s)		BI 836880
Title of protocol		A First-in Human Phase I, non-randomized, open-label, multi-center dose escalation trial of BI 836880 administered by repeated intravenous infusions in patients with solid tumors.
To be implemented only after approval of the IRB / IEC / Competent Authorities	X	
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		Flow Chart
Description of change		Footnote N°18 was added about the 2 ongoing patients and procedures to be performed: For the 2 ongoing patients, minimum set of procedures is mandatory. This includes safety lab, vital signs including blood pressure, adverse events, and pregnancy test if applicable. However, other assessments as indicated in the flowchart of the protocol or single lab values can be omitted according to investigator's opinion.
Rationale for change		Clarification provided about mandatory procedures to be performed for the 2 ongoing patients based on flow chart and medical opinion of the investigator
Section to be changed		4.1.1 Identity of BI Investigational product(s) and comparator product(s)
Description of change		• Explanation is provided about the change in BI836880 formulation, the following paragraph was added: In this trial, the IMP BI836880 will be switched to a new pharmaceutical formulation which is to be diluted in a standard 5% Glucose/dextrose solution.

		The New formulation will be made available in this trial at the latest before expiry of the old formulation prepared with a drug specific diluent. Details of the trial medication BI836880 and respective diluent are presented in the table below, in the IB's for BI836880 as well as in the instructions for the pharmacist (filed in ISF) • Table 4.1.1: 2 was deleted as this diluent will not be used.
Rationale for change		Clarification about the new pharmaceutical formulation of BI836880 and new diluent (standard 5% Glucose /dextrose)
Section to be changed		4.1.6 Packaging, labelling, and re-supply
Description of change		**The following text:** BI 836880 will be supplied in 10ml 10R vial containing 100mg BI 836880 [10mg/ml] solution for infusion. The BI 836880 vials will be packed in one vial per box. Diluent for BI 836880 drug product will be supplied in 50R vial containing 50ml Diluent for BI 836880 drug product. The Diluent vials will be packed in one vial per box. **Was changed to:** BI 836880 will be supplied in 10ml 10R vial containing 100mg BI 836880 [10mg/ml] solution for infusion. The BI 836880 vials will be packed in one vial per box. ~~Diluent for BI 836880 drug product will be supplied in 50R vial containing 50ml Diluent for BI 836880 drug product. The Diluent vials will be packed in one vial per box.~~
Rationale for change		Section adapted according to change in the new pharmaceutical formulation of BI836880 which will be diluted with a standard 5% Glucose/dextrose.
Section to be changed		4.1.7 Storage conditions
Description of change		**The following text:** BI 836880 vials and Diluent Buffer vials must be stored in their original packaging. The study product must be stored according to the

		instructions on the label. The Investigator, the Pharmacist, or other personnel is allowed to store and dispense investigational product. They will be responsible for ensuring that the investigational product used in the study is securely maintained as specified by the sponsor and in accordance with the applicable regulatory requirements. **Was changed to:** BI 836880 vials ~~and Diluent Buffer vials~~ must be stored in their original packaging. The study product must be stored according to the instructions on the label. The Investigator, the Pharmacist, or other personnel is allowed to store and dispense investigational product. They will be responsible for ensuring that the investigational product used in the study is securely maintained as specified by the sponsor and in accordance with the applicable regulatory requirements.
Rationale for change		Section adapted according to change in the new pharmaceutical formulation of BI836880 which will be diluted with a standard 5%
Section to be changed		5.3.6 Electrocardiogram (ECG)
Description of change		**The following text:** **…..** In case of drug-related ECG changes and whenever the investigator deems necessary, additional ECG monitoring will be performed in the respective and later cycles of treatment. The ECGs will be recorded by a digital ECG machine and send for evaluation by a central vendor, which will conduct the analysis in a blinded fashion. QTcF and other variables of interest will be described in a separate ECG plan. Data from this central review will be taken for retrospective data analysis. **Was changed to:** In case of drug-related ECG changes and whenever the investigator deems necessary, additional ECG monitoring will be performed in the respective and later cycles of treatment.

		~~The ECGs will be recorded by a digital ECG machine and send for evaluation by a central vendor, which will conduct the analysis in a blinded fashion. QTcF and other variables of interest will be described in a separate ECG plan. Data from this central review will be taken for retrospective data analysis~~.
Rationale for change		Centralized ECG will not be used anymore for the 2 ongoing patients. Standard ECG will be performed and any significant finding based on medical opinion of the investigator should be reported in the eCRF.

APPROVAL / SIGNATURE PAGE

Document Number: c02441868 **Technical Version Number:7.0**

Document Name: clinical-trial-protocol-version-06

Title: A First-in Human Phase I, non-randomized, open-label, multi-center dose escalation trial of BI 836880 administered by repeated intravenous infusions in patients with solid tumors.

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Trial Leader	[redacted]	11 Mar 2019 16:51 CET
Approval-Therapeutic Area [redacted]		11 Mar 2019 17:06 CET
Author-Trial Statistician		11 Mar 2019 18:04 CET
Author-Trial Clinical Pharmacokineticist		12 Mar 2019 07:17 CET
Approval-Clinical Program [redacted]		12 Mar 2019 10:22 CET
Approval-Translational Medicine Expert		12 Mar 2019 19:21 CET
Verification-Paper Signature Completion		13 Mar 2019 09:17 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed