Clinical Trial Protocol

	Document Number:	**c03124055-06**
EudraCT No.:	2015-001132-38	
BI Trial No.:	1336.6	
BI Investigational Product(s):	BI 836880	
Title:	Phase I, non-randomized, open-label, multi-center dose escalation trial of BI 836880 administered by weekly repeated intravenous infusions in patients with advanced solid tumors.	
Brief Title:	Weekly BI 836880 in patients with advanced solid tumors	
Clinical Phase:	I	
Clinical Trial Leader:	Phone: Fax:	
Coordinating Investigator: **Principal Investigator:**	Phone: Fax: Tel Fax	
Status:	Final Protocol (Revised Protocol based on global amendment 3)	
Version and Date:	**Version:**	**Date:**
Revised Protocol	4.0	13 Mar 2019

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		Not applicable	
Name of active ingredient:		BI 836880	
Protocol date: 10 Dec 2015	**Trial number:** 1336.6		**Revision date:** **13 Mar 2019**

Title of trial:	Phase I, non-randomized, open-label, multi-center dose escalation trial of BI 836880 administered by weekly repeated intravenous infusions in patients with advanced solid tumors
Coordinating Investigator: **Principal Investigator**	Phone: Fax: Tel Fax
Trial site(s):	Multicentre-trial conducted in 2 countries
Clinical phase:	I
Objective(s):	To determine the maximum tolerated dose (MTD) and provide preliminary safety data of BI 836880 given as intravenous infusion and to determine recommended phase II dose.
Methodology:	Non randomized, uncontrolled, open-label, dose escalation
No. of patients:	Approximately 40 patients to be enrolled
total entered:	Approximately 25 patients
each treatment:	Approximately 25 patients will receive study treatment
Diagnosis :	Advanced or metastatic/ refractory solid tumors

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		Not applicable	
Name of active ingredient:		BI 836880	
Protocol date: 10 Dec 2015	**Trial number:** 1336.6		**Revision date:** **13 Mar 2019**

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. patients 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 • 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) and sensory peripheral neuropathy CTCAE grade < 2
Test product(s):	BI 836880 and Diluent for BI 836880
dose:	Starting dose of 40 mg weekly infusion
mode of administration:	Intravenous weekly in a 21-day treatment course
Comparator products:	Not applicable
dose:	Not applicable
mode of administration:	Not applicable
Duration of treatment:	Continuous treatment in the absence of disease progression or unacceptable toxicity
Endpoints	Primary endpoint • Maximum Tolerated Dose (MTD) Secondary endpoint • Drug related AEs leading to dose reduction or discontinuation during treatment period
Safety criteria:	Adverse events according to Common Terminology Criteria (CTCAE version 4.03), incidence of dose limiting toxicities, physical examination, vital signs, safety laboratory parameters, ECOG
Statistical methods:	Descriptive and exploratory statistics analyses. Dose escalation guided by a Bayesian logistic regression model with over dose control

FLOW CHART COURSE 1

Trial periods	**Screening**	**Treatment course*** **					**EOT***	**EoR***	**FU****
Course		1							
Visit	Screen	V1			V2	V3			
Day	-21 to -1	1	2	3	8 ±2	15±2		EoT+42 d	
Informed consent [1]	x								
Demographics	x								
Medical history	x								
Inclusion/exclusion criteria	x	x							
Physical examination[2]	x	x	x	x	x	x	x	x	
Height	x								
Weight	x	x					x		
Body temperature[3]	x	x	x		x	x	x		
Blood pressure[4], heart rate	x	x	x	x	x	x	x	x	
ECOG performance status	x	x					x		
Administration of BI 836880 infusion		x			x	x			
Safety Lab parameters[5]	x	x			x	x	x		
Pregnancy test	x	x					x		
Tumor assessment[6]	x						x		x
12-lead ECG[7]	x	x	x		x	x	x		
Echocardiography[8]	x						x		
Pharmacokinetics[9]		x	x	x	x	x	x	x	x (FU1)
Anti-drug antibodies[10]		x					x	x	x (FU1)

Trial periods	**Screening**	**Treatment course*** **					**EOT***	**EoR***	**FU****
Course		1							
Visit	Screen	V1			V2	V3			
Day	-21 to -1	1	2	3	8±2	15±2		EoT+42 d	
Biomarker : Myriad Ang MAP panel[11]		x		x				x	
Biomarker: free/total VEGF-A, Ang2[12]		x	x	x	x	x	x	x	x (FU1)
Concomitant therapy	x	x	x	x	x	x	x	x	x
Adverse events[13]	x	x	x	x	x	x	x	x	x
DCE-MRI[14]	x				x				x
Completion of trial medication							x		
Completion of patient participation									x

FLOW CHART COURSES 2 ONWARDS

Trial periods	**Repeated treatment courses*** **					**EOT***	**EoR***	**FU****
Course	2,3,4,5 onwards							
Visit	V1			V2	V3			
Day	1	2	3	8 ±2	15±2		EoT+42 d	
Physical examination[2]	x			x	x	x	x	
Weight	x					x		
Body temperature[3]	x			x	x	x		
Blood pressure[4], heart rate	x	x(C2,C4)		x	x	x	x	
ECOG performance status	x					x		
Administration of BI 836880 infusion	x			x	x			
Safety Lab parameters[5]	x			x	x	x		
Pregnancy test	x					x		
Tumor assessment[6]	x					x		x
12-lead ECG[7]	x	x (C2,C4)		x (C2,C4)	x (C2,C4)	x		
Echocardiography[8]	x					x		
Concomitant therapy	x	x		x	x	x	x	x
Adverse events[13]	x	x		x	x	x	x	x
DCE-MRI[14]	x (C3, C5)							x
Completion of trial medication						x		
Completion of patient participation								x

(C2, C3, C4, C5) = (courses 2, 3, 4 and 5)
FU1= first follow up visit
*End Of Treatment (EOT) must be performed within 21 days of the last administration of study drug. If last administration of the study drug occurs during a scheduled visit, examinations as defined for EOT should be performed instead of examinations for the scheduled visit.

EoR*= End of Residual Effect Period
**One Follow-up visit (FU1) should be performed 42 calendar days after the discontinuation of study drug for all patients. For patients who discontinue not due to progressive disease, additional FU visits will be performed at 6-week intervals plus /minus 3 days, until progression, lost to follow-up, start of another anti-cancer treatment, death.
After the interim data base lock additional FU visits are no longer required

***Treatment courses are 3 weeks in duration (21 days). All subsequent visit dates should be calculated based on Course 1 Visit 1 date. If one visit is skipped in case of treatment interruption patients may continue on treatment until the criteria for stopping medication are met (see Section 3.3.4)

[1]Written informed consent must be obtained before any trial specific screening assessments are performed.

[2]A complete physical examination (including cardiac, neurological, dermatological pulmological etc..) at screening and before the start of the treatment, EoT and End of Residual Effect Period (EoR). At further time points specified in the Flow Chart, physical examination should be limited to the assessment of the actual health status (including, evaluation of blood pressure, ECG, lab safety parameters, AEs, concomitant therapies, ECOG, as applicable). After the interim data base lock, physical examination, ECOG performance status are no longer mandatory at the specific visits but will be performed at the investigator's discretion. Findings will be documented in the eCRF only if qualifying as (S)AE

[3]Body Temperature: whenever possible the same method should be used for body temperature measurement in one patient. Body temperature $\geq$ 38°C must be re assessed 1 hour after. After the interim data base lock body temperature is no longer mandatory at specific visits but will be performed at the investigator's discretion. Findings will be documented in the eCRF only if qualifying as (S)AE

[4]Blood Pressure : Systolic and diastolic blood pressure as well as pulse rate (electronic or by palpation, count for 1 minute) will be measured after 5 minutes of rest in seated position. The blood pressure measurement should be performed three times at each time point (refer to Appendix 10.2 and Appendix 10.4 for detailed time points). After the interim data base lock blood pressure is no longer mandatory at specific visits but will be performed at the investigator's discretion. Findings will be documented in the eCRF only if qualifying as (S)AE

[5]Haematology, biochemistry and coagulation parameters will be performed locally. Previous safety lab: investigations are acceptable if performed within 72 hours prior to the first treatment administration. For details see Section 5.3.3 After the interim data base lock safety laboratory tests will be performed at investigator's discretion based on the standard medical care. Findings will be documented in the eCRF only if qualifying as (S)AE

[6]Tumor assessment will be performed every 6 weeks after start of treatment with BI 836880 (in the week preceding the start of treatment course 3, 5, 7, 9, 11...) and should include CT scans or MRI. Imaging not older than 28 days at start of treatment will suffice as screening images and don't have to be repeated. The EOT tumor assessment is optional if performed in the previous 4 weeks. In the event of any treatment interruption or treatment delay, the tumor assessment should follow the original schedule
After the interim data base lock, frequency of tumor assessment may be adapted according to local standard of care and in agreement with the sponsor if the patient is deriving clinical benefit (e.g. CR, PR or SD > 6 months).

[7]Triplicate 12-Lead resting digital electrocardiogram (3xECG taken approximately 2-3 minutes apart) will be performed at screening and will be repeated at visits (refer to Section 5.3.4 and Appendix 10.4 for detailed time point).
After the interim data base lock, ECG will be performed as clinically indicated on local machine and the assessment will be done by the investigator. Shipment of ECGs to central vendor is no longer required

[8]Echocardiography will be performed locally at screening (not older than 7 days before start of treatment) and at EoT. During treatment period, echocardiography will be conducted only if clinically indicated. After the interim data base lock findings related to echocardiography will be reported in the eCRF only if qualifying as (S)AE

[13]AEs must be collected and reported from signing the informed consent onwards through the end of treatment (including Residual Effect Period, REP): all AEs (serious and non-serious) and all AESIs must be collected and reported from signing the informed consent onwards through the end of treatment (including Residual Effect Period, REP). After the end of treatment (including the REP) during the extended follow-up period until the individual patient's end of trial: all related SAEs and all related AESIs must be collected and reported. After the individual patient's end of trial: the investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs and relevant AESIs of which the Investigator may become aware of (Please refer to Section 5.3.6 and Section 6.2.3.3)

[14]DCE-MRI measurements will be done only for suitable patients with preferably liver metastases > 2cm. DCE-MRI measurement will be done during the screening period, 1 week after first administration of BI 836880 (C1V2), after the 2nd treatment course (C3V1) and after the 4th treatment course (C5 V1) in absence of progressive disease. In case patient stopped treatment for other reasons than progressive disease, DCE-MRI should still be conducted as long as patient is in Follow up for progression. Time points for 3rd and 4th imaging, depending on when patient stopped treatment, have to be adapted as 6 weeks and 12 weeks after 1st infusion
(refer to Section 5.5.1)

After the interim data base lock, DCE-MRI measurement is no longer mandatory

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ABBREVIATIONS

ABPM	Ambulatory Blood Pressure Measurement
ADA	Anti-Drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine amino transferase
ANC	Absolute neutrophil count
Ang2	Angiopoeitin2
AST	Aspartate amino transferase
AUC	Area under the Curve
BI	Boehringer Ingelheim
BLQ	Below the limit of quantification
BP	Blood Pressure
CA	Competent Authority
CBPM	Conventional Blood Pressure Measurement
CI	Confidence Interval
CPL	Clinical Program Leader
CPPL	Clinical Pharmacology Program Leader
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organisation
CTMF	Clinical Trial Master File
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Clinical Trial Leader
CTM	Clinical Trial Manager
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DCE-MRI	Dynamic Contrast-Enhanced Magnetic Resonance Imaging
DEDP	Drug Exposure During Pregnancy
DBP	Diastolic Blood Pressure
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicity
DSB	Data Safety Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic Acid
EoR	End of Residual effect period
EOT	End of Treatment
EudraCT	European Clinical Trials Database
EWOC	Escalation with overdose control
FC	Flow Chart
FU	Follow up
FDA	Food and Drug Administration

GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HNSTD	Highest No-Severely Toxic Dose
IB	Investigator's Brochure
IC	Informed Consent
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
i.v.	intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web-based Response System
K_{trans}	Volume transfer constant obtained from DCE-MRI data
LMWH	Low Molecular Weight Heparin
MedDRA	Medical Dictionary for Drug Regulatory Activities
MTD	Maximum Tolerated Dose
NCA	Non Compartmental 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-Inflammatory Drug
NYHA	New York Heart Association
OPU	Operative Unit
p.o	Per os (oral)
PD	Progressive Disease
PLGF	Placenta Growth Factor
PK/PD	Pharmacokinetics/Pharmacodynamics
PR	Partial Response
QT	QT interval corrected for heart rate
QTcf	QT interval corrected for heart rate according to Fridericia's formula
eDC	Electronic Data Capture
RECIST	Response Evaluation Criteria In Solid Tumors
REP	Residual Effect Period
RP2D	Recommended Phase II Dose
SAE	Serious Adverse Event
SD	Stable Disease
SBPM	Self-Blood Pressure Measurement
SOP	Standard Operation Procedure
SUSAR	Suspect Unexpected Serious Adverse Event
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
TSE	Turbo Spin Echo
TSTAT	Trial Statistician
ULN	Upper Limit of Normal
UPCR	Urine Protein to Creatinine Ratio
VEGF	Vascular Endothelial Growth Factor

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, existing 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, play 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/Tie2) 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 (VHH) and two constant domains (CH2 and CH3). The cloned and isolated VHH domain is a stable polypeptide harbouring the full

antigen-binding capacity of the original heavy-chain antibody. These newly discovered VHH 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 (VHH, 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).

BI 836880 potently binds to both hVEGF165 and hVEGF121 with similar affinity in the low nanomolar to sub-nanomolar range and completely inhibits binding of hVEGF165 to VEGFR. BI 836880 potently binds to human Ang2 with an affinity constant estimated to be KD=16pM and potently inhibited and fully blocked human Ang2 binding to Tie2 with an IC50 of 50pM in the presence of human serum albumin (c02353882).
BI 836880 is highly potent and showed *in vivo* monotherapy efficacy (tumor growth inhibition) in several tumor xenograft representing colon cancer (CXF 243), non-small cell lung cancer (LXFE 211, LXFE 1422), mammary cancer (MAXF 401), ovarian cancer (OVXF 1353), pancreatic cancer (PAXF 546) and renal cell cancer (RXF 1220) (c02353882).

BI 836880 cross-reacts to cynomolgus VEGF, as well as mouse, rat and cynomolgus Ang2 which points to cynomolgus monkey as the most suitable species for toxicology assessment. Based on this, a 13-week repeat dose administration of BI 836880 was performed in cynomolgus monkeys. Animals received weekly BI 836880 intravenous doses by a 5-minute infusion at doses of 0 (vehicle only), 1, 10 and 60 mg/kg for a total of 14 doses followed by a 13-week recovery period. BI 836880 was well tolerated up to the highest dose of 60 mg/kg. No mortality was attributed directly to BI 836880 administration. But one monkey in the 10 mg /kg dose tier had to be euthanized due to an important immunogenic reaction.

BI 836880 did not demonstrate any effects on neurological, renal, or cardiovascular functions including electrocardiograms (ECGs). In the monkey presenting the immunogenic reaction, membranoproliferative glomerulopathy in the kidney was observed. This finding was considered as a secondary response to immune complex deposition in the glomeruli and not directly related to BI 836880 administration.

No BI 836880 related adverse changes in body weight, food consumption or clinical observations were noted. BI 836880 did not result in ocular changes, changes in physical examination parameters.

No adverse or BI 836880-related changes in hematology, chemistry, coagulation or urinalysis were observed (c02353882).

BI 836880 administration resulted in a microscopic growth plate cartilage change (increased zone of hypertrophy) in the sternum of the males in the ≥10 mg/kg dose groups. This change was of minimal in severity and was considered not adverse since it was not expected to

negatively affect bone growth. Increased thickness of the growth plate zone of hypertrophy is a known effect of angiogenesis inhibitors such as Bevacizumab.

The pharmacokinetics (PK) and immunogenicity of BI 836880 were investigated in cynomolgus monkeys following a single intravenous (i.v.) at 3 dose levels. BI 836880 demonstrated an unexpected dose-dependent clearance and a supra-proportionally $AUC_{0-\infty}$ increase with the increase of dose. Among the nine monkeys in this study, six monkeys were ADA positive post-dose at one or more of the sampling time points. In the 13-week toxicity and toxicokinetics, BI 836880 exposure (C_{max} and AUC_{0-168}) increased approximately dose-proportionally from 1 to 60 mg/kg in weeks 1, 4 and 13. There was a moderate (~ 2-fold) accumulation of BI 836880 after repeated dosing. The C_{max} and AUC_{0-168} values were similar between the male and female monkeys at the same dose level in each sampling week. The discrepancy in dose proportionality between these two studies is likely due to the difference in sampling. More sampling time points (up to 42 days post dosing) in the single dose PK study allowed better characterization of the later portion of the concentration-time profiles (after ~ 240 h), where dose-dependent clearance was more pronounced.

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 settings, 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 Trebananib in ovarian cancer. In a randomized Phase III trial in patient with recurrent ovarian cancer Trebananib 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 blockers and Ang2 blockers is not durable and only a limited number of patients 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 (c02353882).

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 weekly intravenous infusion and to determine recommended phase II dose.

Secondary objective:

- To provide preliminary safety data

2.3 BENEFIT-RISK ASSESSMENT

BI 836880 has not been tested in human so far. In the 13-week 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 (Trebananib) in development is in Phase III in combination with chemotherapy (R14-5440). 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 include 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 trial requires timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to ensure patients´ safety (see also Section 5.3.6.1)

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

A Data Safety Board (DSB) will be appointed to periodically review and monitor data from the trial (refer to Section 3.1.1).

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, multi-centre, 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 200% dose increment for the first dose escalation and 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. For subsequent 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 course, then dose-escalation can occur based on these 2 patients. However, should one of these 2 patients experience a DLT in the first course, a third patient will be enrolled at the same dose level. After all patients in a cohort have either experienced a DLT or have been observed for at least one course (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 the dose escalation scheme 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.

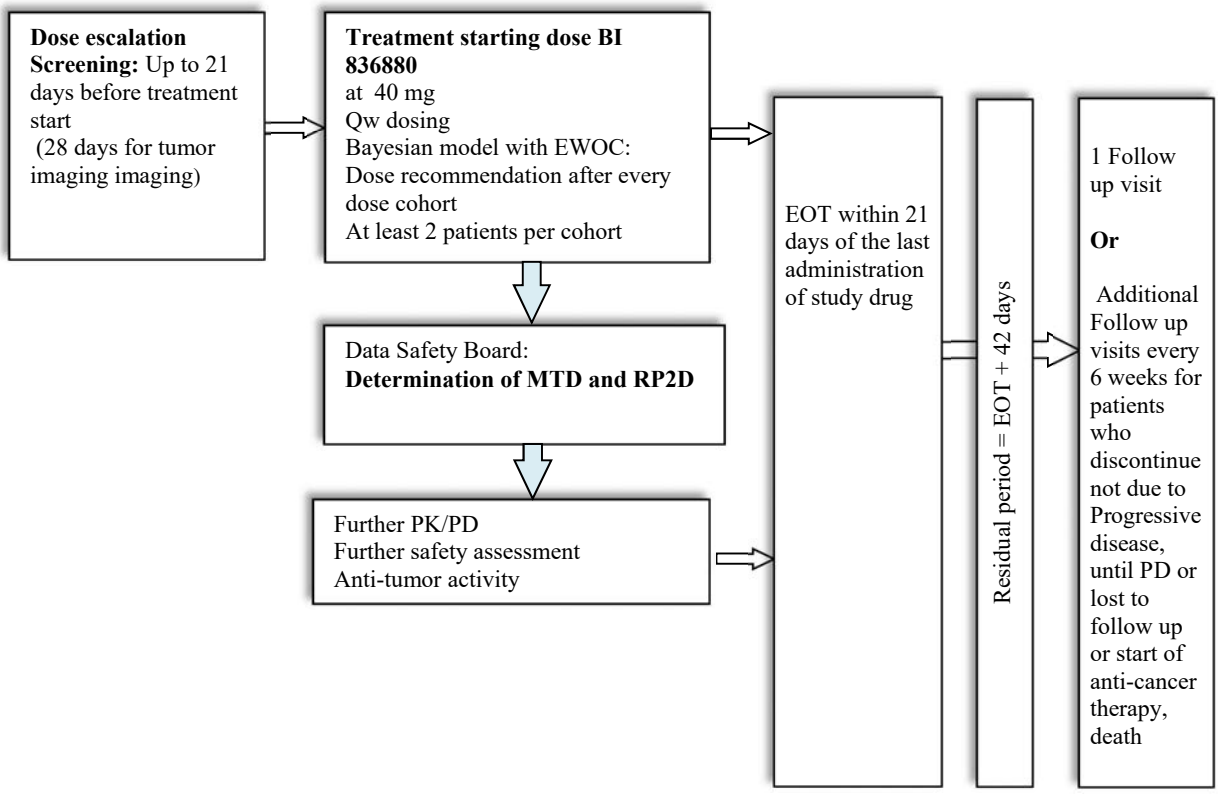

Figure 3.1: 1Study design

All patients eligible after the screening will be administrated with BI 836880 weekly infusion. In case the patient shows a stable disease or even a response, the study treatment will continue until one of the withdrawal criteria listed in Section 3.3.4 is met.

An estimated of about 25-30 patients will be necessary to establish MTD and confirm RP2D. Confirmation of the RP2D will be made based on all available safety, PK and Pharmacodynamics (PD) data at all treatment courses and all dose levels.

All patients will have regular evaluations for assessment of safety parameters as detailed in the Flow Chart.

An End of trial (EOT) evaluation is to be completed when a patient permanently discontinues the study drug, for any reason listed in Section 3.3.4.

A Follow-up evaluation will be completed 42 days after permanent discontinuation of the study drug. Refer to the Flow Chart for details. This visit will be defined as the last visit in the on-study period for the trial.

For adverse event collection, please refer to Section 5.3.6.

After the interim data base lock, the study is considered completed when the last patient in the study has discontinued the study treatment and completed the EoR visit (see Section 6.2.3.5).

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim and will be conducted in two (2) sites. Additional sites may be added to boost the recruitment and recruitment may vary between sites.
The study will be performed by investigators specialized in the treatment of advanced cancers and experienced in phase I trials in oncology.

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 the Recommended Phase II dose, as well as the decision for a tumor type expansion cohort. Members of the DSB will be investigators of participating trial sites, Trial Statistician (TSTAT), Clinical Program Leader (CPL), Clinical Trial Leader (CTL) and BI Lead Risk Management Physician. Clinical Pharmacology Program Leader (CPPL) and Translational Medicine Expert (TME) can be invited as needed, especially for discussion of PK/PD and biomarker.
Minimum data for dose escalation decision will be described in the DSB charter.

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

Exploratory biomarker analyses will be performed by BI and/or a dedicated CRO/ laboratory authorized by Boehringer Ingelheim.

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

Boehringer Ingelheim has appointed a Trial Clinical Leader (CTL), responsible for coordinating all required activities, in order to:

- manage the trial in accordance with applicable regulations and internal 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 Trial Manager (CTM), Clinical Research Associates (CRAs), and Investigators of participating countries.

Data management and statistical evaluation will be done by BI according to BI SOPs.
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 can be found in the ISF.

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 ISF.

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 antitumor activity 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. This expansion will take place after a protocol amendment.

3.3 SELECTION OF TRIAL POPULATION

It is estimated that approximately 40 patients will be enrolled at 2 study sites. The rate of enrolled patients may vary by study site, but it is expected to be approximately 20 patients per site. Among them approximately 25 patients will be treated in this trial.

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.

Patients will be selected based on the eligibility criteria described below.

3.3.1 Main diagnosis for trial entry

All patients that 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 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 patients 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 as defined by the following criteria:
   a. Total bilirubin within normal limits (≤ 1.5x ULN for patient with Gilberts syndrome)
   b.ALT and AST ≤ 1.5x ULN (< 5xULN for patient known liver metastases)
   c.Serum creatinine < 1.5x ULN
   d.INR 0.8-1.2 or PTT < 1.5x ULN
   e.ANC > 1.5 10^9/L
   f.Platelet count > 100x10^9/ L.
   g.Heamoglobin > 10 g/dl (without transfusion within previous week)
5. Signed and dated 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 grade1, except for alopecia (any grade), sensory peripheral neuropathy CTCAE grade ≤ 2 or considered by the investigator as clinically not 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 the study drug according to the 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 at the start of study treatment.

3. Serious concomitant disease (based on investigator judgement), 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 (as judged by the investigator) or bone fracture within 4 weeks of start of study 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 disease (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 tested and relaxed condition >= 140 mmHg, systolic or ≥ 90 mmHg diastolic (with or without medication), measured according to Section 5.3.2 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; low-molecular-weight heparin (LMWH) allowed only for prevention not for curative treatment.

11. Use of alcohol or drug incompatible with patient participation in the study in the investigator opinion

12. Patient unable or unwilling to comply with protocol

13. Women who are pregnant, nursing, or who plan to become pregnant while in the trial

14. Previous enrolment in this 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 for study treatment or study participation, without the need to justify the decision.
- Requiring concomitant drugs that interfere with the investigational product or other trial medication (see Section 4.2.2) or patient who requires 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 patient is no longer able to complete trial visit or trial-required procedures.
- 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 scheme)
- Progressive disease (except in cases with intra-patient dose escalation, (see Section 4.1.3) or start of any new anti-cancer therapy.

A patient can have 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 Clinical Trial Report (CTR). As soon as a patient is withdrawn from the study 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.

Patients who have not completed first course of BI 836880 treatment (3 weeks) for any other reason than BI 836880 related toxicities will be considered not evaluable for MTD evaluation and should be replaced.

Patient who prematurely discontinue study drug for above mentioned reasons or any other reason, should have additional follow up visits until progression, lost to follow up, treatment with another anti-cancer treatment, death and /or end of the trial whichever comes first.

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.

Should the patient become pregnant during the trial, the treatment with BI 836880 must be stopped immediately, and this patient is not allowed to receive further trial medication from that point onward. The patient will be followed up until delivery or termination of pregnancy (see Section 5.3.6.2). The data of the patient will be collected and reported in the CTR until last patient last visit and any events occurring thereafter will be reported in BI drug safety database.
For all patients the reason for withdrawal (e.g. adverse events) must be recorded in the (e)CRF. These data will be included in the trial database and reported.

3.3.5 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 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)

Table 4.1.1: 1 Test product 1

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

Table 4.1.1: 2 Diluent for Test product 1

Substance:	Diluent for BI 836880 drug product
Pharmaceutical formulation:	Diluent to prepare solution for infusion of BI 836880
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	50 ml/vial
Posology	rate controlled infusion
Route of administration:	i.v.
Duration of use	until progression disease or unacceptable toxicity

4.1.2 Method of assigning patients to treatment groups

There is no randomisation, eligible patients will receive treatment.
Allocation to dose cohorts or expansion cohort will be done according to subject temporal availability and depending on dose cohort open for recruitment.
During Visit 1/Day 1 and after the patient's eligibility has been confirmed, the treatment will be assigned via Interactive Response Technology (IRT).
For medication number allocation at each visit, it's possible to conduct IRT call ahead of the planned visit (= day of administration)
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 (refer to Investigator's Brochure for more details (c02353882)).

Based on the 13-week Good Laboratory Practice (GLP) toxicology trial in cynomolgus monkey, the Non-Observed-Adverse-Effect-Level (NOAEL) /Highest Non-Severely Toxic Dose (HNSTD) is defined as 60 mg/kg. According to this method and using a safety factor of 6, the maximum starting dose is 10 mg/kg.

As a second approach, a mathematical PK/PD model was developed to predict the human therapeutic dose of BI 836880. The model was calibrated to data from a cynomolgus monkey PK/PD study and then scaled to human to perform simulations. The model is a two compartment in vivo model that includes the target ligands (VEGF-A and Ang2), their corresponding receptors (VEGFR2 and Tie2) and additional ligand/receptor pairs that share common receptors. Predictions were made for the minimum dose that maintains a high level of reduction in both VEGF:VEGFR2 and Ang2:Tie2 complexes by BI 836880 at steady state. The VEGF-A:VEGFR2 complex and Ang2:Tie2 complex levels were considered surrogates of receptor signaling in *silico*.
The predicted human dose that according to this simulations achieves reduction in both VEGF:VEGFR2 and Ang2:Tie2 complexes at $C_{min,ss}$ is 0,67 mg/kg for a weekly dosing. At a dose level of 0.67 mg/ kg (dosed once every week) the fraction of VEGF-A:VEGFR2 complex is predicted to be reduced to 35% - 55% of the pre-dose level, and the fraction of Ang2:Tie2 complex is predicted to be reduced to below 0.1 (90%) of the pre dose level.

Since the two methods resulted in different starting doses, and the dose based on the PK/PD modeling is expected to allow achieving reduction in both VEGF:VEGFR2 and Ang2:Tie2 complexes, the lowest dose was selected as starting dose in this first in human trial.

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 the targeted C_{min} concentration in plasma that is supposed to maintain a continuous high suppression of VEGF-A:VEGFR2 and Ang2:Tie2 complex formation (>90%).
In a weekly dosing schedule, target C_{min} plasma concentrations are expected to be achieved after 7 infusions of BI 836880 at dose of 2 mg/kg (120 mg), after 2 infusions at dose of 6 mg/kg (360 mg) and after 1 infusion 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 40 mg. Dose escalation ≥120 mg 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)	Approximate increment to next dose
Dose level 1 (starting dose)	40	3x (200%)
Dose level 2	120	1.25x (25%)
Dose level 3	150	1.20x (20 %)
Dose level 4	180	1.3x (30%)
Dose level 5	240	2x (100%)
Dose level 6	480	1.5x (50%)
Dose level 7	720	1.3x (30%)
Dose level 8	960	1.7x (30%)
Dose level 9	1440 limited to 1250*	

*Maximum dose that can be tested due to excipient limitation

Intermediate dose levels can be tested based on DSB decision.

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 courses, deeming to have clinical benefit from treatment and tolerated BI 836880 well (i.e do not show any DLT) could be allowed to receive increased dose. Such decision will be taken in case by case manner on request by the investigator and confirmation by the DSB based on actual patient profile. Intra patient dose escalation can be repeated; however the dose can only be increased to the 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, sampling for ADA as well as sampling for biomarkers (Myriad panel and free/total VEGF-A/ Ang2) 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 according to "Instruction for Pharmacists" which will be filed in ISF**.** Upon notification of an entered patient in the study, the pharmacy will prepare the study drug in the assigned dosage for administration to the patient.

BI 836880 will be given as 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 min. in case no relevant infusion reactions are observed, this may be shortened to about 30 min but should not be prolonged to more than 6 hours even 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 $\geq$ 2 occur (that are not qualifying as DLT according to Section 5.3), the infusion should be temporarily stopped. Upon recovery, infusion should be resumed 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 administrating 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 adaptation of application scheme need to be agreed with sponsor.

BI 836880 will be administrated intravenously starting on course1 day1. In the event of delay or interruption of treatment due to adverse event, BI 836880 infusion should be skipped; and the next scheduled BI 836880 infusion should be administrated upon recovery to CTCAE Grade 1.

Premedication: No premedication will be required for BI 836880 IV infusion.

If a patient experienced sign of infusion reaction at any BI 836880 treatment, a premedication will be **considered** for all subsequent treatment infusions (dosage and schedule according to investigator's decision) comparable to the following scheme:

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

If infusion reaction and /or hypersensitivity reaction occurs in substantial amount of patients (about 30%) of treated patients without premedication, premedication, as described above, will be given to all treated patients. Such decision will be confirmed by the DSB; dosage and schedule should be aligned, and reflect institutional clinical standards.

4.1.4.1 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:

QTcF $\leq$ 470 ms (according to exclusion criterion #5)

No uncontrolled hypertension (according to exclusion criterion #6)

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.

4.1.4.2 Dose reduction scheme

Administration of trial drug has to be stopped temporarily in case of a DLT (see Section 5.3). 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. In this open-label trial, treatment allocation will not be concealed throughout the trial. The CRF will contain information on allocated treatment.

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

Diluent for BI 836880 drug product will be supplied in 50R vial containing 50 ml Diluent for BI 836880 drug product. The Diluent vials will be packed in one vial per box.
Boxes and vials will be labelled according to local regulations.

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

BI 836880 drug re-supply will be managed through IRT by the trial sites and BI personnel.

4.1.7 Storage conditions

BI 836880 vials and Diluent vials, which will be provided by the sponsor and/or a CRO appointed by the sponsor must be kept in their original packaging and in secure limited access storage area according to the recommended storage conditions on the medication label. The Investigator, the Pharmacist, or other personnel allowed to store and dispense.

The Investigator or pharmacist or investigational drug storage manager 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 for documentation.

For details concerning the preparation of the infusion solution of BI 836880, please refer to the ‘instructions for pharmacists’ filed in the ISF.

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 will receive the investigational drugs delivered by the Sponsor after IRB / ethics committee approval of the trial and completion of a clinical trial contract between the Sponsor and the Head of Trial Center.

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)

Rescue medication to reverse the action of BI 836880 is not available.
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 BI 836880 and the patient must have recovered from all clinical relevant reversible toxicities (see exclusion criteria in Section 3.3.3).

Concomitant anti-cancer therapy is not allowed.

Radiotherapy for local symptom control of non-target lesions can be allowed after discussion between the investigator and the sponsor. The irradiated area cannot be used for response assessment.

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. Unplanned surgeries should be postponed whenever possible four weeks after stop of treatment. For urgent interventions patients should not be treated further and does require intense monitoring regarding wound healing and postoperative complications.

4.2.2.2 Restrictions on diet and life style

No restriction

4.3 TREATMENT COMPLIANCE

BI 836880 must be administered as an intravenous infusion under supervision of the investigator or dedicated clinical personnel.
Compliance may be 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 determine the maximum tolerated dose (MTD) based on the number of patients presenting dose limiting toxicity (DLT) using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) V4.03, during the first course (i.e. over the first 3 weeks of treatment) and judged to be related to the study medication.

5.1.2 Secondary Endpoint(s)

- Drug related AEs leading to dose reduction or discontinuation during treatment period

5.2 ASSESSMENT OF EFFICACY

The assessment by the investigator and the local radiologist will be the basis for continuation or discontinuation of the trial in an individual patient (in addition to safety). Tumor assessment will be performed every 6 weeks after start of treatment and at the time points specified in the Flow Chart.
After the interim data base lock, frequency of tumor assessment may be adapted according to local standard of care and in agreement with the sponsor if the patient is deriving clinical benefit (e.g. CR, PR or SD > 6 months).
CT images at baseline should be performed as close as possible to the treatment start and not older than 28 days at start of treatment.
At baseline, the investigator along with the radiologist will record the target (five target lesions maximum and maximum two per organ) and non-target lesions at baseline in the eCRF before the start of treatment. The same method of assessment and the same technique should be used to characterize each reported lesion at baseline and during follow up. Lesions in previously irradiated areas may not be considered measurable at baseline unless the lesions occurred after irradiation. Response will be evaluated according to the response evaluation criteria in solid tumors (RECIST version 1.1 (R09-0262). In the event of a delay, interruption or discontinuation of treatment, tumor assessment should continue to follow the original schedule. The schedule should be followed until progression is observed or until the patient commences further treatment for disease, whichever occurs first.

Results of tumor-specific tumor markers which will be assessed routinely should be documented in the eCRF.

After the interim data base lock, documentation of tumor markers in the e-CRF is no longer required.

5.3 ASSESSMENT OF SAFETY

Dose Limiting Toxicity (DLT)

The following drug-related adverse events will qualify as Dose-Limiting Toxicities:

- CTCAE grade ≥ 3 non haematological toxicity except:
  - Vomiting or diarrhea responding to supporting treatment
  - Fatigue lasting for less than 4 days
  - Transcient Grade 3 infusion reaction (i.e. if infusion- related reaction 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 resolved with appropriate treatment. Clinically relevant abnormalities have to be documented as AE (see Section 5.3.6)
- CTCAE grade 4 neutropenia >7 days or complicated by infection (in case of neutropenia grade 4, close observation of patient is necessary.
- CTCAE grade ≥3 febrile neutropenia
- CTCAE grade = 4 thrombocytopenia
- CTCAE grade ≥ 3 thrombocytopenia with bleeding
- CTCAE grade ≥ 3 proteinuria (urinary protein ≥ 3.5 g/day)
- Hypertension: increase of diastolic blood pressure (BP) by 15 mmHg confirmed by second measurement or ambulatory blood pressure measurement (when indicated; e.g. white coat effect) which cannot be controlled by hypertensive medication and requires a dose reduction of BI 836880 for further treatment course.
- All related AE leading to an interruption of BI 836880 for more than 14 days until recovery to baseline.

The MTD may be considered reached if the probability that the true DLT rate is in target interval (16%-33%) is sufficiently large (for details see Section 7). The DSB may recommend stopping the dose finding phase after the criterion for MTD is fulfilled.

If the 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 and declare this dose as RP2D and no further dose escalation will happen.

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

5.3.1 Physical examination

A complete physical examination including (height at screening only), cardiac, neurological, dermatological pulmological, weight and ECOG performance score, will be performed at screening and before the start of the treatment, EoT and EoR. At further time points specified in the Flow Chart, not a complete physical examination will be performed, but at minimum the actual health status of the patient should be assessed (including, evaluation of blood pressure, ECG, lab safety parameters, AEs, concomitant therapies, ECOG as applicable). During the physical examination, the patient should be assessed for possible AEs.
After the interim data base lock, physical examination, ECOG performance status, weight are no longer mandatory at the specific visits but will be performed at the investigator's discretion. Findings will be documented in the eCRF only if qualifying as (S)AE.

5.3.2 Vital Signs

Vital signs (blood pressure, heart rate and body temperature) will be recorded at every visit indicated in the flow chart.

At day of administration two time points will be evaluated:
1- At pre-dose (-60 minutes to – 5 minutes)
2- Shortly before the end of infusion

In case of an infusion-related reaction, if deemed necessary, the investigator should decide for intensive monitoring of vital signs.

Blood pressure

Systolic and diastolic blood pressure as well as pulse rate (electronic or by palpation, count for 1 minute) will be measured after 5 minutes of rest in seated position. The blood pressure measurement should be performed three times at each time point and values of these measurement will be entered in the CRF (refer to Appendix 10.2 and Appendix 10.4)
After the interim data base lock blood pressure is no longer mandatory at specific visits but will be performed at the investigator's discretion. Findings will be documented in the eCRF only if qualifying as (S)AE

Body temperature

Whenever possible the same method should be used for body temperature measurement in one patient. All methods used should deliver valid reproducible results according to common clinical practice.
Body temperature $\geq$ 38°C must be re assessed 1 hour after, especially in cases of suspected febrile neutropenia (see CTCAE V.4.03).
After the interim data base lock body temperature is no longer mandatory at specific visits but will be performed at the investigator's discretion. Findings will be documented in the eCRF only if qualifying as (S)AE

5.3.3 Safety laboratory parameters

Blood sample for assessment of 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 versus grade 3 needs to be done by quantitative measurement.
Safety laboratory examination will include haematology, biochemistry, coagulation, and urine analysis.

- **Haematology**: Haemoglobin, red blood cell count (RBC), white blood cell count (WBC) and differential, platelets.

- **Biochemistry**: glucose, sodium, potassium, calcium, magnesium, inorganic phosphate, creatinine, aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphatase, lactate deshydrogenase (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)

- **Urinalysis**: pH, glucose, leukocytes, erythrocytes, protein, nitrite will be analysed primarily qualitatively by dipstick. In case of pathological findings, further evaluation should be performed and the findings documented. A positive urine dipstick for protein of ≥ 2+ has to be followed by a determination of urine protein to creatinine ratio (UPCR) in a morning spot urine sample. In case of a ratio ≥ 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 is ≥ 0.5 as often as clinically indicated.

After the interim data base lock, safety laboratory tests (haematology, biochemistry, coagulation, urinalysis) will be performed at the investigator's discretion based on the standard medical care. Findings will be recorded in the e-CRF only if qualifying for (S)AE/AESI.
Pregnancy test: a serum pregnancy test will be performed as outlined in the Flow Chart in women of childbearing potential.

Previous laboratory investigations performed within 72 hours prior to the first treatment administration visit are acceptable to confirm the patient eligibility.

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.

5.3.4 Electrocardiogram (ECG)

12-lead ECGs will be digitally recorded in triplicate and performed for each patient at various time point according to the Flow Chart and Appendix 10.4.

- At screening, visits between administrations of study treatment, and at EoT. Only one time point will be evaluated
- At days of administration, two time points will be evaluated:
  - Pre-dose (-60 min. to -5 min.) and
  - 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 courses of treatment. The ECGs will be recorded using dedicated equipment provided by the vendor.

The ECGs will be sent 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.
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 patient's 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.

After the interim data base lock, ECG will be performed as clinically indicated on local machine and the assessment will be done by the investigator. Shipment of ECGs to central vendor is no longer required.

Echocardiography

Echocardiography will be performed locally at screening (not older than 7 days before start of treatment) and at EoT. During treatment period, echocardiography will be conducted only if clinically indicated.
After the interim data base lock findings related to echocardiography will be reported in the e CRF only if qualifying as (S)AE

5.3.5 Other safety parameters

Not applicable

5.3.6 Assessment of adverse events

5.3.6.1 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.

Adverse reaction
An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

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

- results in death,
- is life-threatening, this 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.
- requires inpatient hospitalisation or
- prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- 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.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

AEs considered "Always Serious"
Every new occurrence of cancer of new histology must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.
In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further 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 eDC system. These events should always be reported as SAEs as described above.

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. AESIs need to be reported to the Sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, please see above.

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 eDC-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.

DLT events
All DLT events (as defined in Section 5.3) in individual patients occurring at any time during the repeated treatment courses or follow-up period must be reported as adverse events of Special Interest (AESI).

Severity of AEs
The severity of adverse events should be classified and recorded in the (e)CRF according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (R12-2532).

Causal relationship of AEs
The definition of an adverse reaction implies at least a reasonable possibility of a causal

relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

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.
Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced
- No medically sound alternative aetiologies that could explain the event (e.g. pre- existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged

5.3.6.2 Adverse event collection and reporting

AE Collection

The Investigator shall maintain and keep detailed records of all AEs in their files.
The following must be collected and documented on the appropriate CRF(s) by the Investigator:

- From signing the informed consent onwards until the end of treatment (including the Residual Effect Period, REP): all AEs (non-serious and serious) and all AESIs.

- After the end of treatment (including the REP) until the individual patient's end of trial: all related SAEs and all related AESIs.
- After the individual patient's end of the trial: the Investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs and relevant AESIs of which the Investigator may become aware of.

The rules for Adverse Event Reporting exemptions still apply.

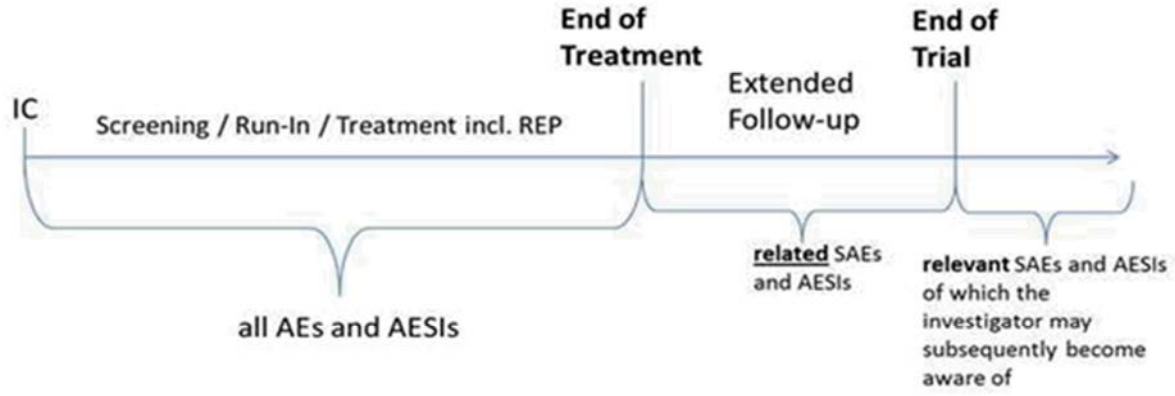

Figure 5.3.6.2: 1AE collection

The REP is defined as 42 days 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.

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). The same timeline applies if follow-up information becomes available**.** 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 CRF pages and the BI SAE form. The Investigator should determine the causal relationship to the trial medication.

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

- Worsening of the underlying disease or of other pre-existing conditions. The rules for Adverse Event Reporting exemptions still apply
- 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 individual patient's end of trial must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

Pregnancy
In rare cases pregnancy may occur in a clinical trial. Once a patient has been enrolled into this clinical trial and has taken trial medication, the Investigator must report immediately (within 24 hours) a potential 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).
The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B).

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

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.

All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.4.1 Assessment of Pharmacokinetics

5.4.2 Methods of sample collection

5.4.3 Analytical determinations

5.4.4 Pharmacokinetic - Pharmacodynamic Relationship

5.5 ASSESSMENT OF EXPLORATORY BIOMARKER(S)

5.5.1 Imaging Pharmacodynamic endpoints

5.6 OTHER ASSESSMENTS

5.6.1 Demographic and medical history

Demographics (sex, birth date, race if allowed by the local law), current medical condition including relevant concomitant diagnosis will be collected during the screening visit. Concomitant therapies present at the study entry and /or during the study will be recorded in the eCRF.

Medical history as follows:

- Type of tumor
- Date of the first histological diagnosis (month and year may be sufficient)
- Primary tumor site
- Differentiation grade (not specified, undifferentiated, poorly differentiated, moderately differentiated
- Tumor stage according to the tumor
- Number of metastatic sites at study entry will be provided
- Previous surgeries an radiotherapy will be reported
- Previous administrated chemotherapy, tyrosine kinase inhibitors, vaccine-therapy, antibodies therapy, immune-therapy, and hormone-therapy including start and end dates (month and year may be sufficient)
- Previous neoadjuvant, adjuvant or palliative therapy
- The date of tumor progression after previous line (s) of therapy for advanced or metastatic disease
- The start and end dates (month and year may be sufficient) of those previous therapies as well the number of courses (when applicable)
- The best response obtained (complete response, partial response, stable disease, progressive disease, unknown
- The reason for leading to treatment discontinuation (completion, PD, AE)

5.6.2 Immunogenicity assessment

5.7 APPROPRIATENESS OF MEASUREMENTS

Determination of the MTD is based on the toxicities grade according to CTCAE version 4.03 (R12-2532). The CTCAE criteria are commonly used in the assessment of adverse events in cancer patients. RECIST version 1.1 criteria (R09-0262) are used for evaluation of tumor response. These criteria are well established and scientifically accepted.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

The study Flow Chart describes all assessments which will be performed in patients treated with BI 836880.
All patients must provide written informed consent before any study related screening procedures can be performed. Time windows for visits are included in the Flow Chart.

Patient will visit the clinic at the time points specified in the Flow Chart. If a visit is missed and the patient report to the Investigator between the missed visit and the next visit, the missed visit should be performed. The current date and the reason for delayed visit should be recorded in the source document. The next visit, however, should take place at the scheduled time after the first administration BI 836880.

To allow close monitoring for infusion-related reactions or other adverse events , patients are required to be hospitalised under close surveillance with access to intensive care for at least 48 hours after the first administration of BI 836880 at course 1 day 1and 24 hours after the second and third administrations of BI 836880 at course 1 day 8 and course 1 day 15 respectively.
After good tolerability of the first course 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 and at investigator's discretion for further courses.

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.

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

After the interim data base lock, mandatory procedures/assessments and documentation in the eCRF will be adapted as described in the Flow Chart and the respective sections of this protocol.

6.2.1 Screening period

All Screening Visit procedures must be performed in the 21 days prior to the first administration of study medication except tumor assessments (CT/MRI) that may be used as screening exams if they were performed within 28 days prior to start of treatment.

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

Patients who meet the eligibility criteria will be allowed to take part to the study.
Refer to the Flow Chart for procedure details. Please review Sections 3.3.2 and 3.3.3 for specific eligibility criteria.

6.2.2 Treatment period(s)

All patients will receive continuous weekly treatment with BI 836880 until the criteria for stopping medication are met (see Section 3.3.4).
Treatment course is defined as 3-week treatment (21 days) in duration. During the treatment phase visits should be performed as scheduled wherever possible.

In the event of any study drug interruption or delay of treatment, the tumor assessment scheduled will not be changed.
After the interim data base lock, frequency of tumor assessment may be adapted according to local standard of care and in agreement with the sponsor if the patient is deriving clinical benefit (e.g. CR, PR or SD > 6 months).

Additional visits are needed at day 2 for courses 1, 2 and 4. For course 3 and from course 5 onwards no additional visits, beside day 1 including drug administration, are requested by protocol.

Refer to the Flow Chart for procedure details.

6.2.3 Follow Up Period and Trial Completion

6.2.3.1 End of treatment visit

The EOT visit will be performed after permanent discontinuation of trial medication for any Reason, as soon as possible, but no later than 21 days 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 5.3.6.2. The End of the Residual period visit (EoR) should not be performed earlier than 42 days after permanent discontinuation of the study drug. 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 Follow-up period for progression

For patients who progress according to RECIST criteria V1.1, one Follow up visit (FU1) will be performed after the EOT (i.e. at EoR, 42 calendar days after discontinuation of trial drug).

For patient who discontinue not due to progressive disease according to RECIST criteria V1.1, additional FU visits will be performed at 6-week intervals plus/minus 3 days, until progression, start of another anticancer treatment, lost to follow up, death.
After the interim data base lock, frequency of tumor assessment may be adapted according to local standard of care and in agreement with the sponsor if the patient is deriving clinical benefit (e.g. CR, PR or SD > 6 months).
During extended Follow up period (i.e. after the end of treatment, including the REP and individual patient's end of trial), all related SAEs or AESIs and Follow up AEs on going since the end of treatment have to be collected and documented on the appropriate eCRF page and SAE form (if applicable).

Refer to Flow Chart for details.

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 (as defined in Section 6.2.3.3)
- Lost to follow-up
- Withdrawal to be followed-up
- Death

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

6.2.3.5 Trial completion

The clinical trial will be considered completed when the last patient has completed the EoR visit. If patients are still on treatment at the time of interim data base lock and the Clinical Trial Report is written, these patients will be maintained in the trial as long as they are deriving clinical benefit (i.e. no disease progression, no drug-related AEs requiring drug discontinuation) or no new anti-cancer treatment started and there are willing to continue. For these patients, no blood sample will be collected for PK/PD and biomarker analysis, only (S)AEs and limited efficacy data will be collected. After the discontinuation of these patients, additional data collected after data base lock will be reported in separate listings and will not

lead to any further update of tables generated 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 tumors. MTD is defined as the highest dose with less than 25% risk of the true DLT probability being above 33%,and 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 Bayesian 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 course at dose d, $d^* = 1250$mg 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 480mg would equal 20%. This yields $\mu_1 = (0.740, 0.798)$. 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 480mg would equal 50%. These assumptions yield $\mu_2 = (0.846, -0.123)$. 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 480mg would equal 2%. These assumptions yield $\mu_3 = (-2.731, 0.193)$, 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 to1 patient, 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	0.740, 0.798	2.000, 1.000	0.000
2: High Tox	0.050	0.846, -0.123	2.000, 1.000	0.000
3: Low Tox	0.050	-2.731, 0.193	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	0.842	0.054	0.104	0.091	0.206	<.001	0.001	0.819
120	0.759	0.076	0.165	0.139	0.249	<.001	0.009	0.897
240	0.673	0.096	0.231	0.193	0.282	<.001	0.036	0.935
480	0.523	0.131	0.346	0.284	0.318	<.001	0.138	0.964
960	0.262	0.143	0.595	0.471	0.332	0.002	0.458	0.984
1250	0.142	0.114	0.744	0.594	0.316	0.012	0.659	0.991

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

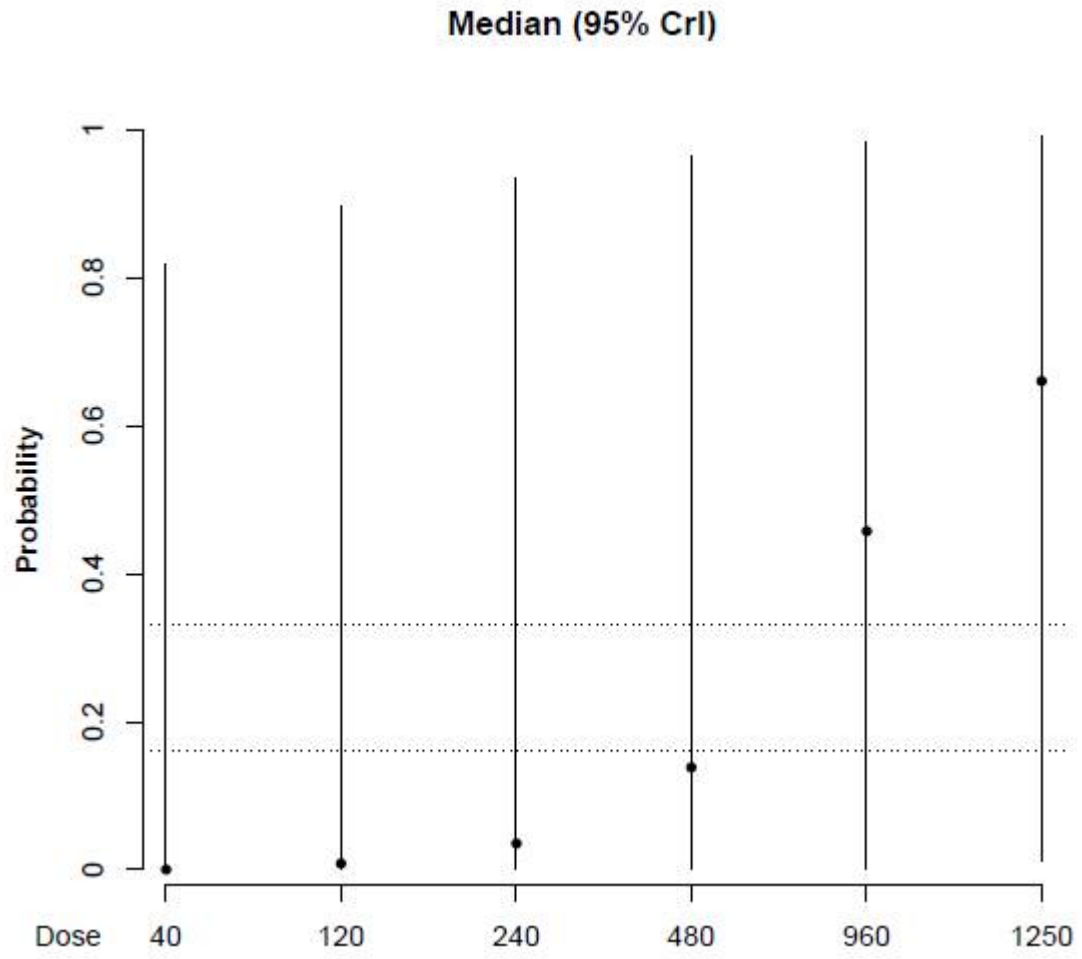

Figure 7.1: 1Prior medians and 95% credible intervals

The MTD may be considered reached if the following criteria are 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 course 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 endpoint.

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 course 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 courses 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. Events that started after 42 days since last administration of treatment will be considered as having occurred post-treatment and will be presented separately.

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 severity 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.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered ‘treatment-emergent’. The residual effect period is defined as 42 days after the last trial medication application. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’.

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).

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.

7.4 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.

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 7.3.4).

7.7 DETERMINATION OF SAMPLE SIZE

About 25-30 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).

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in accordance with the Medical Devices Directive (93/42/EEC) and the harmonized standards for Medical Devices (ISO 14155-01 and ISO 14155-02).

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), and relevant regulations.

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 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.

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

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

Electronic Case Report Forms (e)CRF for individual patients will be provided by the Sponsor. 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 reported on the eCRF must be consistent with the source data or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the trial; current medical records must also 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. 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 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal regulatory reporting obligation and in accordance to the requirements defined in this CTP.

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 last follow up visit as specified in Section 6.2.3.4
After the interim data base lock 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 will be notified about the end of the trial or early termination of the trial.

8.7 PROTOCOL VIOLATIONS

The investigator should document any deviation from the protocol regardless of their reasons. Only when the protocol was not followed in order to avoid an immediate hazard to trial subjects or for other medically compelling reason, the principal investigator should prepare and submit the records explaining the reasons thereof to the sponsor, and retain a copy of the records.

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R15-1720 Jain RK, Duda DG, Willett CG, Sahani DV, Zhu AX, Loeffler JS, Batchelor TT, Sorensen AG. Biomarkers of response and resistance to antiangiogenic therapy. Nat Rev Clin Oncol 2009. 6(6):327-338.

9.2 UNPUBLISHED REFERENCES

c02353882 Investigator’s Brochure: BI 836880 in solid tumors.Version 1. 11 June 2015.

001-MCS-36-472 Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics.

10. APPENDICES

10.1 INSTRUCTIONS FOR USE

10.1.1 Instruction for Pharmacists

Refer to the 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 a 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 described 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 time points 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.

10.6 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 the 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 120 mg. 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.

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 480mg, either. However, the model does not allow the escalation to 960mg 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 480mg. 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. In scenario 8, no DLs are seen in the first three cohorts. Dose was escalated to 960mg after 6 patients were tested on 480mg without DLT. De-escalation occurred as a result of one out of the three patients treated on dose 960mg had DLT.

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	0.019	120	0.862	0.076	0.062
2	1	40	1	3	0.318	N/A	N/A	N/A	N/A
3	1 2	40 120	0 0	2 2	0.018	240	0.841	0.093	0.066
4	1 2	40 120	0 1	2 3	0.231	120	0.451	0.318	0.231
5	1 2	40 120	0 2	2 3	0.623	40	0.455	0.308	0.237
6	1 2 3 4	40 120 240 480	0 0 0 0	2 2 3 3	0.02	480	0.903	0.077	0.020
7	1	40	0	2					
	2	120	0	2					
	3	240	0	3					
	4	480	1	3	0.229	480	0.424	0.347	0.229
8	1	40	0	2					
	2	120	0	2					
	3	240	0	3					
	4	480	0	6					
	5	960	1	3	0.353	480	0.943	0.054	0.003

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	240	480	960	1250
1 (Prior)	P(DLT)	0.091	0.139	**0.193**	**0.284**	0.471	0.594
2 (High Tox)		0.100	**0.227**	0.351	0.500	0.649	0.700
3 (Low Tox)		0.001	0.007	0.022	**0.180**	**0.250**	0.350
4 (Non-Logistic)		0.040	0.100	**0.180**	**0.280**	0.360	0.380
5 (Low-High)		0.001	0.011	0.047	**0.181**	0.500	0.640

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	23.1	56.4	0.1	20.4	16.45 (3 – 34)	2.982 (1 – 10)
2	18.1	38.3	19.6	24.0	16.01 (3 – 36)	3.73 (1 – 11)
3	20.2	79.6	0.2	0	20.42 (17 – 38)	2.248 (1 – 6)
4	19.4	71.4	0.6	8.6	18.42 (3 – 35)	3.09 (1 – 10)
5	25.6	74.0	0.3	0	20.11 (16 – 40)	2.43 (1- 6)

In scenario 1, which reflects the case that the true dose-toxicity is aligned with prior medians, 56.4% of the simulated trials declared a dose as MTD with true DLT rate in the targeted dose range. Note that 20.4% 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 (24.0%) 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 16.0 patients (high-toxicity scenario) to 20.4 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		I
Date of CTP revision		24 Mar 2017
EudraCT number		2015-001132-38
BI Trial number		1336.6
BI Investigational Product(s)		BI 836880
Title of protocol		Phase I, non-randomized, open-label, multi-center dose escalation trial of BI 836880 administered by weekly repeated intravenous infusions in patients with advanced solid tumors.
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as		☐

changes involve logistical or administrative aspects only		
Section to be changed		Synopsis: total entered
Description of change		Approximately 40 patients **Was changed to:** Approximately 40 patients, 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 pharmacodynamic effect can be documented
Section to be changed		Synopsis
Description of change		• 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. patients do not tolerate or have contraindications to otherwise available **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. patients do not tolerate or have contraindications to otherwise available standard therapy and tumour lesions evaluable for Dynamic-enhanced (DCE)-MRI at MTD
Rationale for change		Change was implemented to make sure that a pharmacodynamic effect can be documented
Section to be changed		Flow chart: footnote #3; section 5.3.2
Description of change		Footnote #3 [3]Body Temperature: whenever possible the same method should be used for body temperature measurement in one patient. Acceptable methods could be: oral, rectal measurement with thermometer (digital, mercury, or other fluid). Not acceptable: infrared measurement in ear, forehead or temple. Body temperature > 38°C must be re assessed 1 hour after. Section 5.3.2 body temperature Whenever possible the same method should be used for body temperature measurement in one patient. All methods used should deliver valid reproducible results according to common clinical practice. Acceptable

		methods could be, but not limited to: oral, rectal measurement with thermometer (digital, mercury, or other fluid). Not acceptable/preferred methods include: infrared measurement in ear, forehead or temple. **Was changed to** Footnote #3 [3]Body Temperature: whenever possible the same method should be used for body temperature measurement in one patient. Body temperature ≥ 38°C must be re assessed 1 hour after. Section 5.3.2 body temperature Whenever possible the same method should be used for body temperature measurement in one patient. All methods used should deliver valid reproducible results according to common clinical practice.
Rationale for change		- To allow some flexibility to the sites to measure body temperature according to common clinical practice. -To be consistent with the wording (≥ 38°C) elsewhere in the protocol
Section to be changed		Footnote #5 and section #5.3.3
Description of change		Footnote #5 [5]Haematology, biochemistry and coagulation parameters will be performed locally. Previous safety lab: investigations are acceptable if performed within 72 hours prior to the screening visit. For details see Section 5.3.3 Section #5.3.3 Previous laboratory investigations performed within 72 hours prior to the screening visit are acceptable to confirm the eligibility at for the screening. **Was changed to** Footnote #5 [5]Haematology, biochemistry and coagulation parameters will be performed locally. Previous safety lab: investigations are acceptable if performed within 72 hours prior to the **first treatment administration**. For details see Section 5.3.3 Section #5.3.3 Previous laboratory investigations performed within 72 hours prior to the first treatment administration visit are acceptable to confirm the patient eligibility.
Rationale for change		To confirm patient eligibility before start of study treatment
Section to be changed		3.1
Description of change		Was added: Once a MTD has been reached, a minimum of 12 patients must have tumour lesions evaluable for Dynamic contrast-enhanced (DCE)-MRI to allow a better interpretation of pharmacodynamics (vascular) effect of BI 836880

Rationale for change		Change was implemented to make sure that a pharmacodynamic effect can be documented
Section to be changed		3.1.1
Description of change		Members of the DSB will be investigators of participating trial sites, Trial Statistician (TSTAT), Clinical Program Leader (CPL) and Trial Clinical Monitor (TCM). **Was changed to:** Members of the DSB will be investigators of participating trial sites, Trial Statistician (TSTAT), Clinical Program Leader (CPL), Trial Clinical Monitor (TCM) and BI Lead Risk Management Physician
Rationale for change		Addition of one Data Safety Board member that was omitted in the previous version of the protocol
Section to be changed		3.3.2
Description of change		Histologically 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 patients do not tolerate or have contraindications to otherwise available standard therapy Was changed to: Histologically 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 patients 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 pharmacodynamic effect can be documented
Section to be changed		3.3.2
Description of change		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).

<table>
<tr><td></td><td></td><td></td></tr>
<tr><td>Rationale for change</td><td></td><td>Tubal ligation is no longer considered a highly effective method of contraception and no longer a method of permanent sterilisation</td></tr>
<tr><td>Section to be changed</td><td></td><td>Section 4.1.2</td></tr>
<tr><td>Description of change</td><td></td><td>Was added:
“..For medication number allocation at each visit it’s possible to conduct IRT call ahead of the planned visit (= day of administration)..”</td></tr>
<tr><td>Rationale for change</td><td></td><td>Clarification for logistical reasons</td></tr>
<tr><td>Section to be changed</td><td></td><td>Table 4.1.3:1</td></tr>
<tr><td>Description of change</td><td></td><td>
<table>
<tr><td>Dose level</td><td>Total dose (mg)</td><td>Approximate increment to next dose</td></tr>
<tr><td>Dose level 1
(starting dose)</td><td>40</td><td>3x (200%)</td></tr>
<tr><td>Dose level 2</td><td>120</td><td>2x (100%)</td></tr>
<tr><td>Dose level 3</td><td>240</td><td>2x (100%)</td></tr>
<tr><td>Dose level 4</td><td>480</td><td>1.5x (50%)</td></tr>
<tr><td>Dose level 5</td><td>720</td><td>1.3x (30%)</td></tr>
<tr><td>Dose level 6</td><td>960</td><td>1.7x (30%)</td></tr>
<tr><td>Dose level 7</td><td>1440 limited to 1250*</td><td></td></tr>
</table>
Intermediate dose level of “720 mg” was added and potential dose levels were adapted</td></tr>
<tr><td>Rationale for change</td><td></td><td>Intermediate dose level of “720 mg” was added in the table as requested by the Spanish authority during the approval process</td></tr>
<tr><td>Section to be changed</td><td></td><td>4.1.3</td></tr>
<tr><td>Description of change</td><td></td><td>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, sampling for ADA as well as sampling for biomarkers (Myriad panel and free/total VEGF-A/ Ang2) will be conducted (see flow chart and Appendix 10.4) and patients have</td></tr>
</table>

		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 course 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 course with the escalated dose
Section to be changed		5.2
Description of change		Was added: Results of tumor-specific tumor markers which will be assessed routinely should be documented in the eCRF
Rationale for change		To better assess tumour response in tumors for which tumour marker testing is performed routinely
Section to be changed		5.5
Description of change		Additional assays may be added if new data suggests relevance to the study drug mechanism of action. Furthermore, the collected samples may be used for testing of other disease related biomarkers that may be of scientific interest for understanding mechanisms of the disease (i.e. cancer) after initiation/completion of this trial Was changed to Additional assays may be added if new data suggests relevance to the study drug mechanism of action.
Rationale for change		For clarification, deletion of the sentence suggesting unspecified investigations to be done, also to comply with Spanish authority request during approval process
Section to be changed		5.6.2
Description of change		Was removed: After completion of the study the plasma samples may be used for further ADA characterization or methodological investigations, e.g., for stability testing or isotyping. Any additional characterization data will be reported separately
Rationale for change		For clarification, deletion of the sentence suggesting unspecified investigations to be done, also to comply with Spanish authority request during approval process
Section to be		6.1

changed

Description of change

To allow close monitoring for infusion-related reactions or other adverse events and availability of patients for PK visits, after administration of BI 836880, patients are required to be hospitalised under close surveillance with access to intensive care for at least 48 hours and 24 hours after the first and the second administration of BI 836880, respectively.

Was changed to

To allow close monitoring for infusion-related reactions or other adverse events and availability of patients for PK visits at course 1, patients are required to be hospitalised under close surveillance with access to intensive care for at least 48 hours after the first administration of BI 836880 at course 1 day 1 and 24 hours after the second and third administrations of BI 836880 at course 1 day 8 and course 1 day 15 respectively.

Rationale for change

To clarify patient monitoring during first course

Section to be changed

Table 10.4

Description of change

Blood sampling scheme for PK, ADA and biomarkers

Course	Visit	Day	Time Point (hh:min)	CRF Time / planned time	PK: BI 836880***	ADA***	Bio-marker: Myriad panel	Bio-marker: free/total VEGF-A/ Ang2	ECG	BP
1	V1	3		48:00	x		x	x		x (3x)
	V3	15	Before end of infusion	337:30**					x (3)	x (3x)
			Immediately after the end of infusion*	337:30**	x					

Correction of typo errors at time points C1V1; C1V3

Course	Visit	Day	Time Point (hh:min)	CRF Time / planned time	PK: BI 836880***	ADA***	Bio-marker: Myriad panel	Bio-marker: free/total VEGF-A/ Ang2	ECG	BP
2	V2	8	Before start of BI 836880 infusion	167:55	x			x	x (3x)	x (3x)
			Immediately after end of infusion*	169:30**	x					
	V3	15	Before start of BI 836880 infusion	335:55	x			x	x (3x)	x (3x)

				Start of BI 836880 infusion	336:00						
				Before end of infusion	337:30**					x (3x)	x (3x)
				Immediately after end of infusion*	337:30**	x					

Correction of typo errors at C2V2; and PK time point was added at C2V3 (337:30)

Course	Visit	Day	Time Point (hh:min)	CRF Time / planned time	PK: BI 836880***	ADA***	Bio-marker: Myriad panel	Bio-marker: free/total VEGF-A/ Ang2	ECG	BP
4	V1	2		24:00	x			x	x (3x)	x(3x)
	V3	15	Immediately after end of infusion*	337:30**	x					

One PK time point was added at C4V3, ECG and BP time points were added at C4V1D2

Rationale for change		Corrections of typo errors and PK, ECG and BP time points were added as they were omitted in error in the previous version of the protocol
Section to be changed		Table 10.4 appendices
Description of change		The following footnote was added: In case of an intra-patient dose escalation the 1st course with the higher dose will follow course one at the start of treatment with BI 836880 with regards to sampling PK, ADA as well as Biomarkers (Myriad panel and free/total VEGF-A/ Ang2)
Rationale for change		To provide guidance for patients with an intra-patient dose escalation with regards to assessments to be done within first course with escalated dose

Number of global amendment		2
Date of CTP revision		28 Sep 2017
EudraCT number		2015-001132-38
BI Trial number		1336.6
BI Investigational Product(s)		BI 836880
Title of protocol		Phase I, non-randomized, open-label, multi-center dose escalation trial of BI 836880 administered by weekly repeated intravenous infusions in patients with advanced solid tumors.
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		5.5.1 Imaging Pharmacodynamic endpoints
Description of change		**Methods of sample collection** …..DCE-MRI will be performed on a coronal slice through one or more representative lesions selected and identified by the responsible radiologist from the morphological scans. For DCE-MRI, a T1-weighted inversion recovery-gradient echo sequence is used, for which the patient will receive an intravenous bolus application of the gadolinium contrast agent **Multihance®.** Detailed parameter settings are given in the MR-Protocol. **Was changed to :**

		Methods of sample collection ….DCE-MRI will be performed on a coronal slice through one or more representative lesions selected and identified by the responsible radiologist from the morphological scans. For DCE-MRI, a T1-weighted inversion recovery-gradient echo sequence is used, for which the patient will receive an intravenous bolus application of the gadolinium contrast agent. Detailed parameter settings are given in the MR-Protocol.
Rationale for change		A risk of brain deposits with repeated use of gadolinium-based contrast agents for magnetic resonance imaging (MRI) like **Multihance** previously recommend within this protocol has been reported and radiologists therefore prefer the use of gadolinium-based contrast agents for which this risk has not been reported.
Section to be changed		Section 4.1.3 table 4.1.3:1 potential dose level
Description of change		Was added: dose level of 180 mg
Rationale for change		This intermediate dose level was tested based on Data Safety Board decision

Number of global amendment		3
Date of CTP revision		13 Mar 2019
EudraCT number		2015-001132-38
BI Trial number		1336.6
BI Investigational Product(s)		BI 836880
Title of protocol		Phase I, non-randomized, open-label, multi-center dose escalation trial of BI 836880 administered by weekly repeated intravenous infusions in patients with advanced solid tumors.
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority		☐

approval as changes involve logistical or administrative aspects only		
Section to be changed		• Title page • Abbreviation • Section 3.1.1- administration of the trial
Description of change		Trial Clinical Monitor (TCM) was changed to Clinical Trial Leader (CTL) and Clinical Monitor Local (CML) was changed to Clinical Trial Manager (CTM)
Rationale for change		Administrative changes
Section to be changed		Synopis- methodology
Description of change		Non randomized, uncontrolled, open-label, dose escalation followed by an expansion cohort **Was changed to** Non randomized, uncontrolled, open-label, dose escalation
Rational for change		Expansion cohort is no longer planned for this trial
Section to be changed		Synopsis- N° of patients
Description of change		Approximately 50 patients to be enrolled **Was changed to** Approximately 40 patients to be enrolled
Rational for change		To adapt the sample size since expansion cohort is no longer planned for this trial
Section to be changed		Synopis
Description of change		Approximately 40 patients, including at least 12 patients treated at MTD with tumour lesions evaluable for Dynamic contrast-enhanced (DCE)-MRI. 40 patients will receive study treatment **Was changed to** Approximately 25 patients. Approximately 25 patients will receive study treatment
Rationale for change		It is no longer required to enroll 12 patients with DCE-MRI to be treated at MTD, and to adapt the sample size since expansion cohort is no longer planned for this trial
Section to be changed		Flow chart
Description of change		Change s have been made in the following footnotes and sections: Footnote numbers and sections in the protocol: **: no additional follow up visits required after the interim data base lock - 2: change to frequency of physical examination and ECOG Performance

		- 3: change to frequency of body temperature, following the interim data base lock (refer to section 5.3.2) - 4: change to frequency of blood pressure, following the interim data base lock (refer to section 5.3.2) - 5: change to frequency of laboratory tests, following the interim data base lock (refer to section 5.3.3) - 6: change to frequency of tumor assessment, following the interim data base lock - 7: change to frequency and assessment of ECG and no requirement to send ECGs to central vendor, following the interim data base lock (refer to section 5.3.4) - 8: clarification about echocardiography data entry in the eCRF (refer to section 5.3.4) - 9: no blood samples for PK analysis will be taken following the interim data base lock (refer to appendix 10.4) - 10: no blood samples for ADA analysis will be taken following the interim data base lock (refer to appendix 10.4) - 11; 12: no blood samples for biomarker analysis will be taken following the interim data base lock (refer to appendix 10.4) -14: DCE-MRI measurement is no longer mandatory following the interim data base lock
Rationale for change		At the time of interim data base lock, sufficient data will have been collected for PK, ADA and biomarker analyses, therefore no longer required. Also to provide more flexibility to trial procedures
Section to be changed		Section 3.1 overall trial design and plan
Description of change		**Was deleted:** Once a MTD has been reached, a minimum of 12 patients must have tumour lesions evaluable for Dynamic contrast-enhanced (DCE)-MRI to allow a better interpretation of pharmacodynamics (vascular) effect of BI 836880. Once the RP2D has been determined and in case of anti-tumor activity signals is reported in given tumor type(s), DSB can take the decision for a trial expansion to recruit patients with the same tumor type(s) with the aim to generate safety and preliminary efficacy data specific to such disease. Approximately 10-15 additional patients will be treated in the expansion cohort, sample size will be re evaluated when the expansion cohort is open.
Rationale for change		-Since the Prof of Pharmacological Principal (PoPP) has been determined with the sister trial 1336.1 (3-weekly dosing), enrollment of 12 patients with DCE-MRI in this trial is no longer mandatory. -To reflect the fact that expansion cohort is no longer planned for this trial

Section to be changed		Section 3.1 overall trial design and plan
Description of change		Was added: **After the interim data base lock, the study is considered completed when the last patient in the study has discontinued the study treatment and completed the EoR visit (see Section 6.2.3.5).**
Rationale for change		Clarification on the definition of trial completion after the interim data base lock
Section to be changed		Section 3.3 selection of trial population
Description of change		It is estimated that approximately 50 patients will be enrolled at 2 study sites. The rate of enrolled patients may vary by study site, but it is expected to be approximately 25 patients per site. Among them 40 patients will be enrolled and treated in this trial. **Was changed to** It is estimated that approximately 40 patients will be enrolled at 2 study sites. The rate of enrolled patients may vary by study site, but it is expected to be approximately 20 patients per site. Among them approximately 25 patients will be treated in this trial.
Rationale for change		To adapt the sample size since expansion cohort is no longer planned for this trial
Section to be changed		Section 4.1.3 table 4.1.3:1 potential dose level
Description of change		Was added: dose level of 150 mg
Rationale for change		This intermediate dose level was tested based on Data Safety Board decision
Section to be changed		5.2 assessment of efficacy
Description of change		Was added: **After the interim data base lock, frequency of tumor assessment may be adapted according to local standard of care and in agreement with the sponsor if the patient is deriving clinical benefit (e.g. CR, PR or SD > 6 months).**
Rationale for change		To reduce imaging assessment frequency
Section to be changed		5.2 assessment of efficacy
Description of change		Was added: **After the interim data base lock, collection of tumor markers in the e-CRF is no longer required**.
Rationale for change		Following data the interim data base lock there is no longer requirement to enter tumor maker data in e-CRF
Section to be changed		Abbreviation and section 5.3.6.1 Definition of AEs
Description of change		Remote Data Capture **(**RDC**)** was changed to **Electronic Data Capture (eDC)**
Rationale for change		Administrative

Section to be changed		6.2 - Details of trial procedures at selected visits
Description of change		**Was added**: **After the interim data base lock, mandatory procedures/assessments and documentation in the eCRF will be adapted as described in the flow chart and the respective sections of this protocol**
Rationale for change		To reflect the changes to trial procedures/assessments following the interim data base lock
Section to be changed		6.2.2 treatment period(s) 6.2.3.3 Follow-up period for progression
Description of change		Was added: **After the interim data base lock, frequency of tumor assessment may be adapted according to local standard of care and in agreement with the sponsor if the patient is deriving clinical benefit (e.g. CR, PR or SD > 6 months).**
Rationale for change		To reduce imaging assessment frequency
Section to be changed		Section 6.2.3.5 trial completion
Description of change		**Section 6.2.3.5 was added:** **The clinical trial will be considered completed when the last patient has completed the EoR visit.** **If patients are still on treatment at the time of interim data base lock and the Clinical Trial Report is written, these patients will be maintained in the trial as long as they are deriving clinical benefit (i.e. no disease progression, no drug-related AEs requiring drug discontinuation) or no new anti-cancer treatment started and there are willing to continue. For these patients, no blood sample will be collected for PK/PD and biomarker analysis, only (S)AEs and limited efficacy data will be collected.** **After the discontinuation of these patients, additional data collected after interim data base lock will be reported in separate listings and will not lead to any further update of tables generated for section 15 of the CTR unless deemed necessary.** **These listings will be included in a revised CTR.**
Rationale for change		Clarification for the definition of trial completion following the interim data base lock
Section to be changed		Section 7.7 determination of sample size
Description of change		**Was deleted** Additional 10-15 patients will be included in the expansion cohorts, in case one or more tumor types will be selected for further evaluation. Sample size will be reevaluated when the expansion cohort is open.

Rationale for change		Expansion cohort is no longer planned for this trial
Section to be changed		8.6 End of Trial
Description of change		The trial will end when the last patient has completed the last follow up visit as specified in Section 6.2.3.4 **Was changed to:** **After the interim data base lock 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**
Rationale for change		Clarification for the definition of end of trial, following the interim data base lock

APPROVAL / SIGNATURE PAGE

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Document Name: clinical-trial-protocol-version-04

Title: Phase I non-randomized open-label multi-center dose escalation trial of BI 836880 administered by weekly repeated intravenous infusions in patients with advanced solid tumors

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader		13 Mar 2019 16:46 CET
Approval-Therapeutic Area		13 Mar 2019 17:48 CET
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(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed

Clinical Trial Protocol

	Document Number:	**c03124055-06**
EudraCT No.:	2015-001132-38	
BI Trial No.:	1336.6	
BI Investigational Product(s):	BI 836880	
Title:	Phase I, non-randomized, open-label, multi-center dose escalation trial of BI 836880 administered by weekly repeated intravenous infusions in patients with advanced solid tumors.	
Brief Title:	Weekly BI 836880 in patients with advanced solid tumors	
Clinical Phase:	I	
Clinical Trial Leader:	Phone: Fax:	
Coordinating Investigator: **Principal Investigator:**	Phone: Fax: Tel Fax	
Status:	Final Protocol (Revised Protocol based on global amendment 3)	
Version and Date:	**Version:**	**Date:**
Revised Protocol	4.0	13 Mar 2019

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		Not applicable	
Name of active ingredient:		BI 836880	
Protocol date: 10 Dec 2015	**Trial number:** 1336.6		**Revision date:** **13 Mar 2019**

Title of trial:	Phase I, non-randomized, open-label, multi-center dose escalation trial of BI 836880 administered by weekly repeated intravenous infusions in patients with advanced solid tumors
Coordinating Investigator: **Principal Investigator**	Phone: Fax: Tel Fax
Trial site(s):	Multicentre-trial conducted in 2 countries
Clinical phase:	I
Objective(s):	To determine the maximum tolerated dose (MTD) and provide preliminary safety data of BI 836880 given as intravenous infusion and to determine recommended phase II dose. Further the PK, immunogenicity and PD-profile, as well as primary signs of antitumor activity of BI 836880 should be assessed
Methodology:	Non randomized, uncontrolled, open-label, dose escalation
No. of patients:	Approximately 40 patients to be enrolled
total entered:	Approximately 25 patients
each treatment:	Approximately 25 patients will receive study treatment
Diagnosis :	Advanced or metastatic/ refractory solid tumors

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		Not applicable	
Name of active ingredient:		BI 836880	
Protocol date: 10 Dec 2015	**Trial number:** 1336.6		**Revision date:** **13 Mar 2019**

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. patients 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 • 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) and sensory peripheral neuropathy CTCAE grade < 2
Test product(s):	BI 836880 and Diluent for BI 836880
dose:	Starting dose of 40 mg weekly infusion
mode of administration:	Intravenous weekly in a 21-day treatment course
Comparator products:	Not applicable
dose:	Not applicable
mode of administration:	Not applicable
Duration of treatment:	Continuous treatment in the absence of disease progression or unacceptable toxicity
Endpoints	Primary endpoint • Maximum Tolerated Dose (MTD) Secondary endpoint • Drug related AEs leading to dose reduction or discontinuation during treatment period
Safety criteria:	Adverse events according to Common Terminology Criteria (CTCAE version 4.03), incidence of dose limiting toxicities, physical examination, vital signs, safety laboratory parameters, ECOG
Statistical methods:	Descriptive and exploratory statistics analyses. Dose escalation guided by a Bayesian logistic regression model with over dose control

FLOW CHART COURSE 1

Trial periods	**Screening**	**Treatment course*** **					**EOT***	**EoR***	**FU****
Course		1							
Visit	Screen	V1			V2	V3			
Day	-21 to -1	1	2	3	8 ±2	15±2		EoT+42 d	
Informed consent [1]	x								
Demographics	x								
Medical history	x								
Inclusion/exclusion criteria	x	x							
Physical examination[2]	x	x	x	x	x	x	x	x	
Height	x								
Weight	x	x					x		
Body temperature[3]	x	x	x		x	x	x		
Blood pressure[4], heart rate	x	x	x	x	x	x	x	x	
ECOG performance status	x	x					x		
Administration of BI 836880 infusion		x			x	x			
Safety Lab parameters[5]	x	x			x	x	x		
Pregnancy test	x	x					x		
Tumor assessment[6]	x						x		x
12-lead ECG[7]	x	x	x		x	x	x		
Echocardiography[8]	x						x		
Pharmacokinetics[9]		x	x	x	x	x	x	x	x (FU1)
Anti-drug antibodies[10]		x					x	x	x (FU1)

Trial periods	**Screening**	**Treatment course*** **					**EOT***	**EoR***	**FU****
Course		1							
Visit	Screen	V1			V2	V3			
Day	-21 to -1	1	2	3	8±2	15±2		EoT+42 d	
Biomarker : Myriad Ang MAP panel[11]		x		x				x	
Biomarker: free/total VEGF-A, Ang2[12]		x	x	x	x	x	x	x	x (FU1)
Concomitant therapy	x	x	x	x	x	x	x	x	x
Adverse events[13]	x	x	x	x	x	x	x	x	x
DCE-MRI[14]	x				x				x
Completion of trial medication							x		
Completion of patient participation									x

FLOW CHART COURSES 2 ONWARDS

Trial periods	**Repeated treatment courses*** **					**EOT***	**EoR***	**FU****
Course	2,3,4,5 onwards							
Visit	V1			V2	V3			
Day	1	2	3	8 ±2	15±2		EoT+42 d	
Physical examination[2]	x			x	x	x	x	
Weight	x					x		
Body temperature[3]	x			x	x	x		
Blood pressure[4], heart rate	x	x(C2,C4)		x	x	x	x	
ECOG performance status	x					x		
Administration of BI 836880 infusion	x			x	x			
Safety Lab parameters[5]	x			x	x	x		
Pregnancy test	x					x		
Tumor assessment[6]	x					x		x
12-lead ECG[7]	x	x (C2,C4)		x (C2,C4)	x (C2,C4)	x		
Echocardiography[8]	x					x		
Pharmacokinetics[9]	x	x (C2,C4)		x (C2,C4)	x (C2,C4)	x	x	x (FU1)
Anti-drug antibodies[10]	x					x	x	x (FU1)
Biomarker : Myriad Ang MAP panel[11]	x (C2, C4)						x	
Biomarker: free/total VEGF-A, Ang2[12]	x	x (C2, C4)		x (C2, C4)	x (C2, C4)	x	x	x (FU1)
Concomitant therapy	x	x		x	x	x	x	x
Adverse events[13]	x	x		x	x	x	x	x
DCE-MRI[14]	x (C3, C5)							x
Completion of trial medication						x		
Completion of patient participation								x

(C2, C3, C4, C5) = (courses 2, 3, 4 and 5)
FU1= first follow up visit
*End Of Treatment (EOT) must be performed within 21 days of the last administration of study drug. If last administration of the study drug occurs during a scheduled visit, examinations as defined for EOT should be performed instead of examinations for the scheduled visit.

EoR*= End of Residual Effect Period
**One Follow-up visit (FU1) should be performed 42 calendar days after the discontinuation of study drug for all patients. For patients who discontinue not due to progressive disease, additional FU visits will be performed at 6-week intervals plus /minus 3 days, until progression, lost to follow-up, start of another anti-cancer treatment, death.
After the interim data base lock additional FU visits are no longer required

***Treatment courses are 3 weeks in duration (21 days). All subsequent visit dates should be calculated based on Course 1 Visit 1 date. If one visit is skipped in case of treatment interruption patients may continue on treatment until the criteria for stopping medication are met (see Section 3.3.4)

[1]Written informed consent must be obtained before any trial specific screening assessments are performed.

[2]A complete physical examination (including cardiac, neurological, dermatological pulmological etc..) at screening and before the start of the treatment, EoT and End of Residual Effect Period (EoR). At further time points specified in the Flow Chart, physical examination should be limited to the assessment of the actual health status (including, evaluation of blood pressure, ECG, lab safety parameters, AEs, concomitant therapies, ECOG, as applicable). After the interim data base lock, physical examination, ECOG performance status are no longer mandatory at the specific visits but will be performed at the investigator's discretion. Findings will be documented in the eCRF only if qualifying as (S)AE

[3]Body Temperature: whenever possible the same method should be used for body temperature measurement in one patient. Body temperature $\geq$ 38°C must be re assessed 1 hour after. After the interim data base lock body temperature is no longer mandatory at specific visits but will be performed at the investigator's discretion. Findings will be documented in the eCRF only if qualifying as (S)AE

[4]Blood Pressure : Systolic and diastolic blood pressure as well as pulse rate (electronic or by palpation, count for 1 minute) will be measured after 5 minutes of rest in seated position. The blood pressure measurement should be performed three times at each time point (refer to Appendix 10.2 and Appendix 10.4 for detailed time points). After the interim data base lock blood pressure is no longer mandatory at specific visits but will be performed at the investigator's discretion. Findings will be documented in the eCRF only if qualifying as (S)AE

[5]Haematology, biochemistry and coagulation parameters will be performed locally. Previous safety lab: investigations are acceptable if performed within 72 hours prior to the first treatment administration. For details see Section 5.3.3 After the interim data base lock safety laboratory tests will be performed at investigator's discretion based on the standard medical care. Findings will be documented in the eCRF only if qualifying as (S)AE

[6]Tumor assessment will be performed every 6 weeks after start of treatment with BI 836880 (in the week preceding the start of treatment course 3, 5, 7, 9, 11...) and should include CT scans or MRI. Imaging not older than 28 days at start of treatment will suffice as screening images and don't have to be repeated. The EOT tumor assessment is optional if performed in the previous 4 weeks. In the event of any treatment interruption or treatment delay, the tumor assessment should follow the original schedule
After the interim data base lock, frequency of tumor assessment may be adapted according to local standard of care and in agreement with the sponsor if the patient is deriving clinical benefit (e.g. CR, PR or SD > 6 months).

[7]Triplicate 12-Lead resting digital electrocardiogram (3xECG taken approximately 2-3 minutes apart) will be performed at screening and will be repeated at visits (refer to Section 5.3.4 and Appendix 10.4 for detailed time point).
After the interim data base lock, ECG will be performed as clinically indicated on local machine and the assessment will be done by the investigator. Shipment of ECGs to central vendor is no longer required

[8]Echocardiography will be performed locally at screening (not older than 7 days before start of treatment) and at EoT. During treatment period, echocardiography will be conducted only if clinically indicated. After the interim data base lock findings related to echocardiography will be reported in the eCRF only if qualifying as (S)AE

[9]Pharmacokinetics: For detailed information about pharmacokinetic (PK) sampling time points and handling procedures refer to Appendix 10.4. The last blood samples for PK, ADA and Biomarkers (myriad ANG Map Panel, free/total VEGF-A, Ang2) will be taken in this trial when the last patient has discontinued the trial treatment and performed the EoT visit. After the interim data base lock no blood sample will be taken for PK analysis

[10]Immunogenicity assessment (ADA): for detailed sampling schedule refer to Appendix 10.4. After the interim data base lock no blood sample will be taken for ADA analysis

[11]Biomarker: myriad Ang Map Panel: for detailed sampling schedule refer to Appendix 10.4. After the interim data base lock no blood sample will be taken for Myriad Ang Map panel analysis

[12]Biomarker: free/total VEGF-A, Ang2: for detailed sampling schedule refer to Appendix 10.4. After the interim data base lock no blood sample will be taken for free/total VEGF-A, Ang2 analysis

[13]AEs must be collected and reported from signing the informed consent onwards through the end of treatment (including Residual Effect Period, REP): all AEs (serious and non-serious) and all AESIs must be collected and reported from signing the informed consent onwards through the end of treatment (including Residual Effect Period, REP). After the end of treatment (including the REP) during the extended follow-up period until the individual patient's end of trial: all related SAEs and all related AESIs must be collected and reported. After the individual patient's end of trial: the investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs and relevant AESIs of which the Investigator may become aware of (Please refer to Section 5.3.6 and Section 6.2.3.3)

[14]DCE-MRI measurements will be done only for suitable patients with preferably liver metastases > 2cm. DCE-MRI measurement will be done during the screening period, 1 week after first administration of BI 836880 (C1V2), after the 2nd treatment course (C3V1) and after the 4th treatment course (C5 V1) in absence of progressive disease. In case patient stopped treatment for other reasons than progressive disease, DCE-MRI should still be conducted as long as patient is in Follow up for progression. Time points for 3rd and 4th imaging, depending on when patient stopped treatment, have to be adapted as 6 weeks and 12 weeks after 1st infusion
(refer to Section 5.5.1)

After the interim data base lock, DCE-MRI measurement is no longer mandatory

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ABBREVIATIONS

ABPM	Ambulatory Blood Pressure Measurement
ADA	Anti-Drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine amino transferase
ANC	Absolute neutrophil count
Ang2	Angiopoeitin2
AST	Aspartate amino transferase
AUC	Area under the Curve
BI	Boehringer Ingelheim
BLQ	Below the limit of quantification
BP	Blood Pressure
CA	Competent Authority
CBPM	Conventional Blood Pressure Measurement
CI	Confidence Interval
CPL	Clinical Program Leader
CPPL	Clinical Pharmacology Program Leader
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organisation
CTMF	Clinical Trial Master File
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Clinical Trial Leader
CTM	Clinical Trial Manager
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DCE-MRI	Dynamic Contrast-Enhanced Magnetic Resonance Imaging
DEDP	Drug Exposure During Pregnancy
DBP	Diastolic Blood Pressure
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicity
DSB	Data Safety Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic Acid
EoR	End of Residual effect period
EOT	End of Treatment
EudraCT	European Clinical Trials Database
EWOC	Escalation with overdose control
FC	Flow Chart
FU	Follow up
FDA	Food and Drug Administration

GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HNSTD	Highest No-Severely Toxic Dose
IB	Investigator's Brochure
IC	Informed Consent
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
i.v.	intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web-based Response System
K_{trans}	Volume transfer constant obtained from DCE-MRI data
LMWH	Low Molecular Weight Heparin
MedDRA	Medical Dictionary for Drug Regulatory Activities
MTD	Maximum Tolerated Dose
NCA	Non Compartmental 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-Inflammatory Drug
NYHA	New York Heart Association
OPU	Operative Unit
p.o	Per os (oral)
PD	Progressive Disease
PLGF	Placenta Growth Factor
PK/PD	Pharmacokinetics/Pharmacodynamics
PR	Partial Response
QT	QT interval corrected for heart rate
QTcf	QT interval corrected for heart rate according to Fridericia's formula
eDC	Electronic Data Capture
RECIST	Response Evaluation Criteria In Solid Tumors
REP	Residual Effect Period
RP2D	Recommended Phase II Dose
SAE	Serious Adverse Event
SD	Stable Disease
SBPM	Self-Blood Pressure Measurement
SOP	Standard Operation Procedure
SUSAR	Suspect Unexpected Serious Adverse Event
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
TSE	Turbo Spin Echo
TSTAT	Trial Statistician
ULN	Upper Limit of Normal
UPCR	Urine Protein to Creatinine Ratio
VEGF	Vascular Endothelial Growth Factor

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, existing 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, play 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/Tie2) 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 (VHH) and two constant domains (CH2 and CH3). The cloned and isolated VHH domain is a stable polypeptide harbouring the full

antigen-binding capacity of the original heavy-chain antibody. These newly discovered VHH 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 (VHH, 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).

BI 836880 potently binds to both hVEGF165 and hVEGF121 with similar affinity in the low nanomolar to sub-nanomolar range and completely inhibits binding of hVEGF165 to VEGFR. BI 836880 potently binds to human Ang2 with an affinity constant estimated to be KD=16pM and potently inhibited and fully blocked human Ang2 binding to Tie2 with an IC50 of 50pM in the presence of human serum albumin (c02353882).
BI 836880 is highly potent and showed *in vivo* monotherapy efficacy (tumor growth inhibition) in several tumor xenograft representing colon cancer (CXF 243), non-small cell lung cancer (LXFE 211, LXFE 1422), mammary cancer (MAXF 401), ovarian cancer (OVXF 1353), pancreatic cancer (PAXF 546) and renal cell cancer (RXF 1220) (c02353882).

BI 836880 cross-reacts to cynomolgus VEGF, as well as mouse, rat and cynomolgus Ang2 which points to cynomolgus monkey as the most suitable species for toxicology assessment. Based on this, a 13-week repeat dose administration of BI 836880 was performed in cynomolgus monkeys. Animals received weekly BI 836880 intravenous doses by a 5-minute infusion at doses of 0 (vehicle only), 1, 10 and 60 mg/kg for a total of 14 doses followed by a 13-week recovery period. BI 836880 was well tolerated up to the highest dose of 60 mg/kg. No mortality was attributed directly to BI 836880 administration. But one monkey in the 10 mg /kg dose tier had to be euthanized due to an important immunogenic reaction.

BI 836880 did not demonstrate any effects on neurological, renal, or cardiovascular functions including electrocardiograms (ECGs). In the monkey presenting the immunogenic reaction, membranoproliferative glomerulopathy in the kidney was observed. This finding was considered as a secondary response to immune complex deposition in the glomeruli and not directly related to BI 836880 administration.

No BI 836880 related adverse changes in body weight, food consumption or clinical observations were noted. BI 836880 did not result in ocular changes, changes in physical examination parameters.

No adverse or BI 836880-related changes in hematology, chemistry, coagulation or urinalysis were observed (c02353882).

BI 836880 administration resulted in a microscopic growth plate cartilage change (increased zone of hypertrophy) in the sternum of the males in the ≥10 mg/kg dose groups. This change was of minimal in severity and was considered not adverse since it was not expected to

negatively affect bone growth. Increased thickness of the growth plate zone of hypertrophy is a known effect of angiogenesis inhibitors such as Bevacizumab.

The pharmacokinetics (PK) and immunogenicity of BI 836880 were investigated in cynomolgus monkeys following a single intravenous (i.v.) at 3 dose levels. BI 836880 demonstrated an unexpected dose-dependent clearance and a supra-proportionally $AUC_{0-\infty}$ increase with the increase of dose. Among the nine monkeys in this study, six monkeys were ADA positive post-dose at one or more of the sampling time points. In the 13-week toxicity and toxicokinetics, BI 836880 exposure (C_{max} and AUC_{0-168}) increased approximately dose-proportionally from 1 to 60 mg/kg in weeks 1, 4 and 13. There was a moderate (~ 2-fold) accumulation of BI 836880 after repeated dosing. The C_{max} and AUC_{0-168} values were similar between the male and female monkeys at the same dose level in each sampling week. The discrepancy in dose proportionality between these two studies is likely due to the difference in sampling. More sampling time points (up to 42 days post dosing) in the single dose PK study allowed better characterization of the later portion of the concentration-time profiles (after ~ 240 h), where dose-dependent clearance was more pronounced.

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 settings, 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 Trebananib in ovarian cancer. In a randomized Phase III trial in patient with recurrent ovarian cancer Trebananib 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 blockers and Ang2 blockers is not durable and only a limited number of patients 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 (c02353882).

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 weekly intravenous infusion and to determine recommended phase II dose.

Secondary objective:

- To provide preliminary safety data

2.3 BENEFIT-RISK ASSESSMENT

BI 836880 has not been tested in human so far. In the 13-week 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 (Trebananib) in development is in Phase III in combination with chemotherapy (R14-5440). 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 include 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 trial requires timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to ensure patients´ safety (see also Section 5.3.6.1)

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

A Data Safety Board (DSB) will be appointed to periodically review and monitor data from the trial (refer to Section 3.1.1).

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, multi-centre, 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 200% dose increment for the first dose escalation and 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. For subsequent 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 course, then dose-escalation can occur based on these 2 patients. However, should one of these 2 patients experience a DLT in the first course, a third patient will be enrolled at the same dose level. After all patients in a cohort have either experienced a DLT or have been observed for at least one course (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 the dose escalation scheme 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.

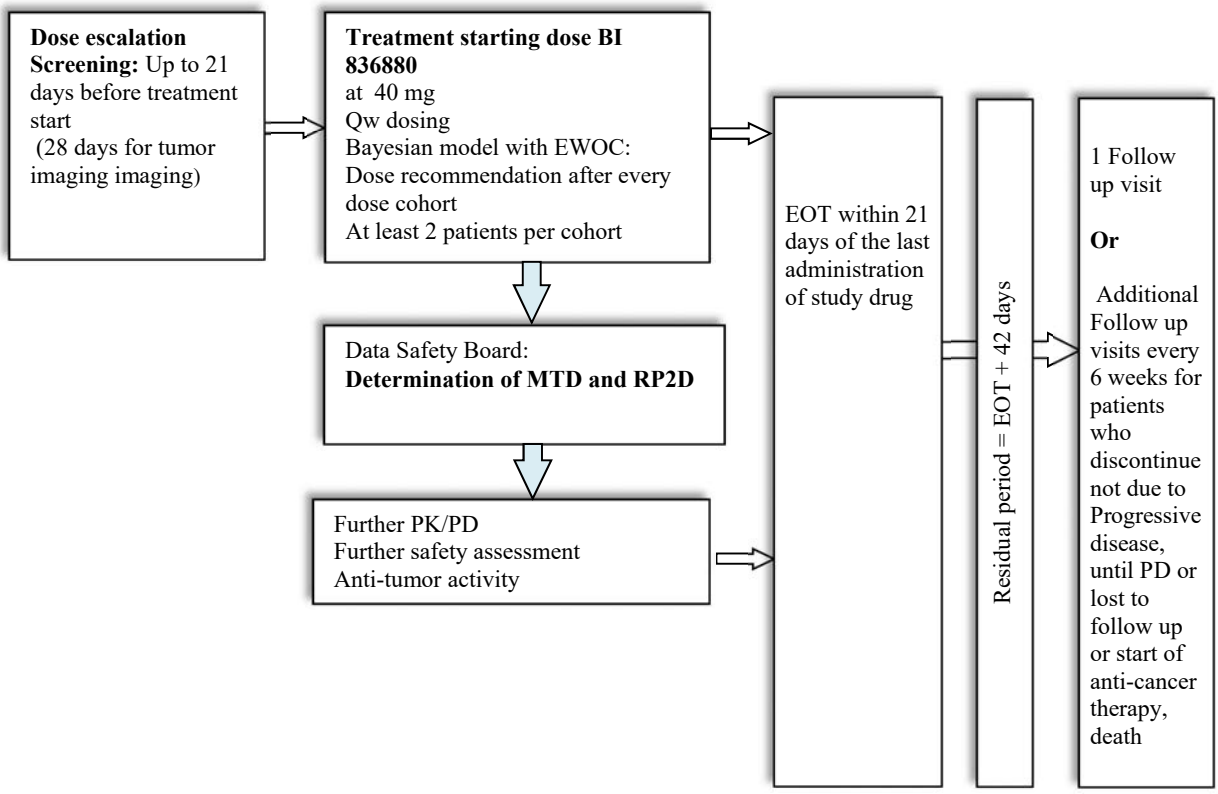

Figure 3.1: 1Study design

All patients eligible after the screening will be administrated with BI 836880 weekly infusion. In case the patient shows a stable disease or even a response, the study treatment will continue until one of the withdrawal criteria listed in Section 3.3.4 is met.

An estimated of about 25-30 patients will be necessary to establish MTD and confirm RP2D. Confirmation of the RP2D will be made based on all available safety, PK and Pharmacodynamics (PD) data at all treatment courses and all dose levels.

All patients will have regular evaluations for assessment of safety parameters as detailed in the Flow Chart.

An End of trial (EOT) evaluation is to be completed when a patient permanently discontinues the study drug, for any reason listed in Section 3.3.4.

A Follow-up evaluation will be completed 42 days after permanent discontinuation of the study drug. Refer to the Flow Chart for details. This visit will be defined as the last visit in the on-study period for the trial.

For adverse event collection, please refer to Section 5.3.6.

After the interim data base lock, the study is considered completed when the last patient in the study has discontinued the study treatment and completed the EoR visit (see Section 6.2.3.5).

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim and will be conducted in two (2) sites. Additional sites may be added to boost the recruitment and recruitment may vary between sites.
The study will be performed by investigators specialized in the treatment of advanced cancers and experienced in phase I trials in oncology.

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 the Recommended Phase II dose, as well as the decision for a tumor type expansion cohort. Members of the DSB will be investigators of participating trial sites, Trial Statistician (TSTAT), Clinical Program Leader (CPL), Clinical Trial Leader (CTL) and BI Lead Risk Management Physician. Clinical Pharmacology Program Leader (CPPL) and Translational Medicine Expert (TME) can be invited as needed, especially for discussion of PK/PD and biomarker.
Minimum data for dose escalation decision will be described in the DSB charter.

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

Exploratory biomarker analyses will be performed by BI and/or a dedicated CRO/ laboratory authorized by Boehringer Ingelheim.

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

Boehringer Ingelheim has appointed a Trial Clinical Leader (CTL), responsible for coordinating all required activities, in order to:

- manage the trial in accordance with applicable regulations and internal 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 Trial Manager (CTM), Clinical Research Associates (CRAs), and Investigators of participating countries.

Data management and statistical evaluation will be done by BI according to BI SOPs.
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 can be found in the ISF.

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 ISF.

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 antitumor activity 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. This expansion will take place after a protocol amendment.

3.3 SELECTION OF TRIAL POPULATION

It is estimated that approximately 40 patients will be enrolled at 2 study sites. The rate of enrolled patients may vary by study site, but it is expected to be approximately 20 patients per site. Among them approximately 25 patients will be treated in this trial.

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.

Patients will be selected based on the eligibility criteria described below.

3.3.1 Main diagnosis for trial entry

All patients that 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 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 patients 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 as defined by the following criteria:
   a. Total bilirubin within normal limits (≤ 1.5x ULN for patient with Gilberts syndrome)
   b.ALT and AST ≤ 1.5x ULN (< 5xULN for patient known liver metastases)
   c.Serum creatinine < 1.5x ULN
   d.INR 0.8-1.2 or PTT < 1.5x ULN
   e.ANC > 1.5 10^9/L
   f.Platelet count > 100x10^9/ L.
   g.Heamoglobin > 10 g/dl (without transfusion within previous week)
5. Signed and dated 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 grade1, except for alopecia (any grade), sensory peripheral neuropathy CTCAE grade ≤ 2 or considered by the investigator as clinically not 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 the study drug according to the 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 at the start of study treatment.

3. Serious concomitant disease (based on investigator judgement), 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 (as judged by the investigator) or bone fracture within 4 weeks of start of study 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 disease (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 tested and relaxed condition >= 140 mmHg, systolic or ≥ 90 mmHg diastolic (with or without medication), measured according to Section 5.3.2 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; low-molecular-weight heparin (LMWH) allowed only for prevention not for curative treatment.

11. Use of alcohol or drug incompatible with patient participation in the study in the investigator opinion

12. Patient unable or unwilling to comply with protocol

13. Women who are pregnant, nursing, or who plan to become pregnant while in the trial

14. Previous enrolment in this 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 for study treatment or study participation, without the need to justify the decision.
- Requiring concomitant drugs that interfere with the investigational product or other trial medication (see Section 4.2.2) or patient who requires 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 patient is no longer able to complete trial visit or trial-required procedures.
- 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 scheme)
- Progressive disease (except in cases with intra-patient dose escalation, (see Section 4.1.3) or start of any new anti-cancer therapy.

A patient can have 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 Clinical Trial Report (CTR). As soon as a patient is withdrawn from the study 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.

Patients who have not completed first course of BI 836880 treatment (3 weeks) for any other reason than BI 836880 related toxicities will be considered not evaluable for MTD evaluation and should be replaced.

Patient who prematurely discontinue study drug for above mentioned reasons or any other reason, should have additional follow up visits until progression, lost to follow up, treatment with another anti-cancer treatment, death and /or end of the trial whichever comes first.

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.

Should the patient become pregnant during the trial, the treatment with BI 836880 must be stopped immediately, and this patient is not allowed to receive further trial medication from that point onward. The patient will be followed up until delivery or termination of pregnancy (see Section 5.3.6.2). The data of the patient will be collected and reported in the CTR until last patient last visit and any events occurring thereafter will be reported in BI drug safety database.
For all patients the reason for withdrawal (e.g. adverse events) must be recorded in the (e)CRF. These data will be included in the trial database and reported.

3.3.5 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 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)

Table 4.1.1: 1 Test product 1

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

Table 4.1.1: 2 Diluent for Test product 1

Substance:	Diluent for BI 836880 drug product
Pharmaceutical formulation:	Diluent to prepare solution for infusion of BI 836880
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	50 ml/vial
Posology	rate controlled infusion
Route of administration:	i.v.
Duration of use	until progression disease or unacceptable toxicity

4.1.2 Method of assigning patients to treatment groups

There is no randomisation, eligible patients will receive treatment.
Allocation to dose cohorts or expansion cohort will be done according to subject temporal availability and depending on dose cohort open for recruitment.
During Visit 1/Day 1 and after the patient's eligibility has been confirmed, the treatment will be assigned via Interactive Response Technology (IRT).
For medication number allocation at each visit, it's possible to conduct IRT call ahead of the planned visit (= day of administration)
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 (refer to Investigator's Brochure for more details (c02353882)).

Based on the 13-week Good Laboratory Practice (GLP) toxicology trial in cynomolgus monkey, the Non-Observed-Adverse-Effect-Level (NOAEL) /Highest Non-Severely Toxic Dose (HNSTD) is defined as 60 mg/kg. According to this method and using a safety factor of 6, the maximum starting dose is 10 mg/kg.

As a second approach, a mathematical PK/PD model was developed to predict the human therapeutic dose of BI 836880. The model was calibrated to data from a cynomolgus monkey PK/PD study and then scaled to human to perform simulations. The model is a two compartment in vivo model that includes the target ligands (VEGF-A and Ang2), their corresponding receptors (VEGFR2 and Tie2) and additional ligand/receptor pairs that share common receptors. Predictions were made for the minimum dose that maintains a high level of reduction in both VEGF:VEGFR2 and Ang2:Tie2 complexes by BI 836880 at steady state. The VEGF-A:VEGFR2 complex and Ang2:Tie2 complex levels were considered surrogates of receptor signaling in *silico*.
The predicted human dose that according to this simulations achieves reduction in both VEGF:VEGFR2 and Ang2:Tie2 complexes at $C_{min,ss}$ is 0,67 mg/kg for a weekly dosing. At a dose level of 0.67 mg/ kg (dosed once every week) the fraction of VEGF-A:VEGFR2 complex is predicted to be reduced to 35% - 55% of the pre-dose level, and the fraction of Ang2:Tie2 complex is predicted to be reduced to below 0.1 (90%) of the pre dose level.

Since the two methods resulted in different starting doses, and the dose based on the PK/PD modeling is expected to allow achieving reduction in both VEGF:VEGFR2 and Ang2:Tie2 complexes, the lowest dose was selected as starting dose in this first in human trial.

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 the targeted C_{min} concentration in plasma that is supposed to maintain a continuous high suppression of VEGF-A:VEGFR2 and Ang2:Tie2 complex formation (>90%).
In a weekly dosing schedule, target C_{min} plasma concentrations are expected to be achieved after 7 infusions of BI 836880 at dose of 2 mg/kg (120 mg), after 2 infusions at dose of 6 mg/kg (360 mg) and after 1 infusion 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 40 mg. Dose escalation ≥120 mg 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)	Approximate increment to next dose
Dose level 1 (starting dose)	40	3x (200%)
Dose level 2	120	1.25x (25%)
Dose level 3	150	1.20x (20 %)
Dose level 4	180	1.3x (30%)
Dose level 5	240	2x (100%)
Dose level 6	480	1.5x (50%)
Dose level 7	720	1.3x (30%)
Dose level 8	960	1.7x (30%)
Dose level 9	1440 limited to 1250*	

*Maximum dose that can be tested due to excipient limitation

Intermediate dose levels can be tested based on DSB decision.

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 courses, deeming to have clinical benefit from treatment and tolerated BI 836880 well (i.e do not show any DLT) could be allowed to receive increased dose. Such decision will be taken in case by case manner on request by the investigator and confirmation by the DSB based on actual patient profile. Intra patient dose escalation can be repeated; however the dose can only be increased to the 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, sampling for ADA as well as sampling for biomarkers (Myriad panel and free/total VEGF-A/ Ang2) 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 according to "Instruction for Pharmacists" which will be filed in ISF**.** Upon notification of an entered patient in the study, the pharmacy will prepare the study drug in the assigned dosage for administration to the patient.

BI 836880 will be given as 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 min. in case no relevant infusion reactions are observed, this may be shortened to about 30 min but should not be prolonged to more than 6 hours even 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 $\geq$ 2 occur (that are not qualifying as DLT according to Section 5.3), the infusion should be temporarily stopped. Upon recovery, infusion should be resumed 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 administrating 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 adaptation of application scheme need to be agreed with sponsor.

BI 836880 will be administrated intravenously starting on course1 day1. In the event of delay or interruption of treatment due to adverse event, BI 836880 infusion should be skipped; and the next scheduled BI 836880 infusion should be administrated upon recovery to CTCAE Grade 1.

Premedication: No premedication will be required for BI 836880 IV infusion.

If a patient experienced sign of infusion reaction at any BI 836880 treatment, a premedication will be **considered** for all subsequent treatment infusions (dosage and schedule according to investigator's decision) comparable to the following scheme:

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

If infusion reaction and /or hypersensitivity reaction occurs in substantial amount of patients (about 30%) of treated patients without premedication, premedication, as described above, will be given to all treated patients. Such decision will be confirmed by the DSB; dosage and schedule should be aligned, and reflect institutional clinical standards.

4.1.4.1 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:

QTcF $\leq$ 470 ms (according to exclusion criterion #5)

No uncontrolled hypertension (according to exclusion criterion #6)

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.

4.1.4.2 Dose reduction scheme

Administration of trial drug has to be stopped temporarily in case of a DLT (see Section 5.3). 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. In this open-label trial, treatment allocation will not be concealed throughout the trial. The CRF will contain information on allocated treatment.

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

Diluent for BI 836880 drug product will be supplied in 50R vial containing 50 ml Diluent for BI 836880 drug product. The Diluent vials will be packed in one vial per box.
Boxes and vials will be labelled according to local regulations.

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

BI 836880 drug re-supply will be managed through IRT by the trial sites and BI personnel.

4.1.7 Storage conditions

BI 836880 vials and Diluent vials, which will be provided by the sponsor and/or a CRO appointed by the sponsor must be kept in their original packaging and in secure limited access storage area according to the recommended storage conditions on the medication label. The Investigator, the Pharmacist, or other personnel allowed to store and dispense.

The Investigator or pharmacist or investigational drug storage manager 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 for documentation.

For details concerning the preparation of the infusion solution of BI 836880, please refer to the ‘instructions for pharmacists’ filed in the ISF.

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 will receive the investigational drugs delivered by the Sponsor after IRB / ethics committee approval of the trial and completion of a clinical trial contract between the Sponsor and the Head of Trial Center.

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)

Rescue medication to reverse the action of BI 836880 is not available.
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 BI 836880 and the patient must have recovered from all clinical relevant reversible toxicities (see exclusion criteria in Section 3.3.3).

Concomitant anti-cancer therapy is not allowed.

Radiotherapy for local symptom control of non-target lesions can be allowed after discussion between the investigator and the sponsor. The irradiated area cannot be used for response assessment.

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. Unplanned surgeries should be postponed whenever possible four weeks after stop of treatment. For urgent interventions patients should not be treated further and does require intense monitoring regarding wound healing and postoperative complications.

4.2.2.2 Restrictions on diet and life style

No restriction

4.3 TREATMENT COMPLIANCE

BI 836880 must be administered as an intravenous infusion under supervision of the investigator or dedicated clinical personnel.
Compliance may be 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 determine the maximum tolerated dose (MTD) based on the number of patients presenting dose limiting toxicity (DLT) using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) V4.03, during the first course (i.e. over the first 3 weeks of treatment) and judged to be related to the study medication.

5.1.2 Secondary Endpoint(s)

- Drug related AEs leading to dose reduction or discontinuation during treatment period

5.2 ASSESSMENT OF EFFICACY

The assessment by the investigator and the local radiologist will be the basis for continuation or discontinuation of the trial in an individual patient (in addition to safety). Tumor assessment will be performed every 6 weeks after start of treatment and at the time points specified in the Flow Chart.
After the interim data base lock, frequency of tumor assessment may be adapted according to local standard of care and in agreement with the sponsor if the patient is deriving clinical benefit (e.g. CR, PR or SD > 6 months).
CT images at baseline should be performed as close as possible to the treatment start and not older than 28 days at start of treatment.
At baseline, the investigator along with the radiologist will record the target (five target lesions maximum and maximum two per organ) and non-target lesions at baseline in the eCRF before the start of treatment. The same method of assessment and the same technique should be used to characterize each reported lesion at baseline and during follow up. Lesions in previously irradiated areas may not be considered measurable at baseline unless the lesions occurred after irradiation. Response will be evaluated according to the response evaluation criteria in solid tumors (RECIST version 1.1 (R09-0262). In the event of a delay, interruption or discontinuation of treatment, tumor assessment should continue to follow the original schedule. The schedule should be followed until progression is observed or until the patient commences further treatment for disease, whichever occurs first.

Results of tumor-specific tumor markers which will be assessed routinely should be documented in the eCRF.

After the interim data base lock, documentation of tumor markers in the e-CRF is no longer required.

5.3 ASSESSMENT OF SAFETY

Dose Limiting Toxicity (DLT)

The following drug-related adverse events will qualify as Dose-Limiting Toxicities:

- CTCAE grade ≥ 3 non haematological toxicity except:
  - Vomiting or diarrhea responding to supporting treatment
  - Fatigue lasting for less than 4 days
  - Transcient Grade 3 infusion reaction (i.e. if infusion- related reaction 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 resolved with appropriate treatment. Clinically relevant abnormalities have to be documented as AE (see Section 5.3.6)
- CTCAE grade 4 neutropenia >7 days or complicated by infection (in case of neutropenia grade 4, close observation of patient is necessary.
- CTCAE grade ≥3 febrile neutropenia
- CTCAE grade = 4 thrombocytopenia
- CTCAE grade ≥ 3 thrombocytopenia with bleeding
- CTCAE grade ≥ 3 proteinuria (urinary protein ≥ 3.5 g/day)
- Hypertension: increase of diastolic blood pressure (BP) by 15 mmHg confirmed by second measurement or ambulatory blood pressure measurement (when indicated; e.g. white coat effect) which cannot be controlled by hypertensive medication and requires a dose reduction of BI 836880 for further treatment course.
- All related AE leading to an interruption of BI 836880 for more than 14 days until recovery to baseline.

The MTD may be considered reached if the probability that the true DLT rate is in target interval (16%-33%) is sufficiently large (for details see Section 7). The DSB may recommend stopping the dose finding phase after the criterion for MTD is fulfilled.

If the 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 and declare this dose as RP2D and no further dose escalation will happen.

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

5.3.1 Physical examination

A complete physical examination including (height at screening only), cardiac, neurological, dermatological pulmological, weight and ECOG performance score, will be performed at screening and before the start of the treatment, EoT and EoR. At further time points specified in the Flow Chart, not a complete physical examination will be performed, but at minimum the actual health status of the patient should be assessed (including, evaluation of blood pressure, ECG, lab safety parameters, AEs, concomitant therapies, ECOG as applicable). During the physical examination, the patient should be assessed for possible AEs.
After the interim data base lock, physical examination, ECOG performance status, weight are no longer mandatory at the specific visits but will be performed at the investigator's discretion. Findings will be documented in the eCRF only if qualifying as (S)AE.

5.3.2 Vital Signs

Vital signs (blood pressure, heart rate and body temperature) will be recorded at every visit indicated in the flow chart.

At day of administration two time points will be evaluated:
1- At pre-dose (-60 minutes to – 5 minutes)
2- Shortly before the end of infusion

In case of an infusion-related reaction, if deemed necessary, the investigator should decide for intensive monitoring of vital signs.

Blood pressure

Systolic and diastolic blood pressure as well as pulse rate (electronic or by palpation, count for 1 minute) will be measured after 5 minutes of rest in seated position. The blood pressure measurement should be performed three times at each time point and values of these measurement will be entered in the CRF (refer to Appendix 10.2 and Appendix 10.4)
After the interim data base lock blood pressure is no longer mandatory at specific visits but will be performed at the investigator's discretion. Findings will be documented in the eCRF only if qualifying as (S)AE

Body temperature

Whenever possible the same method should be used for body temperature measurement in one patient. All methods used should deliver valid reproducible results according to common clinical practice.
Body temperature $\geq$ 38°C must be re assessed 1 hour after, especially in cases of suspected febrile neutropenia (see CTCAE V.4.03).
After the interim data base lock body temperature is no longer mandatory at specific visits but will be performed at the investigator's discretion. Findings will be documented in the eCRF only if qualifying as (S)AE

5.3.3 Safety laboratory parameters

Blood sample for assessment of 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 versus grade 3 needs to be done by quantitative measurement.
Safety laboratory examination will include haematology, biochemistry, coagulation, and urine analysis.

- **Haematology**: Haemoglobin, red blood cell count (RBC), white blood cell count (WBC) and differential, platelets.

- **Biochemistry**: glucose, sodium, potassium, calcium, magnesium, inorganic phosphate, creatinine, aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphatase, lactate deshydrogenase (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)

- **Urinalysis**: pH, glucose, leukocytes, erythrocytes, protein, nitrite will be analysed primarily qualitatively by dipstick. In case of pathological findings, further evaluation should be performed and the findings documented. A positive urine dipstick for protein of ≥ 2+ has to be followed by a determination of urine protein to creatinine ratio (UPCR) in a morning spot urine sample. In case of a ratio ≥ 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 is ≥ 0.5 as often as clinically indicated.

After the interim data base lock, safety laboratory tests (haematology, biochemistry, coagulation, urinalysis) will be performed at the investigator's discretion based on the standard medical care. Findings will be recorded in the e-CRF only if qualifying for (S)AE/AESI.
Pregnancy test: a serum pregnancy test will be performed as outlined in the Flow Chart in women of childbearing potential.

Previous laboratory investigations performed within 72 hours prior to the first treatment administration visit are acceptable to confirm the patient eligibility.

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.

5.3.4 Electrocardiogram (ECG)

12-lead ECGs will be digitally recorded in triplicate and performed for each patient at various time point according to the Flow Chart and Appendix 10.4.

- At screening, visits between administrations of study treatment, and at EoT. Only one time point will be evaluated
- At days of administration, two time points will be evaluated:
  - Pre-dose (-60 min. to -5 min.) and
  - 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 courses of treatment. The ECGs will be recorded using dedicated equipment provided by the vendor.

The ECGs will be sent 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.
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 patient's 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.

After the interim data base lock, ECG will be performed as clinically indicated on local machine and the assessment will be done by the investigator. Shipment of ECGs to central vendor is no longer required.

Echocardiography

Echocardiography will be performed locally at screening (not older than 7 days before start of treatment) and at EoT. During treatment period, echocardiography will be conducted only if clinically indicated.
After the interim data base lock findings related to echocardiography will be reported in the e CRF only if qualifying as (S)AE

5.3.5 Other safety parameters

Not applicable

5.3.6 Assessment of adverse events

5.3.6.1 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.

Adverse reaction
An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

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

- results in death,
- is life-threatening, this 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.
- requires inpatient hospitalisation or
- prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- 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.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

AEs considered "Always Serious"
Every new occurrence of cancer of new histology must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.
In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further 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 eDC system. These events should always be reported as SAEs as described above.

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. AESIs need to be reported to the Sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, please see above.

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 eDC-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.

DLT events
All DLT events (as defined in Section 5.3) in individual patients occurring at any time during the repeated treatment courses or follow-up period must be reported as adverse events of Special Interest (AESI).

Severity of AEs
The severity of adverse events should be classified and recorded in the (e)CRF according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (R12-2532).

Causal relationship of AEs
The definition of an adverse reaction implies at least a reasonable possibility of a causal

relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

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.
Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced
- No medically sound alternative aetiologies that could explain the event (e.g. pre- existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged

5.3.6.2 Adverse event collection and reporting

AE Collection

The Investigator shall maintain and keep detailed records of all AEs in their files.
The following must be collected and documented on the appropriate CRF(s) by the Investigator:

- From signing the informed consent onwards until the end of treatment (including the Residual Effect Period, REP): all AEs (non-serious and serious) and all AESIs.

- After the end of treatment (including the REP) until the individual patient's end of trial: all related SAEs and all related AESIs.
- After the individual patient's end of the trial: the Investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs and relevant AESIs of which the Investigator may become aware of.

The rules for Adverse Event Reporting exemptions still apply.

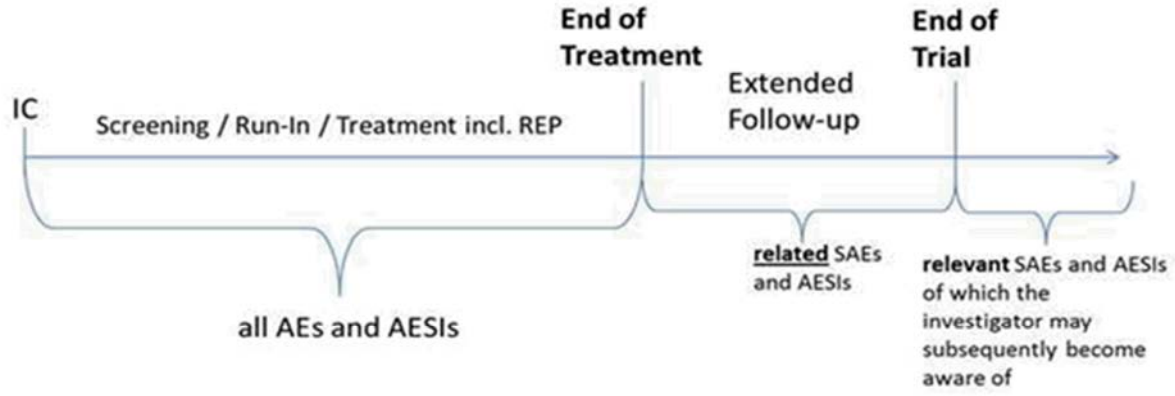

Figure 5.3.6.2: 1AE collection

The REP is defined as 42 days 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.

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). The same timeline applies if follow-up information becomes available**.** 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 CRF pages and the BI SAE form. The Investigator should determine the causal relationship to the trial medication.

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

- Worsening of the underlying disease or of other pre-existing conditions. The rules for Adverse Event Reporting exemptions still apply
- 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 individual patient's end of trial must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

Pregnancy
In rare cases pregnancy may occur in a clinical trial. Once a patient has been enrolled into this clinical trial and has taken trial medication, the Investigator must report immediately (within 24 hours) a potential 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).
The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B).

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

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.

All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

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, if data allow and if scientifically reasonable.

Pharmacokinetic data may additionally be analysed using a 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 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 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 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 10.3 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 exploratory 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 analyses, and the outputs will not be validated. Minor discrepancies between exploratory 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 a K2 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 or below 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, K2 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.

5.4.3 Analytical determinations

BI 836880 will be quantified using a validated bioanalytical assay.
After completion of the PK analysis, remaining plasma samples may be used for additional angiogenesis-related biomarker analyses as described in Section 5.5.

5.4.4 Pharmacokinetic - Pharmacodynamic Relationship

No formal analysis of a pharmacokinetic/pharmacodynamic relationship is planned. Correlation between drug concentration and response may be made if adequate data are available. In addition, exploratory correlation will also be made between drug concentration and AEs.
Data may also be used to develop pharmacokinetic/pharmacodynamic models using nonlinear mixed effect modelling techniques, if feasible. 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.

5.5 ASSESSMENT OF EXPLORATORY BIOMARKER(S)

This section refers to exploratory biomarkers.

Plasma derived protein biomarkers
The biomarkers described below are exploratory in nature and to be seen as hypothesis generating studies, which will be used to expand our understanding of the study drug. The analyses will be performed if considered clinically and/or scientifically justified at the time of the planned analysis. Participation in the biomarker test is mandatory.
Plasma biomarker studies will focus on exploring pharmacodynamic effects. In a screening assay circulating angiogenic factors such as but not limited to angiopoietin-2 (Ang2), sTie2, vascular endothelial growth factor A (VEGF A), sVEGFR1, sVEGFR2, sVEGFR3 and placenta growth factor (PLGF) will be analyzed in plasma (Appendix 10.5).
In addition to the screening assay mentioned above soluble targets such as free and/or total VEGF as well as free and/or total Ang2 will be examined in plasma samples.

Exploratory pharmacodynamic 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 analyte plasma concentrations, analyse data and prepare meaningful outputs. The final exploratory analysis will be performed after the cohort at MTD in the dose finding phase completed the first two treatment courses.

For the purpose of these exploratory analyses, PD plasma samples obtained up to at least 24 hours after drug administration will be used. In contrast to the final PK analysis, the exploratory 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 analyses, and the outputs will not be validated. Minor discrepancies between exploratory and final results may therefore occur.

Methods of sample collection
For circulating angiogenic biomarkers (Myriad panel) such as Ang2, sTie2, VEGF A, sVEGFR1, sVEGFR2, sVEGFR3 and PLGF 3 ml of blood will be taken from the forearm vein at those time points specified in the Flow chart and Appendix 10.4. For quantification of free/total VEGF and free/total Ang2 another 6 ml blood will be taken from the forearm vein

at those time points specified in the Flow chart and in Appendix 10.5.
Plasma samples for protein biomarkers need to be stored at ≤ -70 °C. Detailed instructions for sampling, handling, storage, and shipment of the biomarker samples will be provided in the ISF/lab manual. Date and time of sampling will be recorded in the eCRF.
Details about blood sample collection, plasma preparation, required tubes, labelling of tubes, storage and shipment (frequency and addresses) will be provided in the lab manual.
The samples will be stored for a maximum period of 15 years (under consideration of local legislation) after study termination.

Analytical determinations
Plasma biomarker analysis will be performed using immunoassays.

Additional assays may be added if new data suggests relevance to the study drug mechanism of action.

The analysis will be performed at Boehringer Ingelheim or a CRO with given authorization by BI.

5.5.1 Imaging Pharmacodynamic endpoints

Dynamic contrast-enhanced (DCE)-MRI described below is exploratory in nature and to be seen as hypothesis-generating evaluation, which will be used to expand understanding of mode of action of the study drug. The analyses will be used for the non-invasive quantification of microvascular structure and function properties (vascular permeability, vascular density, regional flow) in solid tumors and be performed in all dose groups to potentially allow for a PK/PD analysis. From the analysis of DCE-MRI data the parameters K_{trans} and $IAUC_{60}$ or more specifically their relative, intra-individual change from baseline after the first and the second treatment course are obtained as measures for treatment-induced changes in tumor vessel permeability and perfusion. Morphological changes (tumor volume, RECIST) can also be quantified from MRI data.

Methods of sample collection
DCE-MRI measurement will be done during the screening period, 1 week (C1V2) after first administration of BI 836880, after the 2nd treatment course (C3V1) and after the 4th treatment course (C5 V1) in absence of progressive disease.
During treatment period, DCE-MRI measurements will be done before study drug administration at the scheduled time points. If not possible then DCE-MRI can be performed one day earlier to the study drug administration.
In case patient stopped treatment for other reasons than progressive disease, DCE-MRI should still be conducted as long as patient is in Follow up period. Time points for 3rd and 4th imaging, depending on when patient stopped treatment, have to be adapted as 6 weeks and 12 weeks after 1st infusion. The exact time points for DCE-MRI have to be calculated according to Flow Chart and can be chosen to coincide with the radiological assessment in a scheduled follow-up visit.

With the objective to minimize methodological variability only patients with lesions considered suitable for DCE-MRI by a radiologist's assessment of the morphological MRI

data (preferably liver metastases > 2cm; other lesions may only be included after consultation with the sponsor) will be included in this evaluation. For certain tumor types suitable lesions will not be available and such patients will not be examined by DCE-MRI. For assessment of the morphological changes of lesions the following sequences are used: T1-weigthed multislice breath-hold FLASH and T2-weigthed multislice breath-hold TSE (Turbo Spin Echo). Slice orientation is preferably axial, other orthograde (but no tilted) orientations can be used when suitable. T_1 and T_2-scans are acquired at identical slice position, the same orientation and position is used for scans at subsequent time points.
DCE-MRI will be performed on a coronal slice through one or more representative lesions selected and identified by the responsible radiologist from the morphological scans. For DCE-MRI, a T1-weighted inversion recovery-gradient echo sequence is used, for which the patient will receive an intravenous bolus application of the gadolinium contrast agent. Detailed parameter settings are given in the MR-Protocol.

5.6 OTHER ASSESSMENTS

5.6.1 Demographic and medical history

Demographics (sex, birth date, race if allowed by the local law), current medical condition including relevant concomitant diagnosis will be collected during the screening visit. Concomitant therapies present at the study entry and /or during the study will be recorded in the eCRF.

Medical history as follows:

- Type of tumor
- Date of the first histological diagnosis (month and year may be sufficient)
- Primary tumor site
- Differentiation grade (not specified, undifferentiated, poorly differentiated, moderately differentiated
- Tumor stage according to the tumor
- Number of metastatic sites at study entry will be provided
- Previous surgeries an radiotherapy will be reported
- Previous administrated chemotherapy, tyrosine kinase inhibitors, vaccine-therapy, antibodies therapy, immune-therapy, and hormone-therapy including start and end dates (month and year may be sufficient)
- Previous neoadjuvant, adjuvant or palliative therapy
- The date of tumor progression after previous line (s) of therapy for advanced or metastatic disease
- The start and end dates (month and year may be sufficient) of those previous therapies as well the number of courses (when applicable)
- The best response obtained (complete response, partial response, stable disease, progressive disease, unknown
- The reason for leading to treatment discontinuation (completion, PD, AE)

5.6.2 Immunogenicity assessment

Methods of ADA sample collection

For the determination of anti-drug antibodies (ADA), approximately 3 mL of blood will be taken from a forearm vein in a K2 EDTA (ethylendiaminetetraacetic acid) anticoagulant blood drawing tube at those time points specified in the Flow Chart and in Appendix 10.4. EDTA plasma will be divided into duplicate aliquots into 2 mL cryovials and stored frozen at approximately -70°C or below at the investigator sites or logistics CRO until shipment on dry ice to the bioanalytical laboratory. The second aliquot will be shipped only after the acknowledgement of receipt of the first aliquot.

Details about sample collection, preparation, storage and shipment are described in the laboratory manual.

Analytical Determination of ADA in Human Plasma Samples

After receipt at the analytical laboratory, plasma samples will be stored at approximately -70°C or below until analysis. The presence of ADA to BI 836880 will be assessed via a tiered approach using a validated electrochemiluminescence assay (screening, confirmatory, and titration analysis as appropriate).

Analyses will be performed preferably at the analytical laboratory listed as follow or at another CRO with given authorisation by Boehringer Ingelheim.

- ICON Development Solutions
- Whitesboro, NY

The study samples will be discarded no later than 15 years after the final study report has been generated.

A detailed description of the assay will be available prior to the start of sample analysis in the validation report.

5.7 APPROPRIATENESS OF MEASUREMENTS

Determination of the MTD is based on the toxicities grade according to CTCAE version 4.03 (R12-2532). The CTCAE criteria are commonly used in the assessment of adverse events in cancer patients. RECIST version 1.1 criteria (R09-0262) are used for evaluation of tumor response. These criteria are well established and scientifically accepted.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

The study Flow Chart describes all assessments which will be performed in patients treated with BI 836880.
All patients must provide written informed consent before any study related screening procedures can be performed. Time windows for visits are included in the Flow Chart.

Patient will visit the clinic at the time points specified in the Flow Chart. If a visit is missed and the patient report to the Investigator between the missed visit and the next visit, the missed visit should be performed. The current date and the reason for delayed visit should be recorded in the source document. The next visit, however, should take place at the scheduled time after the first administration BI 836880.

To allow close monitoring for infusion-related reactions or other adverse events and availability of patients for PK visits at course 1, patients are required to be hospitalised under close surveillance with access to intensive care for at least 48 hours after the first administration of BI 836880 at course 1 day 1and 24 hours after the second and third administrations of BI 836880 at course 1 day 8 and course 1 day 15 respectively.
After good tolerability of the first course 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 courses.

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, PD and circulating biomarkers, 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 (including 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, ADA and circulating biomarkers are given in Sections 5.4 and 5.5.
DCE-MRI will only be performed in patients having suitable lesions. Details are described in Section 5.5.1.

After the interim data base lock, mandatory procedures/assessments and documentation in the eCRF will be adapted as described in the Flow Chart and the respective sections of this protocol.

6.2.1 Screening period

All Screening Visit procedures must be performed in the 21 days prior to the first administration of study medication except tumor assessments (CT/MRI) that may be used as screening exams if they were performed within 28 days prior to start of treatment.

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

Patients who meet the eligibility criteria will be allowed to take part to the study.
Refer to the Flow Chart for procedure details. Please review Sections 3.3.2 and 3.3.3 for specific eligibility criteria.

6.2.2 Treatment period(s)

All patients will receive continuous weekly treatment with BI 836880 until the criteria for stopping medication are met (see Section 3.3.4).
Treatment course is defined as 3-week treatment (21 days) in duration. During the treatment phase visits should be performed as scheduled wherever possible.

In the event of any study drug interruption or delay of treatment, the tumor assessment scheduled will not be changed.
After the interim data base lock, frequency of tumor assessment may be adapted according to local standard of care and in agreement with the sponsor if the patient is deriving clinical benefit (e.g. CR, PR or SD > 6 months).

During course 1, 2 and 4 intensive PK-sampling will be conducted and patients have to be observed closely for any adverse events. Additional visits are needed at day 2 for courses 1, 2 and 4. For course 3 and from course 5 onwards no additional visits, beside day 1 including drug administration, are requested by protocol.

Refer to the Flow Chart for procedure details.

6.2.3 Follow Up Period and Trial Completion

6.2.3.1 End of treatment visit

The EOT visit will be performed after permanent discontinuation of trial medication for any Reason, as soon as possible, but no later than 21 days 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 5.3.6.2. The End of the Residual period visit (EoR) should not be performed earlier than 42 days after permanent discontinuation of the study drug. 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 Follow-up period for progression

For patients who progress according to RECIST criteria V1.1, one Follow up visit (FU1) will be performed after the EOT (i.e. at EoR, 42 calendar days after discontinuation of trial drug).

For patient who discontinue not due to progressive disease according to RECIST criteria V1.1, additional FU visits will be performed at 6-week intervals plus/minus 3 days, until progression, start of another anticancer treatment, lost to follow up, death.
After the interim data base lock, frequency of tumor assessment may be adapted according to local standard of care and in agreement with the sponsor if the patient is deriving clinical benefit (e.g. CR, PR or SD > 6 months).
During extended Follow up period (i.e. after the end of treatment, including the REP and individual patient's end of trial), all related SAEs or AESIs and Follow up AEs on going since the end of treatment have to be collected and documented on the appropriate eCRF page and SAE form (if applicable).

Refer to Flow Chart for details.

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 (as defined in Section 6.2.3.3)
- Lost to follow-up
- Withdrawal to be followed-up
- Death

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

6.2.3.5 Trial completion

The clinical trial will be considered completed when the last patient has completed the EoR visit. If patients are still on treatment at the time of interim data base lock and the Clinical Trial Report is written, these patients will be maintained in the trial as long as they are deriving clinical benefit (i.e. no disease progression, no drug-related AEs requiring drug discontinuation) or no new anti-cancer treatment started and there are willing to continue. For these patients, no blood sample will be collected for PK/PD and biomarker analysis, only (S)AEs and limited efficacy data will be collected. After the discontinuation of these patients, additional data collected after data base lock will be reported in separate listings and will not

lead to any further update of tables generated 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 tumors. MTD is defined as the highest dose with less than 25% risk of the true DLT probability being above 33%,and 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 Bayesian 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 course at dose d, $d^* = 1250$mg 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 480mg would equal 20%. This yields $\mu_1 = (0.740, 0.798)$. 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 480mg would equal 50%. These assumptions yield $\mu_2 = (0.846, -0.123)$. 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 480mg would equal 2%. These assumptions yield $\mu_3 = (-2.731, 0.193)$, 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 to1 patient, 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	0.740, 0.798	2.000, 1.000	0.000
2: High Tox	0.050	0.846, -0.123	2.000, 1.000	0.000
3: Low Tox	0.050	-2.731, 0.193	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	0.842	0.054	0.104	0.091	0.206	<.001	0.001	0.819
120	0.759	0.076	0.165	0.139	0.249	<.001	0.009	0.897
240	0.673	0.096	0.231	0.193	0.282	<.001	0.036	0.935
480	0.523	0.131	0.346	0.284	0.318	<.001	0.138	0.964
960	0.262	0.143	0.595	0.471	0.332	0.002	0.458	0.984
1250	0.142	0.114	0.744	0.594	0.316	0.012	0.659	0.991

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

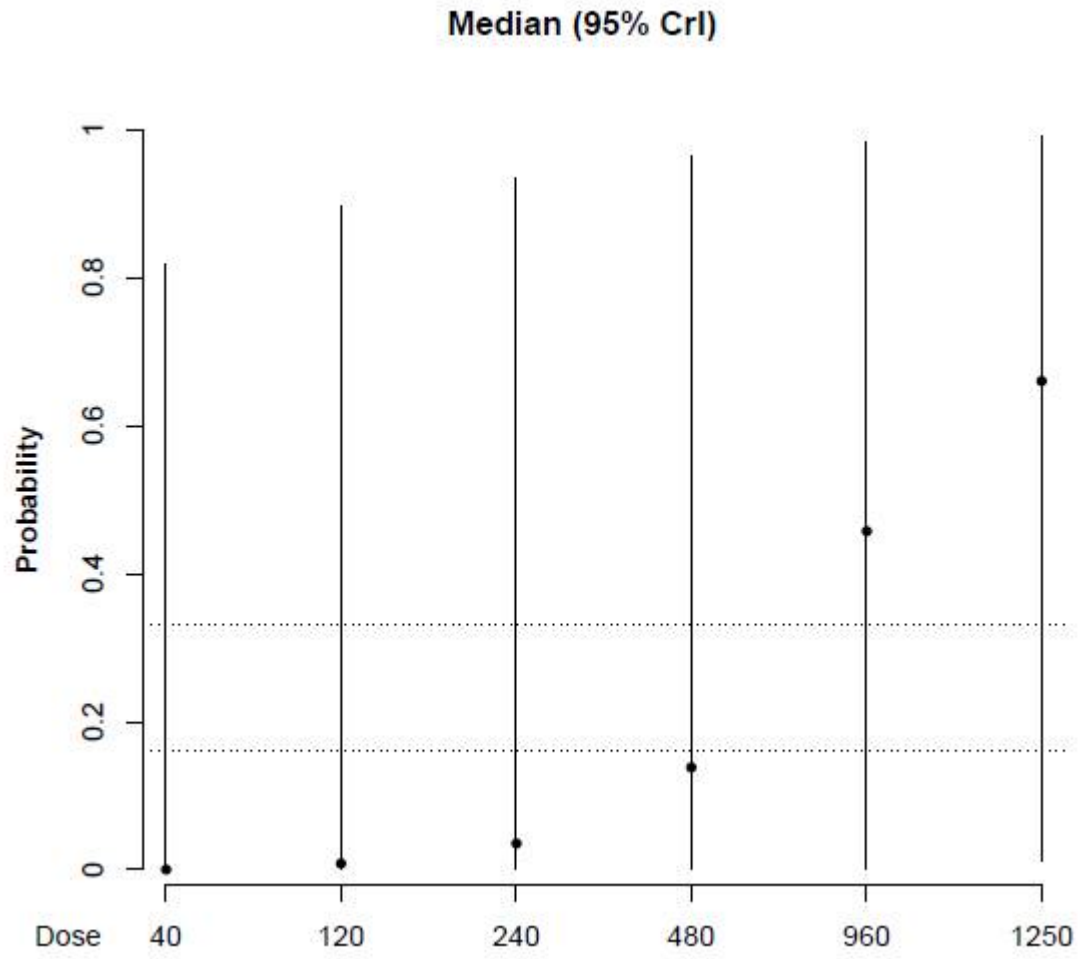

Figure 7.1: 1Prior medians and 95% credible intervals

The MTD may be considered reached if the following criteria are 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 course 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 endpoint.

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 course 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 courses 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. Events that started after 42 days since last administration of treatment will be considered as having occurred post-treatment and will be presented separately.

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 severity 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.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered ‘treatment-emergent’. The residual effect period is defined as 42 days after the last trial medication application. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’.

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).

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 and pharmacodynamic analyses

7.3.5.1 Phamacokinetic analyses

Refer to Section 5.5.1 for pharmacokinetic parameters to be calculated using non-compartmental analysis (NCA). The derivation of pharmacokinetic parameters is described in detail in the BI SOP 001-MCS-36-472.
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. WinNonlin Version 5.2. Only concentrations within the validated concentration range will be used for the calculation of pharmacokinetic parameters. For pre-dose samples, the actual sampling time will be set to zero.

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

The following descriptive statistics will be calculated for analyte concentrations as well as for all pharmacokinetic parameters: N, arithmetic mean, standard deviation, minimum, median,

maximum, 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.

Dose proportionality of BI 836880 will be assessed based on $C_{max,ss}$, $AUC_{\tau,ss}$ and C_{max}, $AUC_{0-\infty}$. The attainment of steady state will be explored by plotting trough concentrations (C_{pre}, $C_{pre,N}$) against time.

Assessment of dose proportionality:
Dose proportionality will be explored using the power model that describes the functional relationship between the dose and PK endpoints, C_{max}, $AUC_{0-\infty}$, $C_{max,ss}$, $AUC_{\tau,ss}$. The basic model consists of a regression model applied to log-transformed data. The corresponding ANCOVA model includes the logarithm of the dose as a covariate. Based on the estimate for the slope parameter β, a two sided 95% confidence interval for the slope will be computed. Perfect dose proportionality would correspond to a slope of 1. The assumption of a linear relationship between the log-transformed pharmacokinetic endpoint and the log-transformed dose will be checked.
If dose proportionality over the entire dose range investigated cannot be shown, an attempt will be made to identify dose range(s), where dose proportionality can be assumed. The model for dose proportionality analysis will be detailed in Trial Statistical Analysis Plan (TSAP).

Attainment of steady state:
The statistical model to explore the attainment of steady state using the trough concentrations described above for each dose level will be a repeated measures linear model on the logarithmic scale including 'subject' as a fixed effect and 'time' as a repeated effect. The corresponding model, if all dose levels are analysed simultaneously, will include the log-transformed 'dose' as a covariate. Both models allow modelling the covariance structure of the data. The structure of the covariance matrix generally is not known in advance and will therefore be determined on a data-driven basis. The strategy/criteria to determine the final structure will be described in the TSAP.
Subsequently, adjusted least square means and two sided 95% confidence intervals will be calculated and back transformed by exponentiation. Furthermore pairwise comparisons of the log-transformed differences between all subsequent time points ($\log(C_{pre,i}/C_{pre,j}) = \log(C_{pre,i}) - \log(C_{pre,j})$ where $j>i$) will be performed including the calculation of two sided 95% confidence intervals using t tests. Comparisons which reveal small p-values will be inspected to determine if the relevant differences between time points are resulting from not yet attaining steady state. In general, all dose levels will be analysed separately. If there is evidence that the patterns (or trend) of the trough concentration profiles are comparable across dose levels they will be analysed simultaneously if this is justified. Other analyses, such as regression over time may be considered as post-hoc analyses.

To support the analyses of dose proportionality, and attainment of steady state, graphical representations of the data might be created. These might include (but are not limited to) individual time-courses of trough plasma concentrations and the (geometric) mean plasma concentration time profiles.

7.3.5.2 Pharmacodynamic analyses

DCE-MRI
Modulation of vascular characteristics and size of suitable tumor lesions (preferably liver lesions) will be assessed by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) before and after treatment with BI 836880. All subjects who received at least two DCE-MRI measurements will be included in the analysis.
The temporal evolution of contrast medium-induced signal intensity within tumor lesions will be acquired quantitatively and be related to the vascular parameters, such as vascular permeability, vascular density, and regional vascular flow.
DCE-MRI images will be analyzed using software designed to allow for the visualization of dynamic enhancement parameters. Quantitative modelling of the tissue gadolinium concentration time curve using a multi-compartmental model will yield the parameters transfer constant (Ktrans) and IAUC60 (Initial Area Under Curve at 60 seconds) for each imaging time point. Time profiles of Ktrans and IAUC60 and their changes from baseline will be summarized by descriptive statistics and visualized by treatment group. Changes in Ktrans and IAUC60 values will be related to dose of BI 836880 and parameters of clinical efficacy. DCE-MRI parameters will be derived at University Medical Center Freiburg, Department of Radiology. Statistical analyses will be done at BI.

7.3.5.3 Biomarker analyses

The exploratory statistical analyses of the biomarker data will be performed separately and results will be covered in a separate 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 analysed), 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 7.3.4).

7.7 DETERMINATION OF SAMPLE SIZE

About 25-30 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).

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in accordance with the Medical Devices Directive (93/42/EEC) and the harmonized standards for Medical Devices (ISO 14155-01 and ISO 14155-02).

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), and relevant regulations.

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 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.

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

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

Electronic Case Report Forms (e)CRF for individual patients will be provided by the Sponsor. 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 reported on the eCRF must be consistent with the source data or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the trial; current medical records must also 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. 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 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal regulatory reporting obligation and in accordance to the requirements defined in this CTP.

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 last follow up visit as specified in Section 6.2.3.4
After the interim data base lock 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 will be notified about the end of the trial or early termination of the trial.

8.7 PROTOCOL VIOLATIONS

The investigator should document any deviation from the protocol regardless of their reasons. Only when the protocol was not followed in order to avoid an immediate hazard to trial subjects or for other medically compelling reason, the principal investigator should prepare and submit the records explaining the reasons thereof to the sponsor, and retain a copy of the records.

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10. APPENDICES

10.1 INSTRUCTIONS FOR USE

10.1.1 Instruction for Pharmacists

Refer to the 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 a 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 described 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 time points 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 and if scientifically reasonable, the following pharmacokinetic parameters of BI 836880 will be evaluated using non compartmental analysis methods according to the internal BI SOP 001-MCS-36-472.

After the first dose:

- C_{max} (maximum measured plasma concentration of BI 836880 in plasma).
- $AUC_{\tau,1}$ (area under the concentration-time curve of the analyte in plasma over a uniform dosing interval τ after administration of the first dose)
- $AUC_{0-\infty}$ (area under the plasma concentration-time curve of the analyte over the time interval from zero extrapolated to infinity).
- AUC_{0-tz} (area under the plasma concentration-time curve of the analyte over the time interval from 0 up to the last quantifiable data point).
- AUC_{0-168} (area under the plasma concentration-time curve over the time interval from 0 to 168 h).
- $\%AUCt_{z-\infty}$ (the percentage of the $AUC_{0-\infty}$ that is obtained by extrapolation)
- AUC_{t1-t2} (area under the concentration time curve of the analyte in plasma over the time interval t_1 to t_2)
- t_{max} (time from dosing to the maximum measured plasma concentration).
- λ_z (terminal rate constant in plasma)
- $t_{1/2}$ (terminal half-life).
- MRT_{inf} (mean residence time after intravenous infusion).
- CL (total clearance of the analyte in plasma).
- V_z (apparent volume of distribution during the terminal phase).
- V_{ss} (volume of distribution after intravenous infusion at steady state).

After repeated doses (steady state parameters will be calculated only, if steady state has been achieved):

- $C_{max,ss}$ (maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ)
- $C_{min,ss}$ (minimum concentration of the analyte in plasma at steady state over a uniform
- dosing interval τ)
- $t_{min,ss}$ (time to reach minimum plasma concentration during the dosing interval τ at steady state)
- C_{avg} (average concentration of the analyte in plasma at steady state)
- $C_{pre,ss}$ (predose concentration of the analyte in plasma at steady state immediately before administration of the next dose)
- $C_{pre,N}$ (The predose concentration immediately before administration of the Nth dose over the dosing interval τ is taken directly from the observed drug plasma concentration-time data)
- $AUC_{\tau,ss}$ (area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ)

- $AUC_{t1\text{-}t2,ss}$ (area under the concentration time curve of the analyte in plasma over the time interval t_1 to t_2 at steady state)
- $t_{max,ss}$ (time from last dosing to maximum concentration of the analyte in plasma at steady state)
- $\lambda_{z,ss}$ (terminal rate constant in plasma at steady state)
- $t_{1/2,ss}$ (terminal half-life of the analyte in plasma at steady state)
- $MRT_{inf,ss}$ (mean residence time of the analyte in the body after intravenous infusion at
- steady state)
- CL_{ss} (total clearance of the analyte in plasma at steady state)
- $V_{z,ss}$ (volume of distribution during the terminal phase after multiple intravascular administrations at steady)
- $V_{ss,ss}$ (volume of distribution after multiple intravascular administrations at steady state).
- RA, C_{max} (accumulation ratio based on C_{max})
- RA, AUC (accumulation ratio based on $AUC_{0\text{-}\tau}$)
- Linearity index
- PTF (Peak-Trough Fluctuation)

If deemed necessary, further appropriate pharmacokinetic parameters might be calculated. Pharmacokinetic parameters will be calculated using non compartmental analysis (NCA). The derivation of pharmacokinetic parameters is described in detail in BI SOP. Blood sampling time points for PK, ADA, biomarker and ECG recording in the phase I part of the study (dose escalation phase)

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

Table 10.4: 1 Blood sampling scheme for PK, ADA and biomarker in courses 1, 2, 3 and from course 4 onwards

Course	Visit	Day	Time Point (hh:min)	CRF Time / planned time	PK: BI 836880 ***	ADA***	Bio-marker: Myriad panel	Bio-marker: free/total VEGF-A/ Ang2	ECG	BP
1	V1	1	Before start of BI 836880 infusion	-0:05	x	x	x	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			x		
		2		24:00	x			x	x (3x)	x (3x)
		3		48:00	x		x	x		x (3x)
	V2	8	Before start of BI 836880 infusion	167:55	x			x	x (3)	x (3x)
			Start of BI 836880 infusion	168:00						
			Before end of infusion	169:30**					x(3)	x (3x)
			Immediately after the end of infusion*	169:30**	x					
	V3	15	Before start of BI 836880 infusion	335:55	x			x	x(3)	x (3x)
			Start of BI 836880 infusion	336:00						
			Before end of infusion	337:30**					x (3)	x (3x)
			Immediately after the end of infusion*	337:30**	x					

Table 10.4: 1(cont'd) Blood sampling scheme for PK, ADA and biomarker 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 ***	ADA***	Bio-marker: Myriad panel	Bio-marker: free/total VEGF-A/ Ang2	ECG	BP
2	V1	1	Before start of BI 836880 infusion	-0:05	x	x	x	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			x		
		2		24:00	x			x	x (3x)	x (3x)
	V2	8	Before start of BI 836880 infusion	167:55	x			x	x (3x)	x (3x)
			Start of BI 836880 infusion	168:00						
			Before end of infusion	169:30**					x (3x)	x (3x)
			Immediately after end of infusion*	169:30**	x					
	V3	15	Before start of BI 836880 infusion	335:55	x			x	x (3x)	x(3x)
			Start of BI 836880 infusion	336:00						
			Before end of infusion	337:30**					x (3x)	x (3x)
			Immediately after end of infusion*	337:30**	x					

Table 10.4: 1(cont'd) Blood sampling scheme for PK, ADA and biomarker 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 ***	ADA***	Bio-marker: Myriad panel	Bio-marker: free/total VEGF-A/ Ang2	ECG	BP
3	V1	1	Before start of BI 836880 infusion	-0:05	x	x		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					

Table 10.4: 1(cont'd) Blood sampling scheme for PK, ADA and biomarker 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 ***	ADA***	Bio-marker: Myriad panel	Bio-marker: free/total VEGF-A/ Ang2	ECG	BP
4	V1	1	Before start of BI 836880 infusion	-0:05	x	x	x	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			x		
		2		24:00	x			x	x(3x)	x(3x)
	V2	8	Before start of BI 836880 infusion	167:55	x			x	x (3x)	x (3x)
			Start of BI 836880 infusion	168:00						
			Before end of BI 836880 infusion	169:30**					x (3x)	x (3x)
			Immediately after end of infusion*	169:30**	x					
	V3	15	Before start of BI 836880 infusion	335:55	x			x	x (3x)	x (3x)
			Start of BI 836880 infusion	336:00						
			Before end of BI 836880 infusion	337:30**					x (3x)	x (3x)
			Immediately after end of infusion*	337:30**	x					

Table 10.4: 1(cont'd) Blood sampling scheme for PK, ADA and biomarker 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 ***	ADA***	Bio-marker: Myriad panel	Bio-marker: free/total VEGF-A/ Ang2	ECG	BP
5-12	V1	1	Before start of BI 836880 infusion	-0:05	x	x		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		x	x (3x)	x (3x)
EoR					x	x	x	x		x (3x)
FU1					x	x		x		

* within 5 min after the end of infusion
** Planned time point 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.
*** The last blood samples for PK, ADA and Biomarkers (myriad Ang Map Panel, free/total VEGF-A, Ang2) will be taken in this trial when the last patient has discontinued the trial treatment and performed the EoT visit.
After the interim data base lock (see Section 6.2.3.5), no blood samples will be collected for PK, ADA and biomarker analyses
**** 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, ADA as well as Biomarkers (Myriad panel and free/total VEGF-A/ Ang2)

10.5 TRIAL BIOMARKER PLAN

Time profiles of plasma derived protein biomarkers and their changes from baseline will be summarized by descriptive statistics and visualized by line plots per dose group to identify treatment related changes. The correlation between the biomarkers and potential associations to clinical endpoints, if applicable, will be investigated and visualized as well.

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 the 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 120 mg. 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.

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 480mg, either. However, the model does not allow the escalation to 960mg 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 480mg. 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. In scenario 8, no DLs are seen in the first three cohorts. Dose was escalated to 960mg after 6 patients were tested on 480mg without DLT. De-escalation occurred as a result of one out of the three patients treated on dose 960mg had DLT.

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	0.019	120	0.862	0.076	0.062
2	1	40	1	3	0.318	N/A	N/A	N/A	N/A
3	1 2	40 120	0 0	2 2	0.018	240	0.841	0.093	0.066
4	1 2	40 120	0 1	2 3	0.231	120	0.451	0.318	0.231
5	1 2	40 120	0 2	2 3	0.623	40	0.455	0.308	0.237
6	1 2 3 4	40 120 240 480	0 0 0 0	2 2 3 3	0.02	480	0.903	0.077	0.020
7	1	40	0	2					
	2	120	0	2					
	3	240	0	3					
	4	480	1	3	0.229	480	0.424	0.347	0.229
8	1	40	0	2					
	2	120	0	2					
	3	240	0	3					
	4	480	0	6					
	5	960	1	3	0.353	480	0.943	0.054	0.003

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	240	480	960	1250
1 (Prior)	P(DLT)	0.091	0.139	**0.193**	**0.284**	0.471	0.594
2 (High Tox)		0.100	**0.227**	0.351	0.500	0.649	0.700
3 (Low Tox)		0.001	0.007	0.022	**0.180**	**0.250**	0.350
4 (Non-Logistic)		0.040	0.100	**0.180**	**0.280**	0.360	0.380
5 (Low-High)		0.001	0.011	0.047	**0.181**	0.500	0.640

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	23.1	56.4	0.1	20.4	16.45 (3 – 34)	2.982 (1 – 10)
2	18.1	38.3	19.6	24.0	16.01 (3 – 36)	3.73 (1 – 11)
3	20.2	79.6	0.2	0	20.42 (17 – 38)	2.248 (1 – 6)
4	19.4	71.4	0.6	8.6	18.42 (3 – 35)	3.09 (1 – 10)
5	25.6	74.0	0.3	0	20.11 (16 – 40)	2.43 (1- 6)

In scenario 1, which reflects the case that the true dose-toxicity is aligned with prior medians, 56.4% of the simulated trials declared a dose as MTD with true DLT rate in the targeted dose range. Note that 20.4% 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 (24.0%) 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 16.0 patients (high-toxicity scenario) to 20.4 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		I
Date of CTP revision		24 Mar 2017
EudraCT number		2015-001132-38
BI Trial number		1336.6
BI Investigational Product(s)		BI 836880
Title of protocol		Phase I, non-randomized, open-label, multi-center dose escalation trial of BI 836880 administered by weekly repeated intravenous infusions in patients with advanced solid tumors.
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as		☐

changes involve logistical or administrative aspects only		
Section to be changed		Synopsis: total entered
Description of change		Approximately 40 patients **Was changed to:** Approximately 40 patients, 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 pharmacodynamic effect can be documented
Section to be changed		Synopsis
Description of change		• 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. patients do not tolerate or have contraindications to otherwise available **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. patients do not tolerate or have contraindications to otherwise available standard therapy and tumour lesions evaluable for Dynamic-enhanced (DCE)-MRI at MTD
Rationale for change		Change was implemented to make sure that a pharmacodynamic effect can be documented
Section to be changed		Flow chart: footnote #3; section 5.3.2
Description of change		Footnote #3 [3]Body Temperature: whenever possible the same method should be used for body temperature measurement in one patient. Acceptable methods could be: oral, rectal measurement with thermometer (digital, mercury, or other fluid). Not acceptable: infrared measurement in ear, forehead or temple. Body temperature > 38°C must be re assessed 1 hour after. Section 5.3.2 body temperature Whenever possible the same method should be used for body temperature measurement in one patient. All methods used should deliver valid reproducible results according to common clinical practice. Acceptable

		methods could be, but not limited to: oral, rectal measurement with thermometer (digital, mercury, or other fluid). Not acceptable/preferred methods include: infrared measurement in ear, forehead or temple. **Was changed to** Footnote #3 [3]Body Temperature: whenever possible the same method should be used for body temperature measurement in one patient. Body temperature ≥ 38°C must be re assessed 1 hour after. Section 5.3.2 body temperature Whenever possible the same method should be used for body temperature measurement in one patient. All methods used should deliver valid reproducible results according to common clinical practice.
Rationale for change		- To allow some flexibility to the sites to measure body temperature according to common clinical practice. -To be consistent with the wording (≥ 38°C) elsewhere in the protocol
Section to be changed		Footnote #5 and section #5.3.3
Description of change		Footnote #5 [5]Haematology, biochemistry and coagulation parameters will be performed locally. Previous safety lab: investigations are acceptable if performed within 72 hours prior to the screening visit. For details see Section 5.3.3 Section #5.3.3 Previous laboratory investigations performed within 72 hours prior to the screening visit are acceptable to confirm the eligibility at for the screening. **Was changed to** Footnote #5 [5]Haematology, biochemistry and coagulation parameters will be performed locally. Previous safety lab: investigations are acceptable if performed within 72 hours prior to the **first treatment administration**. For details see Section 5.3.3 Section #5.3.3 Previous laboratory investigations performed within 72 hours prior to the first treatment administration visit are acceptable to confirm the patient eligibility.
Rationale for change		To confirm patient eligibility before start of study treatment
Section to be changed		3.1
Description of change		Was added: Once a MTD has been reached, a minimum of 12 patients must have tumour lesions evaluable for Dynamic contrast-enhanced (DCE)-MRI to allow a better interpretation of pharmacodynamics (vascular) effect of BI 836880

Rationale for change		Change was implemented to make sure that a pharmacodynamic effect can be documented
Section to be changed		3.1.1
Description of change		Members of the DSB will be investigators of participating trial sites, Trial Statistician (TSTAT), Clinical Program Leader (CPL) and Trial Clinical Monitor (TCM). **Was changed to:** Members of the DSB will be investigators of participating trial sites, Trial Statistician (TSTAT), Clinical Program Leader (CPL), Trial Clinical Monitor (TCM) and BI Lead Risk Management Physician
Rationale for change		Addition of one Data Safety Board member that was omitted in the previous version of the protocol
Section to be changed		3.3.2
Description of change		Histologically 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 patients do not tolerate or have contraindications to otherwise available standard therapy Was changed to: Histologically 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 patients 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 pharmacodynamic effect can be documented
Section to be changed		3.3.2
Description of change		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).

<table>
<tr><td></td><td></td><td></td></tr>
<tr><td>Rationale for change</td><td></td><td>Tubal ligation is no longer considered a highly effective method of contraception and no longer a method of permanent sterilisation</td></tr>
<tr><td>Section to be changed</td><td></td><td>Section 4.1.2</td></tr>
<tr><td>Description of change</td><td></td><td>Was added:
“..For medication number allocation at each visit it’s possible to conduct IRT call ahead of the planned visit (= day of administration)..”</td></tr>
<tr><td>Rationale for change</td><td></td><td>Clarification for logistical reasons</td></tr>
<tr><td>Section to be changed</td><td></td><td>Table 4.1.3:1</td></tr>
<tr><td>Description of change</td><td></td><td>
<table>
<tr><td>Dose level</td><td>Total dose (mg)</td><td>Approximate increment to next dose</td></tr>
<tr><td>Dose level 1
(starting dose)</td><td>40</td><td>3x (200%)</td></tr>
<tr><td>Dose level 2</td><td>120</td><td>2x (100%)</td></tr>
<tr><td>Dose level 3</td><td>240</td><td>2x (100%)</td></tr>
<tr><td>Dose level 4</td><td>480</td><td>1.5x (50%)</td></tr>
<tr><td>Dose level 5</td><td>720</td><td>1.3x (30%)</td></tr>
<tr><td>Dose level 6</td><td>960</td><td>1.7x (30%)</td></tr>
<tr><td>Dose level 7</td><td>1440 limited to 1250*</td><td></td></tr>
</table>
Intermediate dose level of “720 mg” was added and potential dose levels were adapted</td></tr>
<tr><td>Rationale for change</td><td></td><td>Intermediate dose level of “720 mg” was added in the table as requested by the Spanish authority during the approval process</td></tr>
<tr><td>Section to be changed</td><td></td><td>4.1.3</td></tr>
<tr><td>Description of change</td><td></td><td>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, sampling for ADA as well as sampling for biomarkers (Myriad panel and free/total VEGF-A/ Ang2) will be conducted (see flow chart and Appendix 10.4) and patients have</td></tr>
</table>

		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 course 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 course with the escalated dose
Section to be changed		5.2
Description of change		Was added: Results of tumor-specific tumor markers which will be assessed routinely should be documented in the eCRF
Rationale for change		To better assess tumour response in tumors for which tumour marker testing is performed routinely
Section to be changed		5.5
Description of change		Additional assays may be added if new data suggests relevance to the study drug mechanism of action. Furthermore, the collected samples may be used for testing of other disease related biomarkers that may be of scientific interest for understanding mechanisms of the disease (i.e. cancer) after initiation/completion of this trial Was changed to Additional assays may be added if new data suggests relevance to the study drug mechanism of action.
Rationale for change		For clarification, deletion of the sentence suggesting unspecified investigations to be done, also to comply with Spanish authority request during approval process
Section to be changed		5.6.2
Description of change		Was removed: After completion of the study the plasma samples may be used for further ADA characterization or methodological investigations, e.g., for stability testing or isotyping. Any additional characterization data will be reported separately
Rationale for change		For clarification, deletion of the sentence suggesting unspecified investigations to be done, also to comply with Spanish authority request during approval process
Section to be		6.1

changed

Description of change

To allow close monitoring for infusion-related reactions or other adverse events and availability of patients for PK visits, after administration of BI 836880, patients are required to be hospitalised under close surveillance with access to intensive care for at least 48 hours and 24 hours after the first and the second administration of BI 836880, respectively.

Was changed to

To allow close monitoring for infusion-related reactions or other adverse events and availability of patients for PK visits at course 1, patients are required to be hospitalised under close surveillance with access to intensive care for at least 48 hours after the first administration of BI 836880 at course 1 day 1 and 24 hours after the second and third administrations of BI 836880 at course 1 day 8 and course 1 day 15 respectively.

Rationale for change

To clarify patient monitoring during first course

Section to be changed

Table 10.4

Description of change

Blood sampling scheme for PK, ADA and biomarkers

Course	Visit	Day	Time Point (hh:min)	CRF Time / planned time	PK: BI 836880***	ADA***	Bio-marker: Myriad panel	Bio-marker: free/total VEGF-A/ Ang2	ECG	BP
1	V1	3		48:00	x		x	x		x (3x)
	V3	15	Before end of infusion	337:30**					x (3)	x (3x)
			Immediately after the end of infusion*	337:30**	x					

Correction of typo errors at time points C1V1; C1V3

Course	Visit	Day	Time Point (hh:min)	CRF Time / planned time	PK: BI 836880***	ADA***	Bio-marker: Myriad panel	Bio-marker: free/total VEGF-A/ Ang2	ECG	BP
2	V2	8	Before start of BI 836880 infusion	167:55	x			x	x (3x)	x (3x)
			Immediately after end of infusion*	169:30**	x					
	V3	15	Before start of BI 836880 infusion	335:55	x			x	x (3x)	x (3x)

				Start of BI 836880 infusion	336:00						
				Before end of infusion	337:30**					x (3x)	x (3x)
				Immediately after end of infusion*	337:30**	x					

Correction of typo errors at C2V2; and PK time point was added at C2V3 (337:30)

Course	Visit	Day	Time Point (hh:min)	CRF Time / planned time	PK: BI 836880***	ADA***	Bio-marker: Myriad panel	Bio-marker: free/total VEGF-A/ Ang2	ECG	BP
4	V1	2		24:00	x			x	x (3x)	x(3x)
	V3	15	Immediately after end of infusion*	337:30**	x					

One PK time point was added at C4V3, ECG and BP time points were added at C4V1D2

Rationale for change		Corrections of typo errors and PK, ECG and BP time points were added as they were omitted in error in the previous version of the protocol
Section to be changed		Table 10.4 appendices
Description of change		The following footnote was added: In case of an intra-patient dose escalation the 1st course with the higher dose will follow course one at the start of treatment with BI 836880 with regards to sampling PK, ADA as well as Biomarkers (Myriad panel and free/total VEGF-A/ Ang2)
Rationale for change		To provide guidance for patients with an intra-patient dose escalation with regards to assessments to be done within first course with escalated dose

Number of global amendment		2
Date of CTP revision		28 Sep 2017
EudraCT number		2015-001132-38
BI Trial number		1336.6
BI Investigational Product(s)		BI 836880
Title of protocol		Phase I, non-randomized, open-label, multi-center dose escalation trial of BI 836880 administered by weekly repeated intravenous infusions in patients with advanced solid tumors.
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		5.5.1 Imaging Pharmacodynamic endpoints
Description of change		**Methods of sample collection** …..DCE-MRI will be performed on a coronal slice through one or more representative lesions selected and identified by the responsible radiologist from the morphological scans. For DCE-MRI, a T1-weighted inversion recovery-gradient echo sequence is used, for which the patient will receive an intravenous bolus application of the gadolinium contrast agent **Multihance®.** Detailed parameter settings are given in the MR-Protocol. **Was changed to :**

		Methods of sample collection ….DCE-MRI will be performed on a coronal slice through one or more representative lesions selected and identified by the responsible radiologist from the morphological scans. For DCE-MRI, a T1-weighted inversion recovery-gradient echo sequence is used, for which the patient will receive an intravenous bolus application of the gadolinium contrast agent. Detailed parameter settings are given in the MR-Protocol.
Rationale for change		A risk of brain deposits with repeated use of gadolinium-based contrast agents for magnetic resonance imaging (MRI) like **Multihance** previously recommend within this protocol has been reported and radiologists therefore prefer the use of gadolinium-based contrast agents for which this risk has not been reported.
Section to be changed		Section 4.1.3 table 4.1.3:1 potential dose level
Description of change		Was added: dose level of 180 mg
Rationale for change		This intermediate dose level was tested based on Data Safety Board decision

Number of global amendment		3
Date of CTP revision		13 Mar 2019
EudraCT number		2015-001132-38
BI Trial number		1336.6
BI Investigational Product(s)		BI 836880
Title of protocol		Phase I, non-randomized, open-label, multi-center dose escalation trial of BI 836880 administered by weekly repeated intravenous infusions in patients with advanced solid tumors.
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority		☐

approval as changes involve logistical or administrative aspects only		
Section to be changed		• Title page • Abbreviation • Section 3.1.1- administration of the trial
Description of change		Trial Clinical Monitor (TCM) was changed to Clinical Trial Leader (CTL) and Clinical Monitor Local (CML) was changed to Clinical Trial Manager (CTM)
Rationale for change		Administrative changes
Section to be changed		Synopis- methodology
Description of change		Non randomized, uncontrolled, open-label, dose escalation followed by an expansion cohort **Was changed to** Non randomized, uncontrolled, open-label, dose escalation
Rational for change		Expansion cohort is no longer planned for this trial
Section to be changed		Synopsis- N° of patients
Description of change		Approximately 50 patients to be enrolled **Was changed to** Approximately 40 patients to be enrolled
Rational for change		To adapt the sample size since expansion cohort is no longer planned for this trial
Section to be changed		Synopis
Description of change		Approximately 40 patients, including at least 12 patients treated at MTD with tumour lesions evaluable for Dynamic contrast-enhanced (DCE)-MRI. 40 patients will receive study treatment **Was changed to** Approximately 25 patients. Approximately 25 patients will receive study treatment
Rationale for change		It is no longer required to enroll 12 patients with DCE-MRI to be treated at MTD, and to adapt the sample size since expansion cohort is no longer planned for this trial
Section to be changed		Flow chart
Description of change		Change s have been made in the following footnotes and sections: Footnote numbers and sections in the protocol: **: no additional follow up visits required after the interim data base lock - 2: change to frequency of physical examination and ECOG Performance

		- 3: change to frequency of body temperature, following the interim data base lock (refer to section 5.3.2) - 4: change to frequency of blood pressure, following the interim data base lock (refer to section 5.3.2) - 5: change to frequency of laboratory tests, following the interim data base lock (refer to section 5.3.3) - 6: change to frequency of tumor assessment, following the interim data base lock - 7: change to frequency and assessment of ECG and no requirement to send ECGs to central vendor, following the interim data base lock (refer to section 5.3.4) - 8: clarification about echocardiography data entry in the eCRF (refer to section 5.3.4) - 9: no blood samples for PK analysis will be taken following the interim data base lock (refer to appendix 10.4) - 10: no blood samples for ADA analysis will be taken following the interim data base lock (refer to appendix 10.4) - 11; 12: no blood samples for biomarker analysis will be taken following the interim data base lock (refer to appendix 10.4) -14: DCE-MRI measurement is no longer mandatory following the interim data base lock
Rationale for change		At the time of interim data base lock, sufficient data will have been collected for PK, ADA and biomarker analyses, therefore no longer required. Also to provide more flexibility to trial procedures
Section to be changed		Section 3.1 overall trial design and plan
Description of change		**Was deleted:** Once a MTD has been reached, a minimum of 12 patients must have tumour lesions evaluable for Dynamic contrast-enhanced (DCE)-MRI to allow a better interpretation of pharmacodynamics (vascular) effect of BI 836880. Once the RP2D has been determined and in case of anti-tumor activity signals is reported in given tumor type(s), DSB can take the decision for a trial expansion to recruit patients with the same tumor type(s) with the aim to generate safety and preliminary efficacy data specific to such disease. Approximately 10-15 additional patients will be treated in the expansion cohort, sample size will be re evaluated when the expansion cohort is open.
Rationale for change		-Since the Prof of Pharmacological Principal (PoPP) has been determined with the sister trial 1336.1 (3-weekly dosing), enrollment of 12 patients with DCE-MRI in this trial is no longer mandatory. -To reflect the fact that expansion cohort is no longer planned for this trial

Section to be changed		Section 3.1 overall trial design and plan
Description of change		Was added: **After the interim data base lock, the study is considered completed when the last patient in the study has discontinued the study treatment and completed the EoR visit (see Section 6.2.3.5).**
Rationale for change		Clarification on the definition of trial completion after the interim data base lock
Section to be changed		Section 3.3 selection of trial population
Description of change		It is estimated that approximately 50 patients will be enrolled at 2 study sites. The rate of enrolled patients may vary by study site, but it is expected to be approximately 25 patients per site. Among them 40 patients will be enrolled and treated in this trial. **Was changed to** It is estimated that approximately 40 patients will be enrolled at 2 study sites. The rate of enrolled patients may vary by study site, but it is expected to be approximately 20 patients per site. Among them approximately 25 patients will be treated in this trial.
Rationale for change		To adapt the sample size since expansion cohort is no longer planned for this trial
Section to be changed		Section 4.1.3 table 4.1.3:1 potential dose level
Description of change		Was added: dose level of 150 mg
Rationale for change		This intermediate dose level was tested based on Data Safety Board decision
Section to be changed		5.2 assessment of efficacy
Description of change		Was added: **After the interim data base lock, frequency of tumor assessment may be adapted according to local standard of care and in agreement with the sponsor if the patient is deriving clinical benefit (e.g. CR, PR or SD > 6 months).**
Rationale for change		To reduce imaging assessment frequency
Section to be changed		5.2 assessment of efficacy
Description of change		Was added: **After the interim data base lock, collection of tumor markers in the e-CRF is no longer required**.
Rationale for change		Following data the interim data base lock there is no longer requirement to enter tumor maker data in e-CRF
Section to be changed		Abbreviation and section 5.3.6.1 Definition of AEs
Description of change		Remote Data Capture **(**RDC**)** was changed to **Electronic Data Capture (eDC)**
Rationale for change		Administrative

Section to be changed		6.2 - Details of trial procedures at selected visits
Description of change		**Was added**: **After the interim data base lock, mandatory procedures/assessments and documentation in the eCRF will be adapted as described in the flow chart and the respective sections of this protocol**
Rationale for change		To reflect the changes to trial procedures/assessments following the interim data base lock
Section to be changed		6.2.2 treatment period(s) 6.2.3.3 Follow-up period for progression
Description of change		Was added: **After the interim data base lock, frequency of tumor assessment may be adapted according to local standard of care and in agreement with the sponsor if the patient is deriving clinical benefit (e.g. CR, PR or SD > 6 months).**
Rationale for change		To reduce imaging assessment frequency
Section to be changed		Section 6.2.3.5 trial completion
Description of change		**Section 6.2.3.5 was added:** **The clinical trial will be considered completed when the last patient has completed the EoR visit.** **If patients are still on treatment at the time of interim data base lock and the Clinical Trial Report is written, these patients will be maintained in the trial as long as they are deriving clinical benefit (i.e. no disease progression, no drug-related AEs requiring drug discontinuation) or no new anti-cancer treatment started and there are willing to continue. For these patients, no blood sample will be collected for PK/PD and biomarker analysis, only (S)AEs and limited efficacy data will be collected.** **After the discontinuation of these patients, additional data collected after interim data base lock will be reported in separate listings and will not lead to any further update of tables generated for section 15 of the CTR unless deemed necessary.** **These listings will be included in a revised CTR.**
Rationale for change		Clarification for the definition of trial completion following the interim data base lock
Section to be changed		Section 7.7 determination of sample size
Description of change		**Was deleted** Additional 10-15 patients will be included in the expansion cohorts, in case one or more tumor types will be selected for further evaluation. Sample size will be reevaluated when the expansion cohort is open.

Rationale for change		Expansion cohort is no longer planned for this trial
Section to be changed		8.6 End of Trial
Description of change		The trial will end when the last patient has completed the last follow up visit as specified in Section 6.2.3.4 **Was changed to:** **After the interim data base lock 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**
Rationale for change		Clarification for the definition of end of trial, following the interim data base lock

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader		13 Mar 2019 16:46 CET
Approval-Therapeutic Area		13 Mar 2019 17:48 CET
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Approval-Clinical Program		14 Mar 2019 11:29 CET
Author-Trial Statistician		15 Mar 2019 14:16 CET
Verification-Paper Signature Completion		18 Mar 2019 09:37 CET

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Meaning of Signature	Signed by	Date Signed