CLINICAL TRIAL PROTOCOL

	Document Number:	**c25769893-03**
BI Trial No.	1336-0012	
BI Investigational Medicinal Product(s)	BI 836880 BI 754091	
Title	An open label, Phase I study of BI 836880 monotherapy and combination therapy of BI 836880 and BI 754091 in Japanese patients with advanced solid tumours	
Lay Title	A study to find the best dose of BI 836880 alone and in combination with BI 754091 in Japanese patients with different types of advanced cancer	
Clinical Phase	I	
Clinical Trial Leader	[redacted] Telephone: [redacted], Fax: [redacted]	
Coordinating Investigator	[redacted] Telephone: [redacted]	
Status	Final Protocol / Revised Protocol (based on global amendment 2)	
Version and Date	**Version: 3.0**	**Date: 21 Aug 2019**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	20 Dec 2018
Revision date	21 Aug 2019
BI trial number	1336-0012
Title of trial	An open label, Phase I study of BI 836880 monotherapy and combination therapy of BI 836880 and BI 754091 in Japanese patients with advanced solid tumours
Coordinating Investigator	[redacted] Telephone: [redacted]
Trial site(s)	Multi-centre trial conducted in Japan
Clinical phase	I
Trial rationale	The trial is required to define the maximum tolerated dose (MTD) and/or the recommended phase 2 dose (RP2D) of the BI 836880 monotherapy and combination therapy of BI 836880 and BI 754091 in Japanese patients to conduct the later phase clinical development in Asian populations.
Trial objective(s)	The main objectives of the trial are to investigate the following in patients with advanced solid tumours: • MTD and/or RP2D of BI 836880 monotherapy and the combination therapy of BI 836880 and BI 754091. • Safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (Pd) of BI 836880 monotherapy. • Safety, tolerability, PK and Pd of combination therapy of BI 836880 and BI 754091.
Trial endpoints	Part I (monotherapy part) Primary: - Maximum tolerated dose (MTD). - Number of patients with DLTs in the MTD evaluation period. Secondary: - PK parameters of BI 836880: C_{max} and area under the curve $(AUC)_{0\text{-}504h}$ Part II (combination therapy part) Primary: - Maximum tolerated dose (MTD). - Number of patients with DLTs in the MTD evaluation period.

	Secondary: - PK parameters of BI 836880 and of BI 754091: C_{max} and AUC_{0-504h}
Trial design	Open label, uncontrolled, non-randomised, dose-escalation design
Total number of patients treated	Approximately 24
Number of patients on each treatment	Approximately 24
Diagnosis	Patients with a confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumours
Main in- and exclusion criteria	Main inclusion criteria: • Patients with a confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumours (any type) • Patients with no therapy of proven efficacy, or who are not amenable to standard therapies • Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 • Adequate organ function defined with laboratory values Main exclusion criteria: • Known hypersensitivity to the trial drugs or their excipients • Known HIV, HBV, or HCV infection • History of severe hypersensitivity reactions to other mAbs • Significant cardiovascular/cerebrovascular diseases, or uncontrolled hypertension • History of severe haemorrhagic or thromboembolic events in the past 12 months • Patients who require full-dose anticoagulation • Untreated brain metastasis(es) that may be considered active • Haematological malignancies • History (including current) of interstitial lung disease or pneumonitis within the last 5 years • Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of trial medication
Test product(s)	BI 836880 BI 754091 (Part 2 only)
dose	**Part 1**: BI 836880: starting dose 360 mg every three weeks **Part 2**: BI 836880: starting dose 120 mg every three weeks BI 754091: starting dose 240 mg every three weeks The starting dose of BI 836880 may be adapted via protocol amendment based on the most recent safety information from another ongoing trial, 1336-0011.
mode of administration	Intravenous infusion

Comparator product(s)	Not applicable
dose	Not applicable
mode of administration	Not applicable
Duration of treatment	Administration will continue until progressive disease (PD), unacceptable toxicity, or other withdrawal criteria.
Statistical methods	**Part 1:** Dose escalation will be guided by Bayesian Logistic Regression Models (BLRMs) with overdose control that will be fitted to binary toxicity outcomes. The estimate of parameters will be updated as data are accumulated using BLRM. At the end of dose escalation, the toxicity probability at each dose (mono) level will be calculated to guide an estimate of the MTD and/or RP2D of BI 836880. **Part 2:** Dose escalation will be guided by Bayesian Logistic Regression Models (BLRMs) with overdose control that will be fitted to binary toxicity outcomes. The estimate of parameters will be updated as data are accumulated using BLRM. At the end of dose escalation, the toxicity probability at each dose (combination) level will be calculated to guide an estimate of the MTD and/or RP2D of the combination of BI 836880 plus BI 754091.

FLOW CHART

		Treatment Period[a] Cycle = 21 Days						Post-Treatment Period	
	Screening	Cycles 1, 2, 3, and 4[l]					Cycle 5 onwards	End-of-Treatment[j] (EoT) Visit	Safety follow-up Visit
Visit		**1[k]**	**2a**	**2b (C1,2 only)**	**3**	**4**	**1[k]**		
Day; visit window [days]	**-14 to -1 unless otherwise specified**	**1[k]**	**2**	**3; (+1d)**	**8; (-1/+2d)**	**15; (-1/+2d)**	**1[k]**	**Within 7 days of discontinuation**	**Last admin +42d (+3d)**
Informed consent / IRT call	X (-28 to -1)								
Inclusion/Exclusion criteria	X								
Medical history and Demographics	X								
Physical Examination	X	X					X	X	X
ECOG performance status	X	X					X	X	
Blood pressure, pulse rate, SpO_2[c]	X	X	X	X	X	X	X	X	X
Body temperature[c]	X	X			X (C1,2)		X	X	
12-lead ECG	X	X	X (C1,2)				X	X	
Echocardiography[d]	X (-7 to -1)							X	
General safety laboratory parameters[b]	X (-10 to -1)	X		X	X	X	X	X	
Pregnancy Test for Women of Child-Bearing Potential[b, f]	X	X					X	X	
Chest X-ray[b]	X	X[m]					X[m]	X	
Concomitant therapy	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X

		Treatment Period[a] Cycle = 21 Days						**Post-Treatment Period**	
	Screening	**Cycles 1, 2, 3, and 4[l]**					**Cycle 5 onwards**	**End-of-Treatment[j] (EoT) Visit**	**Safety follow-up Visit**
Visit		**1[k]**	**2a**	**2b (C1,2 only)**	**3**	**4**	**1[k]**		
Day; visit window [days]	**-14 to -1 unless otherwise specified**	**1[k]**	**2**	**3; (+1d)**	**8; (-1/+2d)**	**15; (-1/+2d)**	**1[k]**	**Within 7 days of discontinuation**	**Last admin +42d (+3d)**
Tumour assessment[e]	X (-28 to -1)	Every 6 weeks ±3 days for 6 months (then every 9 weeks ±3 days thereafter)							
Study drug administration		X					X		
Pharmacokinetics[g]		X	X (C1-4 for Part I, C1 and 4 for Part II)	X (Part I)	X (C1,2,4 for Part I, C1 and 4 for Part II)	X (C1,2,4 for Part I, C1 and 4 for Part II)	X (C5-12)	X	X

[redacted]

a All cycles are 3 weeks (21 days) in duration. Patients will continue treatment with the study drugs until progressive disease (PD) by RECIST and/or iRECIST (see Section 5.1.1), withdrawal of patient consent, or occurrence of unacceptable toxicity, whichever occurs first. Day 1 of Cycle 1 is defined as the day when the study medication is first administered.

b Safety laboratory assessments including haematology, clinical biochemistry, and urinalysis will be performed locally. If screening laboratory assessments, pregnancy testing, and chest X-ray are performed within 3 days before initiation of treatment, they do not need to be repeated on Cycle 1 Day 1. Refer to Section 5.2 for additional details.

c Vital signs include systolic and diastolic blood pressure, pulse rate, arterial oxygen saturation (SpO_2), and body temperature. Details including the timing of assessment of blood pressure and pulse rate are provided in Section 5.2.3.

d Echocardiography should be performed at screening and EoT visits. During the treatment period, echocardiography should be performed if clinically indicated.

e Screening tumour assessments (scans) should be performed ≤28 days prior to initiation of treatment. Scans obtained prior to study participation can be used for the study as long as they are not older than 28 days at the day of first treatment. Tumour assessments should be done according to RECIST v1.1 and iRECIST and should include computed tomography/positron emission tomography (CT/PET) scans of the chest and abdomen and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g., pelvis, brain) using an appropriate method (CT/PET scan or magnetic resonance imaging [MRI]). The same radiographic procedure must be used throughout the trial. In case of suspected (but not confirmed) bone metastasis at screening, tumour assessment at screening should include a bone scan. If bone lesions are already known or confirmed at screening, correlative imaging (X-ray or CT scan) should be performed. Correlative imaging should then be repeated at each tumour assessment. Assessments will be performed by the Investigator at screening and every 2 cycles (meaning every 6 weeks ±3 days if there are no delays in cycles but as close as possible to the end of the second of the 2 cycles of treatment if there was a delay) for the first 6 months of treatment, once every 3 cycles (meaning every 9 weeks ±3 days if there are no delays in cycles but as close as possible to the end of the third of the 3 cycles of treatment if there was a delay), and at the discretion of the Investigator and copies will be collected by the sponsor or designee.

f Women of child-bearing potential must have a serum beta human chorionic gonadotropin (βHCG) pregnancy test at screening. Thereafter, this test can be done in either serum or urine on Day 1 of each cycle, and at the EoT visit (see Section 5.2.4.5).

g The detailed blood sampling time points for pharmacokinetics (PK), [redacted] are provided in Appendix 10.4.

[redacted]

j If the decision to permanently discontinue the study treatment is made during a scheduled visit, the EoT visit should be performed instead of the scheduled visit assessments. In the combination treatment part (Part II), both BI 836880 and BI 754091 should be discontinued together if necessary.

k Before initiating a new treatment cycle, the criteria to administer the study drug(s) should be checked (see Section 4.1.6)

l Patients are required to be hospitalized under close surveillance with access to intensive care for at least 48 hours after the first administration of trial medication(s). Based on an individual risk assessment by investigator, the duration of surveillance may be shorten to 8 hours for cycles 2, 3, and 4, and at investigator's discretion for further cycles (see Section 6.1).

m Chest X-ray is to be performed at Day 1 of every treatment cycle. Except for cycle 1, the chest X-ray examination for each cycle may be omitted if a chest CT scan is performed within 7 days prior to the drug administration on Day 1 for that cycle.

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ABBREVIATIONS

ADA	Anti-Drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original, and Accurate
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
Ang2	Angiopoietin-2
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area under the Curve
BI	Boehringer Ingelheim
BLRM	Bayesian Logistics Regression Model
BUN	Blood Urea Nitrogen
CA	Competent Authority
CKD-EPI	Chronic Kidney Disease Epidemiology
C_{max}	Maximum Concentration
CRA	Clinical Research Associate
CK	Creatine Kinase
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CR	Complete Response
CRO	Contract Research Organisation
CTCAE	Common Terminology Criteria for Adverse Events
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical Trial Protocol
DCE-MRI	Dynamic Contrast-Enhanced Magnetic Resonance Imaging
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
EoT	End of Treatment
EWOC	Escalation With Overdose Control
FDA	(United States) Food and Drug Administration
FGF	Fibroblast Growth Factor
GCP	Good Clinical Practice
GEP	Gene-Expression Profile
GMP	Good Manufacturing Practice
HBc	Hepatitis B core
HBs	Hepatitis B surface
HBV	Hepatitis B Virus
HIV	Human Immunodeficiency Virus
irAE	Immune related Adverse Event
i.v.	intravenous
IB	Investigator's Brochure
ICH	International Council on Harmonisation
[redacted]	
IEC	Independent Ethics Committee
INR	International Normalised Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
[redacted]	
LDH	Lactate Dehydrogenase
LMWH	Low Molecular Weight Heparin
LPLT	Last Patient Last Treatment
LVEF	Left Ventricular Ejection Fraction
mAb	Monoclonal Antibody
MAP	Meta-Analytic Predictive
MedDRA	Medical Dictionary for Drug Regulatory Activities

MDSC	Myelo-derived suppressor cell
MRI	Magnetic Resonance Imaging
MSI	Microsatellite Instability
MTD	Maximum Tolerated Dose
NK	Natural Killer
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
NSCLC	Non-Small Cell Lung Cancer
NYHA	New York Heart Association
OPU	Operative Unit
OR	Objective Response
p.o.	per os (oral)
Pd	Pharmacodynamics
PD	Progressive disease
PD-1	Programmed-cell-death-protein-1
PD-L1	Programmed-cell-death ligand-1
PD-L2	Programmed-cell-death ligand-2
PK	Pharmacokinetics
PR	Partial Response
PT	Prothrombin Time
QTcF	Corrected QT interval by Fredericia
RECIST	Response Evaluation Criteria In Solid Tumours
REP	Residual Effect Period
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SD	Stable Disease
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
SpO_2	Arterial oxygen saturation
SUSAR	Suspected Unexpected Serious Adverse Reactions
$t_{1/2}$	Half Life Time
t_{max}	Timepoint of Maximum Plasma Concentration
TMB	Tumour Mutation Burden

TNM	Tumour, Node, Metastasis
Treg	Regulatory T-cell
TSAP	Trial Statistical Analysis Plan
ULN	Upper Level of Normal
UPCR	Ration of Urine Protein to Creatinine
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
WHO	World Health Organisation
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Despite the recent advancements in cancer treatment, cancer remains a leading cause of death globally. In 2018, the estimated number of new cancer cases was approximately 18 million, and 9.5 million cancer-related deaths worldwide (R18-3204). In the majority of cases, the disease is diagnosed in late stages and the vast majority of patients progress on available treatment and succumb to their disease. These statistics clearly highlight the urgent need for novel therapeutic agents and treatment strategies to improve the treatment outcome for cancer patients.

Studies in mice have shown that Angiopoietin-2 (Ang2), a ligand of a tyrosine kinase receptor called Tie2 receptor, controls vascular remodelling by enabling the functions of other angiogenic factors, such as Vascular Endothelial Growth Factor (VEGF) (R12-3593). Ang2 is primarily expressed by endothelial cells, strongly induced by hypoxia and other angiogenic factors and has been demonstrated to regulate tumour vessel plasticity, allowing vessels to respond to VEGF and Fibroblast Growth Factor 2 (FGF2) (R12-3834).

The normal role of the immune system is to protect the body against the invasion of foreign agents such as bacteria, viruses and parasites as well as the body's own malfunctioning cells. Once a mounted immune response (adaptive or innate) completes its task of eliminating the threat, the immune system deploys the immune system checkpoint program to dampen the immune response and minimize collateral immune-mediated damage to healthy tissue. The programmed-cell-death-protein-1 (PD-1) receptor and its ligands, programmed-cell-death ligand-1 (PD-L1) and programmed-cell-death ligand-2 (PD-L2) are the major immune checkpoint master switches. The expression of PD-1 on immune cells, including T and B lymphocytes, natural killer (NK) cells and antigen presenting cells is upregulated in response to inflammation in peripheral tissue. As with PD-1 level, the expression of PD-L1 is also induced as a result of peripheral tissue inflammation. The interaction of PD-1 and PD-L1 results in an inhibitory signal that interferes with antigen receptor signalling, marked changes in the cytokine profile decreased T-cell activation, increased activation of regulatory T-cells (Tregs) and increase in cytotoxic T-cell apoptosis. Collectively, these events lead to an immune suppressive environment and dampening of the immune response. Tumour immune evasion is achieved when PD-L1 within the tumour microenvironment engages PD-1 expressed on activated tumour infiltration T-cells and initiates the immune suppressive tumour microenvironment in which activated cytotoxic T-cells are inactivated and some are sent down an apoptotic pathway.

Angiogenesis is the formation of new blood vessels from pre-existing vasculature and is a key process in tumour growth. The Ang2/Tie2 and the VEGF/VEGFR2 pathways have been identified as key pathways mediating tumour 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 mAb (monoclonal antibody) bevacizumab has demonstrated anti-tumour activity in clinical trials and is currently approved for several indications and setting, mainly in combination with

standard chemotherapy regimens (R15-1222). High circulation level of Ang2 was observed in several tumour type and correlate with poor prognosis. Anti-tumour activity was reported with Ang2 inhibition in Phase I trials.

VEGF-A induces accumulation of Myelo-derived suppressor cells (MDSCs), immature DC, Treg and tumour-associated macrophage. MDSCs are able to control activation of T-cell and NK cells. Anti-VEGF treatment significantly enhances dendritic cell maturation (R17-4036, R17-4037), decrease Treg either by inhibiting the accumulation of MDSCs and immature dendritic cells (DC) in tumour environment, or directly through VEGF/ Vascular Endothelial Growth Factor Receptor (VEGFR) pathway inhibition of Treg (R17-4038, R17-4039). Ang2 Blockade facilitates the extravasation and perivascular accumulation of activated interferon alpha-expressing CD-8 cytotoxic T lymphocytes.

Preclinical evidence of interaction between these 2 pathways was shown as well as encouraging anti-tumour activity of the combination of VEGF blockade and PD-1/PD-L1 blockade (c02353883).

1.2 DRUG PROFILE

1.2.1 BI 836880

The [redacted] 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. 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, [redacted]). 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 (c02353883).

BI 836880 is highly potent and showed in vivo monotherapy efficacy (tumour growth inhibition) in several tumour 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) .

A 13-week repeat dose administration of BI 836880 was performed in cynomolgus monkeys. BI 836880 was well tolerated up to the highest dose of 60 mg/kg. No mortality was attributed directly to BI 836880 administration. BI 836880 did not demonstrate any effects on neurological, renal, or cardiovascular functions including electrocardiograms (ECGs). In a monkey presenting the immunogenic reaction, membrano-proliferative glomerulopathy in the kidney was observed. This finding was considered a secondary response to immune complex deposition in the glomeruli and not directly related to BI 836880 administration.

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 anti-drug antibodies (ADA) positive post-dose at one or more of the sampling time points. No Changes in pharmacokinetic parameters were observed in these animals. In the 13-week toxicity and toxicokinetics, BI 836880 exposure (maximum concentration [C_{max}] and area under the curve [$AUC]_{0-168}$) increased approximately dose proportionally from 1 to 60 mg/kg in weeks 1, 4 and 13. There was a moderate accumulation (~ 2-fold). BI 836880 is currently tested in monotherapy in 2 phase I trials.

BI 836880 monotherapy is currently tested in two phase I trials, trial 1336-0001 for every 3 week administration schedule and trial 1336-0006 for weekly administration schedule, both conducted in Europe. 29 and 18 patients received BI 836880 in trial 1336-0001 and in trial 1336-0006 respectively. Dose levels between 40 mg and 1000 mg of BI 836880 are tested. In trial 1336-0001, the dose of 720 mg was defined as MTD and recommended phase 2 dose (RP2D).

In these two trials, the most commonly reported adverse events (AEs) are hypertension, asthenia, nausea, vomiting, diarrhoea and constipation. Other relevant AEs (mode of action related) include, peripheral oedema, bleeding (epistaxis), and proteinuria. The Safety profile of BI 836880 is as expected based on its mode of action. New antihypertensive treatment or change in previous antihypertensive treatment was needed in very few patients.

An exploratory, preliminary biomarker analysis performed in these two trials has shown that systemic VEGF levels are completely blocked already at the lowest dose of 40 mg i.v., while systemic ANG2 levels were blocked dose-dependently showing complete inhibition at dosages starting at 360 mg 3-weekly or 120 mg weekly. At these dosages both, systemic VEGF and ANG2, remain below limit of quantitation even before start of next treatment.

From exploratory, preliminary PK analysis, plasma concentrations of BI 836880 increased dose-dependently (based on C_{max} and AUC), over the dose ranges 40-1000 mg (1336-0001 q3w) and 40-180 mg (1336-0006 qw). A slight accumulation could be observed over treatment cycles 1, 2 and 4 based on C_{max} and partial AUCs in both trials (accumulation ratios were up to 1.5) while the elimination seemed dose-independent. In 1336-0001 (q3w), the gmean half-life over all dose groups was 197 hours (cycle 1, n=12), 238 hours (cycle 2, n=7), and 343 hours (cycle 4, n=4). It seems as if the required trough values of 20 mg/L (according to preclinical experiments) could be achieved at dosages starting from 720 mg q3w.

Furthermore, to assess the vascular pharmacodynamics (Pd) effect of BI 836880, dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) were performed in 1336-0001 trial at the two highest dose level (7 patients at 750 mg and 1 patient at 1000 mg). DCE-MRI imaging were performed at baseline and 1 week after dosing. Changes in Ktrans (compared to basline value) were evaluated for vascular perfusion changes. Amongst the 8 patients, Ktrans decrease was observed in 7 patient (> 40% in 4 patients, 20-40% in 2 patient and 10-20% in 1 patient).

Objective responses (ORs) were reported in 3 patients in trial 1336-0001 and 2 patients in trial 1336-0006. Those patient had ovarian cancer (two patients), endometrial cancer, breast cancer and nasopharyngeal cancer (one patient each tumour type)

The combination therapy of BI 836880 and BI 754091 is being investigated in patients with non small cell lung cancer (NSCLC) as well as other indications in Boehringer Ingelheim (BI) trial 1336-0011, which is being conducted in Western countries. The planned dose levels of BI 836880 in trial 1336-0011 are 360, 500, and 720 mg once every three weeks, combined with BI 754091 dose of 240 mg once every three weeks.

The Residual Effect Period (REP) of BI 836880 is 42 days.

For a more detailed description of the drug profile refer to the current Investigator's Brochure (IB) (c02353883).

1.2.2 BI 754091

BI 754091 is a humanized IgG4 pro-monocolonal antibody showing potent and selective binding to human PD-1. BI 754091 has highly human frameworks and a low predicted immunogenicity score. The BI 754091 molecule has a molecular weight approximately 148 kilodaltons. The antibody is composed of 2 heavy chains (446 amino acids each) and 2 light chains (218 amino acids each). The 4 polypeptide chains of the antibody are linked together by disulfide bonds. Each heavy chain contains one consensus sequence for N-linked glycosylation.

BI 754091 shows anti-tumour effects in *vivo* several mice model including in the syngenic MC-38 mouse model.

A 13-week repeat dose administration of BI 754091 was performed in cynomolgus monkeys. BI 754091 was well tolerated and no related mortality or clinical signs, or changes to body weight, food consumption, respiratory rate or electrocardiogram were observed.

BI 754091 exposure increased dose-proportionally and accumulated with repeat dosing for all tested dose levels. BI 754091 was still detectable after 4 week recovery period in the highest dose level (100 mg/kg). Engagement of BI 754091 with target was assessed by measuring available BI 754091-free PD-1 on $CD3^+/CD95^+$ T cells. After 13 weeks of dosing BI 754091 resulted in in vivo target engagement at all dose levels. After 4 week recovery period; available PD-1 remained decreased in the 100 mg dose group demonstrating sustained target engagement throughout the recovery period.

BI 754091 is currently being tested in patients in several BI clinical trials either in monotherapy or in combination with other treatments.

Trial 1381-0001 is a phase I clinical trial of BI 754091 monotherapy, conducted in Western countries. In the dose-escalation cohorts, 80 mg, 240 mg, and 400 mg dose levels administered once every three weeks were investigated and 3 patients were dosed at each dose level. No dose limiting toxicities (DLTs) or protocol defined immune-related AEs

(irAEs) were reported and the maximum tolerated dose (MTD) was not reached in the dose escalation cohorts. The recommended dose for further investigation was determined to be 240 mg. An exploratory analysis of biomarker performed in the 9 patients treated at 80 mg, 240 mg and 400 mg shows 100% PD-1 receptor occupancy in peripheral blood in all on-treatment patient samples compared to baseline throughout one treatment cycle. Plasma concentration of BI 754091 appears to increase linearly (based on $AUC_{0\text{-}504h,}$ C_{max} and C_{pre}).

Trial 1381-0004 is a phase I clinical trial of BI 754091 monotherapy, conducted in Asian countries. In the dose-finding part, 6 Japanese patients were treated with 240 mg dose level administered once every three weeks and no DLTs or protocol defined irAEs were reported. MTD was not reached and the RP2D was determined to be 240 mg.

The Residual Effect Period (REP) of the combination therapy of BI 836880 and BI 754091 is 42 days.

For a more detailed description of the drug profile refer to the current IB (c07895879).

1.3 RATIONALE FOR PERFORMING THE TRIAL

Most patients with locally advanced or metastatic tumours will succumb to their disease, justifying the substantial need for novel therapeutic strategies to improve the outcome for patients with advanced or metastatic malignancies.

It is well established that pro-angiogenic factors (e.g. VEGF-A) have an immunosuppressive effect in the tumour microenvironment. Preclinical data showed modulation of immunosuppressive cells by an anti-VEGF treatment and enhancement of anti-tumour effect with the combination of VEGF and PD-1 inhibition. Furthermore, internal BI preclinical data showed an additive effect of the angiopoietin inhibition on the top of the dual VEGF and PD-1 inhibition. (see BI 836880 IB, c02353883). Ang2 Blockade facilitates the extravasation and perivascular accumulation of activated interferon alpha-expressing CD-8 cytotoxic T lymphocytes. Combination of VEGF and Ang2 blockade promote perivascular T cell accumulation.

This scientific rationale and preclinical data support a combination trial of the triple inhibition of VEGF, Ang-2 and PD-1 inhibition.

This trial is intended to assess the safety, efficacy and pharmacokinetics (PK) and pharmacodynamics (Pd) of BI 836880 monotherapy and combination of BI 836880 and BI 754091 in Japanese patients to establish a safe combination dose that will enable Asian patients to be included in global clinical trials with this same combination.

In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking (please see Section 5.5). If the patient agrees, banked samples may be used for future biomarker research and drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an AE, or to gain a mechanistic or genetic understanding of drug effects and thereby better match patients with therapies.

In summary, the unmet medical need in patients with advanced solid tumours, the manageable anticipated safety profiles of BI 836880 and BI 754091 and scientific and clinical rationale for increased benefit from this combination warrant its evaluation in a global population including Asian (Japanese) patients. While safety and tolerability as well as early signs of activity in Western population will be investigated in separate ongoing trials, this study will provide supporting evidence for mono- and combination therapy in the Japanese population.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

This trial is for patients with advanced cancer and for whom there are no therapy options of proven efficacy, or who are not amenable to currently available standard therapies. BI 836880 is an investigational antiangiogenic agent and BI 754091 is an investigational immune checkpoint inhibitor. There are many antiangiogenic agents already approved to treat various types of cancer. Similarly there are many immune checkpoint inhibitors approved in various types of cancers. By participating in this trial and receiving study medication(s) either as monotherapy or in combination, patients with advanced cancer may have a better chance to delay tumour progression, compared with no anti-cancer treatment.

Based on the mode of action of BI 836880 and BI 754091, published and internal preclinical data, and available clinical data, it is anticipated that treatment with this combination will potentially improve response rate with prolonged duration of response as compared to each monotherapy.

1.4.2 Risks

Both BI 836880 and BI 754091 are investigational agents. Table 1.4.2: 1 displays the anticipated side effects of the study drugs, based on the mechanism of action, observed clinical data from ongoing studies, and published clinical data for drugs targeting VEGF, Ang2, and PD-1.

Table 1.4.2: 1 Potential risks, their rationale, and mitigation strategy

Potential risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product BI 836880 (monotherapy)		
Hypertension	This is a class effect and has been identified as an expected AE in this trial. In Phase I trials, Grade 1 or 2 hypertension has occurred in 31.0% of patients and Grade 3 hypertension in 27.6% of patients. All hypertensive	Patients with uncontrolled hypertension are excluded. Frequent blood pressure monitoring is implemented.

	episodes were transient requiring no treatment or resolved with the initiation or intensification of anti-hypertensive agents.	
Thromboembolic events (e.g. pulmonary embolism, deep vein thrombosis)	This is a class effect and expected AE with antiangiogenics.	Patients with history of severe thromboembolic event in the past 12 months are excluded.
Bleeding	This is a class effect and expected AE with antiangiogenics.	Patients with history of severe haemorrhagic event in the past 12 months are excluded. Full-dose anticoagulation (according to local guidelines) with Vitamin K antagonist and other anticoagulation are not allowed during the trial conduct.
Infusion related reactions	As with any mAb, allergic reactions to study medication administration is possible and they are potentially severe.	Patients with history of severe hypersensitivity reactions to other mAbs are excluded. A 48-hour hospitalisation with access to intensive care is mandated for all patients after the first study drug administration to secure the patient safety.
Drug-induced liver injury (DILI)	Rare but can be a potentially severe event, thus under constant surveillance by sponsors and regulators for all drugs in development.	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients' safety.
Investigational Medicinal Product BI 754091 (monotherapy)		
Immune-related adverse events (irAEs)	irAEs are associated with immune mediated mode of action and can be potentially severe.	Recommendations for the management of irAEs are provided. Investigators involved in this trial have experience in managing irAE and sites have facilities. A 48-hour

		hospitalisation with access to intensive care is mandated for all patients after the first study drug administration to secure the patient safety.
Infusion related reactions	As with any mAb, allergic reactions to study medication administration is possible and they are potentially severe	Patients with history of severe hypersensitivity reactions to other mAbs are excluded. A 48-hour hospitalisation with access to intensive care is mandated to secure the patient safety.
Drug-induced liver injury (DILI)	Rare but can be a potentially severe event, thus under constant surveillance by sponsors and regulators for all drugs in development.	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients' safety.
Trial procedures		
Biopsies	Biopsies are mandatory for Part II. Patients may experience biopsy related AEs such as pain or bleeding.	The risks are clearly explained in the informed consent document.
Dose escalation/DLT assessment	Assessment of DLT may be difficult if any safety assessments specified in cycle 1 are missing or not evaluable.	The Safety Monitoring Committee (SMC) will assess the data from all patients, and discuss if a patient is evaluable for DLT or any replacement is required.
Other risks		
NA		

1.4.3 Discussion

Both BI 836880 and BI 754091 are currently tested in early phase clinical trials as monotherapy and as a combination.

The observed clinical data from the on-going BI 836880 phase I trials (1336-0001 and 1336-0006) have been consistent with the anticipated possible side effects of VEGF and Ang2 inhibition, with hypertension, asthenia, nausea, vomiting, diarrhoea and constipation being the most commonly reported AEs. Most of these reported AEs were grade 1-2 (Common Terminology Criteria for Adverse Events [CTCAE] version 4.03) (See BI 836880 IB, c02353883). In trial 1336-0001, utilizing q3 week administration, a DLT (pulmonary embolism) was observed in 1 patient receiving BI 836880 at 1000 mg. In trial 1336-0006, utilizing weekly administration, 4 patients experienced DLT(s). These DLTs consisted of proteinuria (1 patient treated at 120 mg dose level, proteinuria and hypertension (1 patient treated at 240 mg), LVEF decrease (1 patient treated at 240 mg) and hypertension (1 patient treated at 180 mg). Dose level of BI 836880 given at 180 mg is currently expanded to confirm the MTD. In trial 1336-0011, two patients were treated at the dose level of BI 836880 360 mg and BI 754091 240 mg by 15 October 2018, and DLT (pulmonary embolism) was observed in one patient. The MTD information from trial 1336-0011 is expected in Jun 2019.

BI 754091 is tested in monotherapy and in combination with other compounds. In the first phase I trial (1381-0001), three doses of BI 754091 (80, 240 and 400 mg) were tested in the dose escalation part, and no DLTs or protocol defined irAEs were reported during the MTD evaluation period at any dose level. The most common AEs were nausea, fatigue, decrease appetite, constipation and arthralgia. Based on this dose escalation data, the dose of 240 mg was recommended for further development in monotherapy or as a starting dose in combination trials. In trial 1381-0004, 6 Japanese patients received BI 754091 at 240 mg and and no DLTs or protocol defined irAEs were reported.

The combination of an immune checkpoint inhibitor with a VEGF blocker has previously been tested in a phase I and II trials combining atezolizumab with bevacizumab in patients with renal cell carcinoma (R18-3778). This combination was well tolerated with most reported AEs as mild or moderate in severity. The only grade 3-4 reported events were hypertension. Reported AEs included check-point inhibitor related events such as fatigue, chills, diarrhoea, rash and pruritus and other AEs related to VEGF blockade (fatigue, hypertension, and epistaxis).

Patients should be advised and carefully monitored for the potential risk of side effects from these investigational drugs. Due to the potential for severe hypertension and potential infusion reactions, a 48 hours hospitalization is required after the first administration of trial medication(s) for closer observation with access to intensive care for ensuring patient safety. Patients with uncontrolled hypertension, with history of severe haemorrhage or thromboembolism are not allowed to participate in this trial. The clinical trial sites qualified to participate in this trial will be comprehensive cancer centres with good experience in treating patients with investigational drugs and have the necessary infrastructure. The investigators and sponsor will form a Safety Monitoring Committee (SMC). The SMC will

meet regularly and at minimum after all patients in each dose cohort have completed cycle 1. The sponsor will continuously assess risk benefit based on accumulating clinical data from all clinical trials with these two investigational agents. Any significant change in risk-benefit will be communicated to investigator and patients.

There is a guidance from health authorities to carefully monitor a potential for drug-induced liver injury (DILI). Although rare, a potential for DILI is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety, see also Section 5.2.9.1.4, adverse events of special interest (AESI).

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2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

2.1.1.1 Primary objective:

The primary objective of this trial is:

Part I
- To determine Maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of BI 836880 monotherapy

Part II
- To determine MTD and/or RP2D of the combination therapy of BI 836880 and BI 754091

The definition of MTD and RP2D are as follows:
- MTD: the highest dose with less than 25% risk of the true DLT rate being equal or above 33% during the MTD evaluation period
- RP2D: RP2D is determined by SMC and it may be any dose which fulfils the escalation with overdose control (EWOC) criterion. The SMC may decide to declare a dose as RP2D without determining the MTD, in consideration of all available data including the one from preceding trials.

The MTD will be determined based on the frequency of patients experiencing DLTs during the MTD evaluation period. The MTD evaluation period is defined as first treatment cycle.

2.1.1.2 Secondary objective

The secondary objectives are:

Part I
- To document the safety and tolerability, and characterise pharmacokinetics (PK) of BI 836880 as monotherapy

Part II
- To document the safety and tolerability, and characterise PK of the combination therapy of BI 836880 and BI 754091

2.1.2 Primary endpoint(s)

Part I and II:
- Maximum tolerated dose (MTD).

- Number of patients with DLTs in the MTD evaluation period.

For definition of DLTs, refer to Section 4.1.7.

A BLRM (Bayesian Logistics Regression Model) employing the escalation with overdose control (EWOC) principle will be used during the escalation phase for selection of doses and for estimation of the MTD. Cohorts of patients will receive escalating doses of BI 836880 single agent or combination of BI 836880 and BI 754091 until the MTD is reached, or RP2D is determined. Each cohort will consist of newly enrolled patients. Estimation of the MTD during the escalation phase of the trial will be based upon the estimation of the probability of a DLT in the MTD evaluation period in the set of evaluable patients for MTD. The corresponding methodology is described in Section 7 and Appendix 10.5.

2.1.3 Secondary endpoint(s)

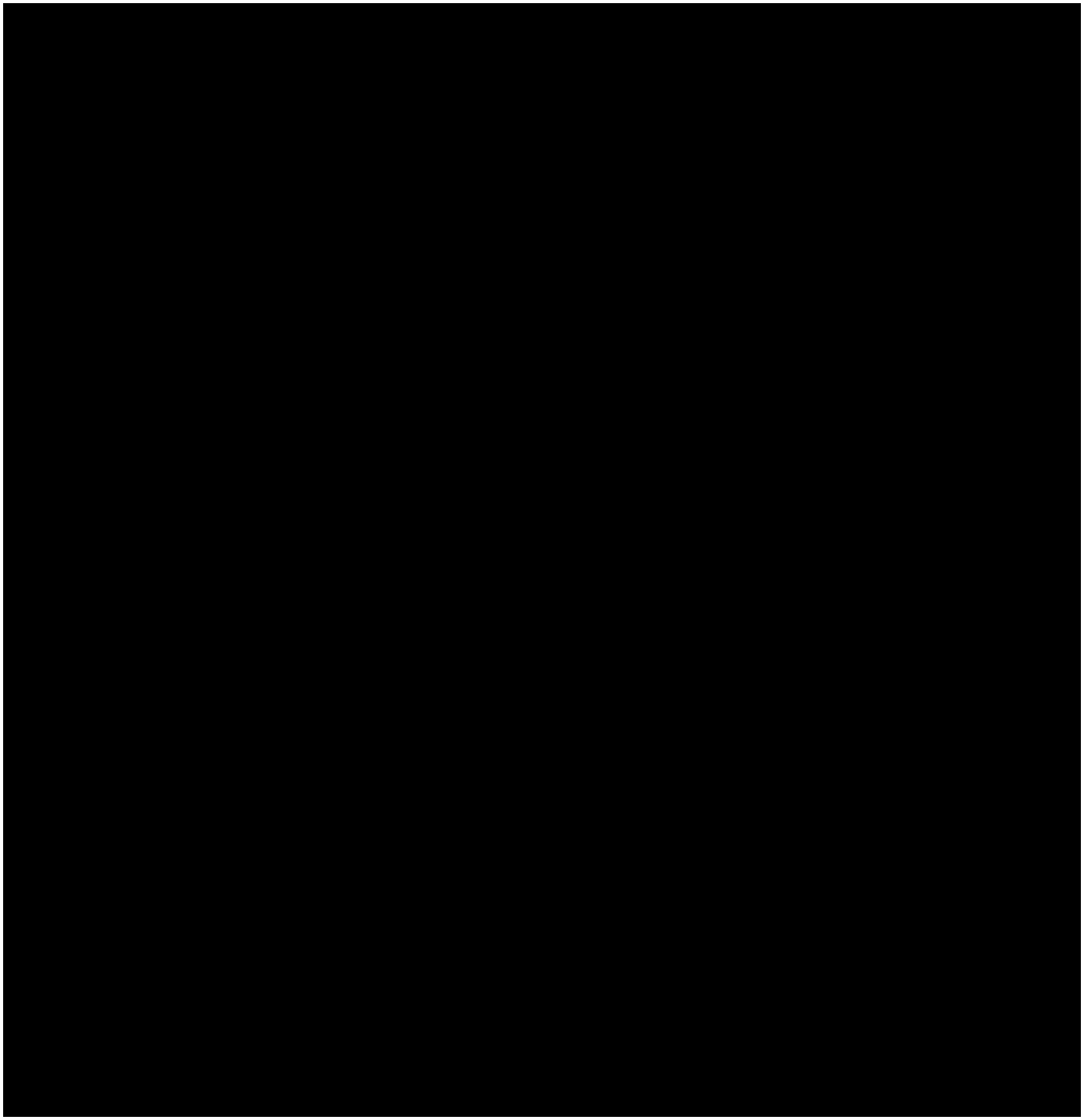
Part I

- The following PK parameters of BI 836880 will be calculated in cycles 1, 2 and 4:
  - C_{max}: maximum measured concentration of BI 836880 in plasma
  - $AUC_{0\text{-}504h}$: area under the concentration-time curve of BI 836880 in plasma over the time interval from 0 to 504 hours

Part II

- The following PK parameters of BI 836880 and BI 754091 will be calculated in cycles 1 and 4:
  - C_{max}: maximum measured concentration of BI 836880 and BI 754091 in plasma
  - $AUC_{0\text{-}504h}$: area under the concentration-time curve of BI 836880 and BI 754091 in plasma over the time interval from 0 to 504 hours

[redacted]



3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a Phase I, non-randomized, uncontrolled, open-label, dose escalation trial of BI 836880 monotherapy and combination therapy of BI 836880 and BI 754091, which are administered intravenously every 3 weeks. The eligible patient population will be advanced solid tumours. The trial consists of two Parts; Part I (monotherapy part) and Part II (combination therapy part). Part II will commence after completion of Part I.

The data obtained from the trial will determine the MTD estimate based on a Bayesian logistic regression model with overdose control (R13-4803). The BLRM estimates the MTD by updating estimates of the probability of observing a DLT in the MTD evaluation period for each dose level in the trial as patient information becomes available. At any time in the trial, it will not be permitted to escalate to a dose which does not fulfil the escalation with overdose control (EWOC) principle (refer to Section 7).

Successive cohorts of patients will receive increasing doses of BI 836880 single agent or combination of BI 836880 and BI 754091 until the MTD is reached or RP2D is determined. For any dose-escalation cohort, at least 3 patients will be required (refer to Section 7). However, in the case that only 2 patients are evaluable and neither has experienced a DLT within the MTD evaluation period, then dose-escalation can occur based on these 2 patients.

Doses may be de-escalated based on the occurrence of DLT and overall safety data. For the first cohort, 3 patients are planned to be treated. A cohort size of at least 3 patients will be treated at each subsequent cohorts. After all patients in a cohort have either experienced a DLT or have been observed for at least the MTD evaluation period without experiencing a DLT, the Bayesian model will be updated with the newly accumulated data. The overdose risk will then be calculated for each dose, and dose escalation will be permitted to all doses which fulfil the EWOC criterion and dose escalation rules according to Section 4.1.3. Decision on further recruitment (dose escalation, de-escalation or cohort expansion) will be made by the Safety Monitoring Committee (SMC) based on the collected safety data as well as other data when available. The doses will not exceed the RP2D established in the preceding trials in Western patients.

If DLTs are observed in the first 2 consecutive patients of a previously untested dose level, subsequent enrolment to that cohort will be stopped. The BLRM will be re-run to confirm that the dose-level still fulfils the EWOC principle. Based on this information, the SMC will evaluate whether the next patients will be enrolled at the same dose level, or if they will be enrolled at a lower dose level.

The SMC may recommend stopping the dose escalation phase after the criterion for MTD (Section 7.1) is fulfilled. Further patients may be included to confirm this MTD estimate, i.e. to confirm that the EWOC criterion is still fulfilled. If no DLT is observed at a dose of which the efficacy is considered sufficient, the SMC may decide to include an additional number of

patients at the same dose level and/or to declare this dose as the recommended dose for further development (RP2D).

The SMC can declare any dose fulfilling the EWOC criterion as RP2D, independent of the MTD estimate.

BI 836880 and BI 754091 will be administered every 3 weeks. The study treatment can be continued until progressive disease, unacceptable toxicity, or other withdrawal criteria are observed.

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

Dose levels and cohort size will be determined based on the recommendation of the SMC, guided by a BLRM with overdose control. An EWOC 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 an efficient method due to its ability to identify the dose with a desired toxicity rate and its allocation of a greater proportion of patients to doses at or close to that desired dose (R13-4802; R13-4804; R13-4805). The use of Bayesian models for Phase I studies has also been advocated by the European Medicines Agency (EMA) guideline on small populations (R07-4856) and by the United States Food and Drug Administration (FDA) (R13-4881).

The results from this trial will form the basis for decisions for future studies.

3.3 SELECTION OF TRIAL POPULATION

Screening of patients for this trial is competitive, i.e. screening for the trial will stop at all sites at the same time once a sufficient number of patients has been screened. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this trial.

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the Investigator Site File (ISF) irrespective of whether they have been treated with investigational drug or not.
If a patient is enrolled in error (does not meet all inclusion criteria or meets one or more exclusion criteria on the day of enrolment), the sponsor should be contacted immediately.

3.3.1 Main diagnosis for trial entry

Patients with a confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumour are the target population of this trial.

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. Of legal age (according to local legislation) at screening. No upper limit.
2. Signed and dated written informed consent in accordance with International Council on Harmonisation (ICH) Good Clinical Practice (GCP) and local legislation prior to admission to the trial.
3. Male or female patients. Women of childbearing potential (WOCBP)[1] and men able to father a child must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly, starting with the screening visit and through 6 months after the last dose of study treatment. A list of contraception methods meeting these criteria is provided in the patient information. The requirement of contraception does not apply to women of no childbearing potential and men not able to father a child, but they must have an evidence of such at screening.
4. Patients with a confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumours (any type). Measurable lesion not mandatory for participation in this trial.
5. Patients with no therapy of proven efficacy, or who are not amenable to standard therapies
6. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1
7. Recovery from all reversible adverse events of previous anti-cancer therapies to baseline or CTCAE grade 1, except for alopecia (any grade), sensory peripheral neuropathy, must be ≤ CTCAE grade 2 or considered not clinically significant.
8. Adequate organ function defined as all of the following (all screening labs should be performed at local lab within 10 days prior to treatment initiation):

Table 3.3.2: 1 Definition of adequate organ function

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1.5 x 10^9/L (≥1500/mm^3)
Platelets	≥75 x 10^9/L (≥75,000/mm^3)
Haemoglobin	≥9.0 g/dL
Renal	
Serum creatinine **OR** estimated glomerular filtration rate (eGFR) (Chronic Kidney Disease Epidemiology [CKD-EPI] Collaboration equation)	≤ 1.5 x upper limit of normal (ULN) **OR** ≥50 mL/min for patients with creatinine levels >1.5x ULN (confirmation of eGFR is only required when creatinine is >1.5 X ULN)
Hepatic	
Total bilirubin	≤1.5 times the upper limit of normal (ULN).
Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)	≤2.5 x ULN **OR** ≤5 x ULN for patients with liver metastases.

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
Tubal ligation is NOT a method of permanent sterilisation.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Coagulation	
• International Normalised Ratio (INR) or Prothrombin Time (PT)	• ≤1.5xULN. If the patient is receiving anticoagulant therapy, a prolonged INR or PT is acceptable as long as it is within therapeutic range of intended use of anticoagulants.
• Activated Partial Thromboplastin Time (aPTT)	• ≤1.5xULN. If the patient is receiving anticoagulant therapy, a prolonged aPTT is acceptable as long as it is within therapeutic range of intended use of anticoagulants.

3.3.3 Exclusion criteria

1. Known hypersensitivity to the trial drugs or their excipients or risk of allergic of anaphylactic reaction to drug product according to Investigator judgement (e.g. patient with history of anaphylactic reaction or autoimmune disease that is not controlled by nonsteroidal anti-inflammatory drugs (NSAIDs), inhaled corticosteroids, or the equivalent of ≤10 mg/day prednisone).
2. Known history of human immunodeficiency virus (HIV) infection. Test results obtained in routine diagnostics are acceptable if done within 14 days before the informed consent date.
3. Any of the following laboratory evidence of hepatitis virus infection.
    - Positive results of hepatitis B surface (HBs) antigen
    - Presence of hepatitis B core (HBc) antibody together with hepatitis virus B (HBV) Deoxyribonucleic acid (DNA)
    - Presence of hepatitis virus C (HCV) Ribonucleic acid (RNA)

   Test results obtained in routine diagnostics are acceptable if done within 14 days before the informed consent date.
4. History of severe known hypersensitivity reactions to other mAbs.
5. Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of trial medication.
6. Any investigational or anti-tumour treatment within 4 weeks or 5 half-life periods (whichever is shorter) prior to the initiation of trial treatment.
7. Serious concomitant disease, especially those affecting compliance with trial requirements or which are considered relevant for the evaluation of the endpoints of the trial drug, such as neurologic, psychiatric, infectious disease or active ulcers (gastrointestinal 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.
8. Major injuries and/or surgery or bone fracture within 4 weeks of start of treatment, or planned surgical procedures during the trial period.
9. Patients with personal or family history of QT prolongation and/or long QT syndrome, or prolonged QTcF (Corrected QT interval by Fredericia) at screening (>470 ms).
10. Significant cardiovascular/cerebrovascular diseases (i.e. uncontrolled hypertension, unstable angina, history of infarction within past 6 months, congestive heart failure > NYHA [New York Heart Association] class II).
    Uncontrolled hypertension is defined as follows: Blood pressure in rested and relaxed condition ≥140 mmHg, systolic or ≥90 mmHg diastolic (with or without medication), measured according to Appendix 10.3.
11. Left Ventricular Ejection Fraction (LVEF) <50% measured locally by echocardiography

12. History of severe haemorrhagic or thromboembolic event in the past 12 months (excluding central venous catheter thrombosis and peripheral deep vein thrombosis).
13. Known inherited predisposition to bleeding or to thrombosis in the opinion of the investigator.
14. Untreated brain metastasis(es) that may be considered active. Patients with previously treated brain metastases may participate provided they are stable (i.e., without evidence of PD by imaging for at least 4 weeks prior to the first dose of trial treatment, and any neurologic symptoms have returned to baseline), and there is no evidence of new or enlarging brain metastases
15. 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.
16. History (including current) of interstitial lung disease or pneumonitis within the last 5 years.
17. Patients who must or wish to continue the intake of restricted medications (see Section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial
18. Patients not expected to comply with the protocol requirements or not expected to complete the trial as scheduled. (e.g. chronic alcohol or drug abuse or any other condition that, in the investigator's opinion, makes the patient an unreliable trial participant).
19. Patients who were previously treated in this trial.
20. Patients with haematological malignancies.
21. Women who are pregnant, nursing, or who plan to become pregnant while in the trial. Female patients of childbearing potential must have a negative urine or serum pregnancy test within 3 days prior to taking study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the patient to be eligible. Women who are nursing can be enrolled if they stop nursing. In this case, the patient cannot resume nursing even after discontinuation of study treatment.

In this trial, patients with history of anti-PD-1 treatment will not be excluded, as it is considered that such patients still have chance to respond. Preclinical data showed modulation of immunosuppressive cells by an anti-VEGF treatment and enhancement of anti-tumour effect with the combination of VEGF, Ang2 and PD-1 inhibition.

3.3.4 Withdrawal of patients from treatment or assessments

Patients may discontinue trial treatment or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications; please see Sections 3.3.4.1 and 3.3.4.2 below.
Every effort should be made to keep the patients in the trial: if possible on treatment, or at least to collect important trial data.
Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal.
The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and the case report form (CRF). If the reason

for discontinuation is death, this should be reported on the serious adverse event (SAE) form as well, regardless of causal relationship. If applicable, consider the requirements for Adverse Event collection reporting (please see Sections 5.2.9.2.1 and 5.2.9.2).

3.3.4.1 Discontinuation of trial treatment

An individual patient will discontinue trial treatment if:

- The patient wants to discontinue trial treatment, without the need to justify the decision.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
- The patient needs to use concomitant medication that interferes with the investigational medicinal product or trial assessments. Refer to Section 4.2.2.1 for prohibited concomitant medications.
- The patient can no longer receive trial treatment for medical reasons (such as surgery, adverse events, other diseases, or pregnancy). Refer to Section 4.1.6 for AEs that require treatment discontinuation.
- The patient experiences unequivocal PD by RECIST v1.1 and/or iRECIST (iRECIST applies to Part II only). Refer to Section 5.1.1 for details.

Even if the trial treatment is discontinued, the patient remains in the trial and, will undergo the procedures for the end of treatment (EoT) visit and follow up as outlined in the Flow Chart and Section 6.2.3.

For all patients the reason for withdrawal from trial treatment (e.g. AEs) must be recorded in the CRF. These data will be included in the trial database and reported.

During the dose finding part, patients withdrawn for a reason other than having a DLT or patients who miss more than one visit during MTD evaluation period may be replaced after discussion in the SMC if the information that needed to be collected during that visit is not available and makes the patient non-evaluable for the PK analyses or safety parameters (including evaluation for DLTs).

Patients who come off trial due to a DLT will not be replaced.

If a patient should become pregnant during the trial, the study treatment must be immediately stopped. The patient will be followed up until delivery or termination of pregnancy (see Section 5.2.9.2.3 for information on pregnancy forms). The data of the patient will be collected and reported in the electronic case report form (eCRF) until the last patient's last visit and any events occurring thereafter will be reported in the BI drug safety database.

3.3.4.2 Withdrawal of consent to trial participation

Patients may withdraw their consent to trial participation at any time without the need to justify the decision.
If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between trial treatment discontinuation and

withdrawal of consent to trial participation, as well as explain the options for continued follow up after trial treatment discontinuation, please see Section 3.3.4.1 above.

3.3.4.3 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. Deviations from GCP, the trial protocol, or the contract impairing 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 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

Details of the trial medications, BI 836880, and BI 754091, are presented in Tables 4.1.1: 1, and 4.1.1: 2. Additional details are presented in the BI 836880 and BI 754091 IB and the instruction for pharmacist.

Table 4.1.1: 1 BI 836880

Substance:	BI 836880
Pharmaceutical formulation:	Solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	10 mg/ml (vials with 10 ml)
Posology	rate controlled infusion on Day 1 of each 3-week cycle
Route of administration:	i.v.

Table 4.1.1: 2 BI 754091

Substance:	BI 754091
Pharmaceutical formulation:	Solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	20 mg /mL (15 mL vial)
Posology	rate controlled infusion on Day 1 of each 3-week cycle
Route of administration:	i.v.

4.1.2 Selection of doses in the trial

4.1.2.1 Selection of dose in Part I

BI 836880 will be tested from a starting dose of 360 mg in every 3 week administration schedule. The dose-finding will be guided by the BLRM, and the final decision will be made by the SMC (see Section 8.7)

BI 836880 monotherapy is currently tested in two phase I trials, trial 1336-0001 for every 3 week administration schedule and trial 1336-0006 for weekly administration schedule, both conducted in Europe. Since the RP2D was already defined in trial 1336-0001 and patient convenience, the every 3 week schedule will be used in this trial. The starting dose was selected based on the data obtained in trial 1336-0001.

In trial 1336-0001, 29 patients were treated with BI 836880, at dose levels between 40 mg and 1000 mg. Amongst them 17 patients received BI 836880 at the recommended Phase 2 dose (RP2D) of 720 mg (Table 4.1.2.1: 1). The majority of these patients were females (62.1%) with a median age of 57 years. The trial included 6 patients with pancreatic cancer, 4 patients with breast cancer, 4 patients with colorectal cancer 3 patients with oesophageal cancer, as well as other cancer types each represented by 1-2 patients.
BI 836880 was well tolerated in this trial with 1 DLT (pulmonary embolism, CTCAE grade 3) reported at the highest tested dose of 1000 mg.

Table 4.1.2.1: 1 Number of evaluable patients and DLTs in trial 1336-0001

Dose level	BI 836880 dose	Number of evaluable patients	Number of DLTs
1	40 mg	2	0
2	120 mg	2	0
3	360 mg	2	0
4	720 mg	17	0
5	1000 mg	5	1
Total	-	28	1

As of August 2018, 47 patients were treated with BI 836880 monotherapy in trial 1336-0001 or 1336-0006.

Exploratory PK and Pd analysis was performed. BI 836880 plasma exposure is dose-proportional over the dose ranges 40-1000 mg based on C_{max} and partial AUCs. The gmean half-life over all dose groups was 197 hours (cycle 1, n=12), 238 hours (cycle 2, n=7), and 343 hours (cycle 4, n=4). The required trough values of 20 mg/L (according to preclinical experiments) could be achieved at dosages starting from 720 mg every 3 weeks.

Biomarker analysis has shown complete systemic VEGF levels blocked at the lowest dose of 40 mg. Systemic ANG2 levels were blocked dose-dependently showing complete inhibition at dosages starting at 360 mg. These inhibition remained before start of next treatment.

Based on safety data as well as PK and PD analysis, the dose of 720 mg is selected as RP2D. The dose level of 360 mg, one level lower than RP2D, was also safe and showed complete inhibition of systemic targets, and will be used for the starting dose of the Part I of the current trial.

4.1.2.2 Selection of dose in Part II

BI 836880 will be tested from a starting dose of 120 mg in every 3 week administration schedule. The escalating dose of BI 836880 will be administered in combination with the dose of BI 754091 at 240 mg, which is also administered in every 3 week schedule.

The starting dose of BI 836880 may be adapted via protocol amendment based on the most recent safety information from another ongoing trial, 1336-0011. As of 15 Oct 2018, one DLT was reported in the cohort of BI 836880 360 mg and BI 754091 240 mg cohort.

BI 754091 was tested in monotherapy in the dose-escalation part of trials 1381-0001 and 1381-0004, which were conducted in North America and Japan respectively.

In trial 1381-0001, a total of 9 patients received BI 754091 at 3 dose levels (80 mg, 240 mg and 400 mg) in the dose escalation cohorts. There were no DLTs or drug-related SAEs in any cohort. The most common reported AEs were nausea, fatigue, decreased appetite, constipation and arthralgia. Eight additional patients have been treated at dose of 240 mg in the expansion part of this trial. No grade 4, Grade 5 AE or DLT was reported.

The exploratory analysis of biomarker performed in these 9 patients shows 100% PD-1 receptor occupancy in peripheral blood in all on-treatment patient samples compared to baseline throughout one treatment cycle.
Plasma concentration of BI 754091 appears to increase in dose proportional manner (based on $AUC_{0\text{-}504h,}$ C_{max} and C_{pre}). Furthermore, the observed BI 754091 PK was compared with model simulated pembrolizumab PK (R17-2460). Observed BI 754091 PK profiles overlap with those simulated for pembrolizumab at a dose of 200 mg.

The dose of 240 mg of BI 754091 once every 3 weeks was chosen to be further explored in monotherapy trials and is recommended as a starting dose in combination trials.

In trial 1381-0004, a total of 6 Japanese patients received BI 754091 in the dose-finding part at 240 mg dose level, and none of them experienced DLT or drug related SAE.

4.1.3 Dose-finding scheme

The dose is planned to be tested in cohorts at pre-defined provisional dose levels. The provisional dose levels to be assigned to different cohorts of patients are listed in Table 4.1.3:

1 and 4.1.3: 2. Intermediate or lower dose levels may be investigated if agreed in the SMC, depending on the number of DLTs observed in the trial.

In Part II, increasing doses of BI 836880 will be administered in combination with BI 754091 at 240 mg. The dose of BI 754091 may also be titrated based on DLTs and the overall safety profile of the combination.

Table 4.1.3: 1 Example of dose escalation in Part I*

Dose level	Proposed dose of BI 836880	Increment from previous dose
0	360 mg	Starting dose
1	720 mg*	100%

*Actual dose assignments for a cohort will be communicated separately as determined by the SMC. Intermediate dose level(s) may be investigated depending on the latest DLT rate estimate. Dose levels which are higher than the recommended dose in trial 1336-0001 (720 mg) will not be investigated.

Table 4.1.3: 2 Example of dose escalation in Part II*

Dose level	Proposed dose of BI 836880	Proposed dose of BI 754091	Increment from previous dose (BI 836880)
0	120 mg*	240 mg*	Starting dose
1	360 mg*	240 mg*	200%
2-a	500 mg*	240 mg*	39% (from 360 mg)
2-b	720 mg*	240 mg*	100% (from 360 mg)

*Actual dose assignments for a cohort will be communicated separately as determined by the SMC. Intermediate dose level(s) may be investigated depending on the latest DLT rate estimate. Dose levels which are higher than the recommended dose in trial 1336-0011 will not be investigated. For dose level 2, level 2-a or 2-b will be investigated based on the information from trial 1336-0011.

There will be no dose escalations of BI 836880 or BI 754091 in any one patient.

When the last patient in each cohort completes Cycle 1, the SMC will evaluate the available data. The SMC will review all safety data including, but not limited to, DLTs and all CTCAE Version 5 Grade ≥2 toxicity data during cycle 1. Updated safety data on other ongoing patients, including data beyond cycle 1, will be discussed as well. Based on that, a decision on the next dose level to be tested will be made.

4.1.4 Method of assigning patients to treatment groups

There will be no randomisation in this trial, as it is a single-arm open-label trial. After assessment of all inclusion and exclusion criteria, each eligible patient will be assigned a dose of medication available at the time of enrolment.

To determine the dose or doses for subsequent cohorts, the available safety data (including DLTs, AEs that are not DLTs, and AE information), as well as the recommendations from the BLRM, will be evaluated by the SMC members.

The SMC must reach a consensus on whether to declare the MTD, escalate the dose any further, or de-escalate and/or expand recruitment into particular cohorts. Dose-finding of BI 836880 monotherapy in Part I will continue until the MTD is reached and/or RP2D is determined whichever occurs earlier. Similarly, dose-finding of BI 836880 and BI 754091 combination in Part II will continue until the MTD is reached and/or RP2D is determined, whichever occurs earlier.

To further characterise the safety (e.g., specific suspected treatment-related AEs) or PK profiles of BI 836880 monotherapy or BI 836880 plus BI 754091 combination, one or several doses may be expanded. Dose-finding may be terminated at any time based on emerging safety concerns without establishing the RP2D or the MTD.

4.1.5 Drug assignment and administration of doses for each patient

Patients will be assigned to their doses based on the available toxicity information (including DLTs, AEs that are not DLTs, and AE information post MTD evaluation period), PK, and anti-tumour activity information, as well as the recommendations from the SMC members following the dose decision meeting, please see Section 4.1.2.

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

The study treatment will be administered by authorized site staffs 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”. Appropriate drugs and medical equipment to treat anaphylactic reactions must be immediately available and study personnel must be trained to recognize and treat anaphylaxis.

No premedication will be required for BI 836880 infusion or BI 754091 infusion. If a patient had signs or symptoms of infusion reaction at any BI 836880 treatment, a premedication will be considered for all subsequent treatment infusions (dosage and schedule according investigator’s decision) comparable to following scheme:

- Acetaminophen/Paracetamol 650 mg - 1000 mg per os (p.o. [oral]), or equivalent
- Antihistamine p.o. or i.v., equivalent to Diphenhydramine 50 mg i.v.
- Glucocorticoid i.v., equivalent to prednisolone 100 mg

The expected infusion time is about 60 minutes for BI 836880 and the same for BI 754091. In case no relevant infusion reactions are observed, the infusion time for BI 836880 can be shorten to about 30 minutes, but the infusion time for BI 754091 should be kept at about 60 minutes. The duration of infusion should not be prolonged to more than 6 hours for BI 836880, and more than 3 hours for BI 754091.

If symptoms of an infusion-related reaction CTCAE grade ≤2, but not qualifying as DLT according to Section 4.1.7 occur, the infusion should be temporarily stopped. Upon recovery, it should be infused at 50% of the rate at which the reaction occurred. Depending on the time of occurrence and the severity of the reaction, the investigator may consider administering additional supportive medication, e.g. corticosteroids for re-introduction. Infusion rate and premedication for further treatment cycles should be adapted according to Investigator decision.

In the combination treatment, BI 836880 and BI 754091 will be given as two separate consecutive intra-venous infusions. BI 754091 should be administered first, and BI 836880 will be administered approximately 15 minutes after the end of this infusion of BI 754091.

4.1.6 Dose modifications

Before initiating a new treatment cycle, the actual health status will be assessed according to Flow Chart and described in Section 5.2. To continue treatment with further cycles, all of the following retreatment criteria must be met:

- No uncontrolled hypertension (according to Exclusion-Criterion #10)
- QTcF <=470 ms (according to Exclusion-Criterion #9)
- Acceptable tolerability (in case of an adverse event at the planned start of a treatment cycle 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 the administration of study drug(s) should be delayed. Any case of a delay in treatment cycle for more than 2 weeks should be communicated to the study team at Boehringer Ingelheim. The investigator in agreement with the BI study team will decide about further treatment of individual patient, based on known risk/benefit of BI 836880 and BI 754091.

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.

Administration of trial drugs has to be stopped temporarily in case of a DLT (see Section 4.1.7). Patients may resume the treatment only after recovery from DLT to at least fulfil retreatment criteria. The future dose of BI 836880 must be a tested dose which is one dose level below the dose received by the patient. The dose level for treatment resumption should

be as prescribed in Table 4.1.6: 1. Treatment has to be discontinued in case the DLT is not reversible.

If a patient develops an interstitial lung disease, the treatment has to be discontinued.

Table 4.1.6: 1 Dose reduction recommendations for BI 836880

BI 836880 received dose	BI 836880 reduced dose
720 mg	360 mg
360 mg	120 mg
120 mg	120 mg (no change)

Dose reduction for BI 754091 is not allowed. The dose of BI 754091 may be delayed for a patient for one cycle, plus an additional 3 weeks (i.e. for up to 6 weeks), because of AEs following discussion with the sponsor.

In combination treatment arms, both drugs (BI 836880 and BI 754091) will be stopped, paused, or re-exposed together unless an AE can be attributed to either BI 836880 or BI 754091. Only if a causal relationship to one trial drug can be unequivocally established, the other trial drug may be continued.

4.1.7 Dose limiting toxicities

DLTs will be recorded throughout the trial, and should be reported to the sponsor (AESIs, see Section 5.2.9.1.4) within 24 hours of first knowledge.

Any of the following AEs will be reported as potential DLTs, and will be classified as DLTs following review by the Investigators and the sponsor, unless unequivocally due to underlying malignancy or an extraneous cause.

DLTs observed during the MTD evaluation period will be considered for MTD determination. However, all AEs and SAEs meeting criteria of DLT observed in all treatment cycles will be considered for determining a Recommended Phase 2 Dose (RP2D)

Haematologic toxicities:
- Any Grade 5 toxicity
- Neutropenia Grade 4 lasting for >7 days
- Grade ≥3 documented infection with neutropenia
- Febrile neutropenia (absolute neutrophil count <1.0 X 10^9 cells/L and fever ≥38.5°C or a sustained temperature of ≥38.0°C for more than 1 hour)
- Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with bleeding
- Thrombocytopenia of any Grade which requires platelet transfusions
- Grade 4 anaemia unexplained by underlying disease
- Anaemia of any Grade which requires blood transfusions

Non-haematological toxicities:

- AST or ALT >3 times ULN and concurrent total bilirubin >2 times ULN without initial findings of cholestasis
- ≥ Grade 4 AST or ALT of any duration
- Any ≥ Grade 3 non-haematologic toxicity with the following exceptions:
    - Grade 3 irAE that resolves to ≤ Grade 1 or to baseline with immunosuppressive therapy within 2 weeks
    - Grade 3 fatigue that persists <7 days
    - Grade 3 rash that resolves to ≤ Grade 1 within 2 weeks
    - Grade 3 or 4 elevation in serum amylase and/or lipase that is not associated with clinical or radiographic evidence of pancreatitis
    - Grade 3 electrolyte abnormality that lasts <72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical intervention
    - Grade 3 nausea or vomiting that lasts <48 hours, and resolves to ≤ Grade 1 either spontaneously or with conventional medical intervention
    - Alopecia
    - Grade 3 asymptomatic endocrine disorders (thyroid, pituitary, and/or adrenal insufficiency) that are sufficiently managed with or without systemic corticosteroid therapy and/or hormone replacement therapy.
    - Grade 3 tumour flare
- Any Grade 4 or 5 AE other than disease progression
- Any Grade 2 pneumonitis of any duration
- Any Grade 2 uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks or requires systemic treatment
- Any ≥ Grade 2 toxicity that persists and results in > 14 days delay of administration of study medication (BI 836880 in Part I, BI 836880 and BI 754091 in Part II) on Cycle 2 Day 1
- Hypertension: systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg, confirmed by second measurement of an additional set of 3 BP measurements, or 3 sequential ambulatory blood pressure measurements when indicated (e.g. white coat effect), which cannot be controlled by hypertensive medication and requires a dose reduction/discontinuation of trial medication(s). Refer to Section 10.3 for details of the assessment of blood pressure
- Grade ≥3 proteinuria (urinary protein ≥3.5 g/day). Refer to Section 5.2.4.4 for the assessment of proteinuria

NOTE: Any laboratory abnormality which is considered not clinically relevant by the investigator or resolves spontaneously, or resolves with appropriate treatment is not a DLT. Clinically relevant abnormalities must be documented as AEs.

Late immune-related DLTs are irAEs that meet the same grading criteria as DLT criteria, but occur after Cycle 1 administration during Part 1. These, as well as all toxicities will be monitored throughout the trial. If any late immune-related DLT is reported during dose-escalation, the BLRM will be rerun including the late immune-related DLT, and updated results will be reviewed in the SMC meeting to recommend the next dose level and cohort size.

4.1.8 Definition of evaluable patient

For decisions on dose escalation, an evaluable patient is defined as a patient who has received BI 836880 or BI 836880 plus BI 754091 and either:

- has completed cycle 1 without experiencing DLT

OR

- has experienced DLT during cycle 1

4.1.9 Blinding and procedures for unblinding

4.1.9.1 Blinding

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

4.1.9.2 Unblinding and breaking the code

Not applicable

4.1.10 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI or a designated Contract Research Organisation (CRO). They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an Interactive Response Technology (IRT) system, which will also monitor expiry dates of supplies available at the sites.
For details of packaging and the description of the label, refer to the ISF.

4.1.11 Storage conditions

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

If the storage conditions are found to be outside the specified range, the Clinical Research Associate (CRA) must be contacted immediately.

4.1.12 Drug accountability

The investigator or designee will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol (CTP) by the Institutional Review Board (IRB) / Independent Ethics Committee (IEC),
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site,

- Approval/notification of the regulatory authority, e.g. competent authority (CA),
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated CTP

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics.
The investigator or designee 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 warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational medicinal product and trial patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of return to the sponsor, the investigator or designee must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no other mandatory treatments to be used or special emergency procedures to be followed.

Potential side effects of BI 836880 or BI 754091 have to be treated symptomatically. Symptomatic treatments of side effects or tumour-associated symptoms are allowed.

4.2.1.1 Permitted concomitant medications

- If medically feasible, patients taking regular medication should be maintained on it throughout the trial.
- Pre-medication is not required, but may be utilised following the first dose of study medication. This includes medications for the management of nausea, diarrhoea, and vomiting for which the patient must be treated according to institutional standards.
- Supportive care and other medications that are considered necessary for the patient's well-being may be given at the discretion of the Investigator.
- Blood transfusions are allowed at any time during the trial, except to meet inclusion criteria.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

- No other investigational therapy or anticancer agent should be given to patients. If such agents are required for a patient, then the patient must first be withdrawn from the trial.
- Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor-alpha blockers are prohibited. Use of immunosuppressive medications for the management of investigational product-related AEs or in patients with contrast allergies is acceptable, and does not necessarily warrant immediate treatment discontinuation. In addition, use of inhaled, topical, intranasal corticosteroids or local steroid injections (e.g., intra-articular injection) is permitted. Temporary uses of corticosteroids for concurrent illnesses (e.g., food allergies, computed tomography [CT] scan contrast hypersensitivity) are acceptable.
- Live attenuated vaccines are prohibited during the trial through 30 days after the last dose of investigational product.
- Patients already receiving erythropoietin at the time of screening for the trial may continue it, provided they have been receiving it for more than one month at the time trial treatment is started. Prophylactic erythropoietin should not be started during the first 3 weeks of any cohort, but may be started thereafter.
  In Japan, no erythropoietin product is approved for anaemia associated with cancer chemotherapy.
- Prophylactic granulocyte colony stimulating factors, and palliative radiotherapy are not allowed during the first 3 weeks.
- For symptom control, palliative radiotherapy is permitted for any lesion, except during the first cycle as it could interfere with the DLT evaluation for MTD/RP2D determination. Lesions that have been exposed to radiotherapy are no longer evaluable, and may not be included in the assessment of the non-target lesions and the overall assessment. These lesions may also not be used for a trial biopsy.
- Full-dose anticoagulation (according to local guidelines) with Vitamin K antagonist and other anticoagulation are not allowed during the trial conduct; LMWH is allowed only for prevention but not for curative treatment.
- Any planned surgeries are not allowed (see Exclusion Criteria Section 3.3.3 for further details). Unplanned surgeries should be postponed whenever possible four weeks after stop of treatment. For urgent interventions patients should not be further treated and should be intensely monitored regarding wound healing and post-operative complications.

4.2.2.2 Restrictions on diet and life style

There is no restriction on diet and life style.

4.2.2.3 Contraception requirements

Women of childbearing potential and men able to father a child must use highly effective methods of birth control per ICH M3 (R2) 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.

4.3 TREATMENT COMPLIANCE

BI 836880 and BI 754091 will be administered by i.v. infusion at the sites by the Investigator and/or trained site personnel, and dosing will be recorded in the eCRF. Therefore, actual dosing is expected to precisely follow the prescribed drug regimen. Missed or interrupted doses will be recorded in the eCRF with the associated reasons. The method of collecting dosing information assures that total exposure can be calculated programmatically taking into account any missing doses.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.2 ASSESSMENT OF SAFETY

The safety of BI 836880 and BI 754091 will be assessed by a descriptive analysis of incidence and severity of AEs graded according to CTCAE (Version 5), the incidence of DLTs, laboratory data, and results of physical examinations.

DLTs observed during the MTD evaluation period will be considered for MTD determination. However, all DLTs observed in all treatment cycles will be collected and will be considered for determining a RP2D. The BLRM will be re-run including the DLT information from all

cycles. Based on both estimates, the recommended dose for further development will be selected. If there are too few or no DLTs for BLRM guided dose selection, other data will be taken into consideration for RP2D determination.

5.2.1 Physical examination

A complete physical examination (including cardiac, neurological, dermatological, pulmonological examination) will be performed at the time points specified in the Flow Chart.

The physical examination will include measurement of height (screening only) and of body weight.

5.2.2 ECOG performance status

The ECOG performance status will be assessed at the times indicated in the Flow Chart.

5.2.3 Vital signs

Vital signs will be evaluated at the time points specified in the Flow Chart, prior to blood sampling (if applicable).
This includes systolic and diastolic blood pressure, pulse rate, arterial oxygen saturation (SpO_2), and body temperature. The results must be included in the source documents available at the site.

At days of administration blood pressure and pulse rate will be evaluated at the following time points:

Part I
1. pre-dose (-60 min. to -5 min.), before infusion of BI 836880
2. 5 to 10 minutes after infusion of BI 836880.

Part II
1. pre-dose (-60 min. to -5 min.), before infusion of BI 754091
2. 5 to 10 minutes before infusion of BI 836880,
3. 5 to 10 minutes after infusion of BI 836880.

Blood pressure and pulse rate
Systolic and diastolic blood pressure as well as pulse rate (electronically or by palpation, count for 1 minute) should be measured after a rest in the seated position. The blood pressure measurement should be performed three times at each time point and the values of these measurements will be entered in the eCRF. The mean value will be used for clinical decision. Further details on the procedure for blood pressure measurements are given in Appendix 10.3.

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

Body temperature measurements ≥ 38°C must be re-assessed after 1 hour, especially in cases where febrile neutropenia is suspected.

5.2.4 Safety laboratory parameters

Blood and urine samples for assessment of general safety laboratory examinations have to be collected at the time points specified in the Flow Chart, and will be analysed by the site's local safety laboratories. The laboratory tests should be more frequent in case of relevant findings, e.g. in case of grade 4 neutropenia, which will be counted as DLT if not recovered within 7 days, or proteinurea, for which determination of CTCAE grade 2 or grade 3 need to be done by quantitative measurement, or grade 3 electrolyte abnormality, which will be counted as DLT if not recovered within 72 hours (see Section 4.1.7). Screening laboratory assessments performed within 72 hours of the first trial treatment administration are not required to be repeated on Cycle 1 Day 1. In cases where screening laboratory investigations have been performed >72 hours prior to the first trial treatment administration, the results of the new laboratory investigations performed within 72 hours of the first trial treatment administration must be available to confirm eligibility.

5.2.4.1 Hematology

Hemoglobin, white blood cell count with differential, platelets.

5.2.4.2 Biochemistry

Glucose, sodium, potassium, calcium, magnesium, inorganic phosphate, creatinine (and eGFR if creatinine is >1.5 x ULN), AST, ALT, alkaline phosphatase, lactate dehydrogenase (LDH), bilirubin, urea (or blood urea nitrogen [BUN]), total protein, albumin, uric acid, creatine kinase (CK), CK-MB, serum immunoglobulin levels (IgG, IgM, IgA, and IgE).

A thyroid panel (TSH, free T4, and free T3) will be done at the time of each standard biochemistry panel.

HBV, HCV, and HIV testing should be performed at screening unless test results obtained in routine diagnostics within 14 days before the informed consent date are available

Direct antiglobulin test have to be measured at screening and at occurrence of infusion related reactions.

Additionally, amylase and lipase should be analysed in case of symptoms of pancreatitis.

5.2.4.3 Coagulation

Activated partial thromboplastin time (aPTT), prothrombin time (PT) or international normalised ratio (INR) where indicated (e.g. treatment with vitamin K antagonists)

5.2.4.4 Urinalysis

pH, glucose, erythrocytes, leukocytes, protein, nitrite will be analysed primarily qualitatively by dipstick. In case of clinically relevant findings, further evaluation should be performed and the findings documented. A positive urine dipstick for protein of ≥ 2+ (CTCAE grade 2) has to be followed by a determination of the ratio of urine protein to creatinine (UPCR) in a morning spot urine sample. In case of a ratio ≥ 0.5, a 24 hour urine collection for protein loss has to be performed. The 24 hour urine collection will be repeated every time the UPCR ratio is ≥ 0.5 as often as clinically indicated.

5.2.4.5 Pregnancy test

A serum pregnancy test needs to be obtained at the time points indicated in the Flow Chart in patients of childbearing potential.

5.2.5 Electrocardiogram

The 12-lead ECGs must be performed at the time points specified in the Flow Chart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and assess clinical relevance. ECGs may be repeated for quality reasons and a repeated recording used for analysis.

On the days of administration, ECG should be taken at two time points:

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

In case of drug-related ECG changes and whenever the investigator deems necessary, additional ECG monitoring will be performed in the respective and later cycles of treatment. Cardiac monitoring for patients presenting a QTc interval prolongation CTCAE grade ≥ 3 shall be followed as follows:

- Continuous ECG monitoring until the QTc interval < 470 ms
- Cardiologist opinion for potential treatment of this event as soon as the QTc interval prolongation is observed.
- Cardiologist recommendation after QTc interval normalisation (< 470 ms) and potential follow-up.

In order not to confuse ECG recording, PK samples should be taken after performing the ECG. Decision on patient's eligibility will be taken based on Investigator medical opinion. Pathological ECG results will be recorded as AEs by the investigator.

5.2.6 Echocardiography

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

5.2.7 Chest X-ray

A chest X-ray must be performed at the timepoints specified in the Flow Chart.

5.2.8 Other safety parameters

No assessment planned.

5.2.9 Assessment of adverse events

5.2.9.1 Definitions of AEs

5.2.9.1.1 Adverse event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal 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.

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

- Worsening of pre-existing conditions other than the underlying disease
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.

5.2.9.1.2 Serious adverse event

A serious adverse event (SAE) is defined as any AE, which fulfils at least one of the following criteria:

- results in death,
- is life-threatening, which 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,
- requires prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,

- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. 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.
- AEs which possibly lead to disability will be handled as "deemed serious for any other reason"

5.2.9.1.3 AEs considered "Always Serious"

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 defined above.
The latest list of "Always Serious AEs" can be found in the electronic data capture (eDC) system. A copy of the latest list of "Always Serious AEs" will be provided upon request. These events should always be reported as SAEs as described above.

Every new occurrence of cancer of new histology must be classified as a serious event regardless of the time since the discontinuation of the trial medication and must be reported as described in Section 5.2.9.2, subsections "AE Collection" and "**AE reporting to sponsor and timelines**".

5.2.9.1.4 Adverse events of special interest

The term adverse events of special interest (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 SAEs, please see Section 5.2.9.2.2.

In this trial, dose limiting toxicities, severe hypertension, immune-related adverse events, infusion-related reactions, and hepatic injury are considered as AESIs.

Dose limiting toxicities
All DLTs are considered to be AESIs, and must be reported as such. The definition of DLT is presented in Section 4.1.7.

Severe hypertension
A hypertensive episode will be considered an AESI if:

- Systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg which persist longer than 2 days despite either initiation of antihypertensive agent(s) in a patient without prior history of hypertension, or intensification / addition of new antihypertensive agents in a patient with prior history of hypertension.

Immune-related adverse events (irAEs) (Part II only)

Immune-related AEs are AEs associated with immunotherapy treatments that appear to be associated with the immune therapy's mechanism of action, such as BI 754091 in this study. These adverse reactions, which can be severe, may involve the gastrointestinal, skin, liver, endocrine, respiratory, renal, or other organ systems. The sponsor has defined a list of potential irAEs that could occur with BI 754091 (Appendix 10.1). These irAEs must be reported as AESIs. If an Investigator determines another event (not on the list) should be a potential irAE, the Investigator may also report that event as an AESI.

Recommendations for the management of irAEs are presented in Appendix 10.2.

Infusion-related reactions

In the event of an infusion-related reaction ≤ Grade 2, the infusion should be temporarily stopped. Upon recovery, it should be infused at 50% of the initial rate until completion of the infusion. In patients experiencing infusion-related reactions ≤ Grade 2, subsequent infusions may be administered at 50% of the initial rate.

If a patient experiences an infusion-related reaction, acetaminophen and/or an antihistamine (e.g., diphenhydramine) and/or corticosteroid or equivalent medication per institutional standard may be administered prior to subsequent infusions at the discretion of the Investigator for secondary prophylaxis of infusion-related reactions. If an infusion-related reaction is Grade 3 or higher in severity at any point during the study, treatment with BI 836880 and/or BI 754091 will be permanently discontinued.

As with any mAb, allergic reactions to study medication administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and trial personnel must be trained to recognize and treat anaphylaxis. The trial site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.

The following terms describe those events that are to be considered potential infusion-related AEs. Regardless of grade, these events are considered as AESIs and must be reported to the sponsor within 24 hours of the event:

- Allergic reaction
- Anaphylaxis
- Cytokine-release syndrome
- Serum sickness
- Infusion reactions
- Infusion-like reactions

If the Investigator determines that another event (not on the list) may be a potential infusion related AE, the Investigator may also report that event as an AESI.

Hepatic injury

A potential hepatic injury is defined by the following alterations of hepatic laboratory parameters in patients with normal aminotransferase levels at baseline:

- an elevation of AST (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, or
- aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN.

A potential hepatic injury is defined by the following alterations of hepatic laboratory parameters in patients with abnormal aminotransferase levels of >ULN and ≤2.5 fold ULN at baseline:

- an elevation of AST and/or ALT ≥3 fold the baseline value combined with an elevation of bilirubin ≥2 fold the baseline value measured in the same blood draw sample, or
- aminotransferase (ALT, and/or AST) elevations ≥10 fold the baseline value.

A potential hepatic injury is defined by the following alterations of hepatic laboratory parameters in patients with abnormal aminotransferase levels of >2.5 fold and ≤5 fold ULN at baseline (patients with liver metastases only):

- an elevation of AST and/or ALT ≥2 fold the baseline value combined with an elevation of bilirubin ≥2 fold the baseline value measured in the same blood draw sample, or
- aminotransferase (ALT, and/or AST) elevations ≥3 fold the baseline value.

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” provided in the 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

5.2.9.1.5 Intensity (severity) of AEs

The severity of adverse events should be classified and recorded in the CRF according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.

5.2.9.1.6 Causal relationship of AEs

Medical judgement should be used to determine whether there is a reasonable possibility of a causal relationship between the adverse event and the given study treatment, 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 reduced).

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 trial drug treatment continues or remains unchanged.

5.2.9.2 Adverse event collection and reporting

5.2.9.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files.

The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until the individual patient's end of trial: All AEs (serious and non-serious) and all AESIs.
- After the individual patient's end of trial:
  The investigator does not need to actively monitor the patient for new AEs but should only report any occurrence of cancer of new histology and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see section 5.2.9.2.2), but not on the CRF.

The rules for Adverse Event Reporting exemptions still apply, please see section 5.2.9.2.4.

5.2.9.2.2 AE reporting to the 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. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable" , or no further information can be obtained.

5.2.9.2.3 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.
Pregnancy until 6 months after the last dose of study medication should be reported as a drug exposure during pregnancy.

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 well as non-trial specific information and consent for the pregnant partner.

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.

5.2.9.2.4 Exemptions to SAE reporting

The outcomes "disease progression" / "progressive disease (PD)" / "relapse" / "resistant disease" are used to assess trial endpoints for the analysis of efficacy, and will be recorded on the appropriate page of the eCRF.

If disease progression outcomes do not meet the standard seriousness criteria (see Section 5.2.9.1.2), then they are exempt from AE reporting, and will only be recorded on the appropriate page of the eCRF. For example, asymptomatic disease progression detected on a routine scan would be exempt from AE reporting. However, if there is evidence suggesting a causal relationship between the study drug or study drugs and the progression of the underlying malignancy, the event must be reported as an SAE on the SAE Form and on the eCRF.

If disease progression outcomes meet the standard seriousness criteria (see Section 5.2.9.1.2), they will in addition be recorded on the AE page in the eCRF as well as on the BI SAE form, and the SAE reporting process will be followed.

Clinical symptoms and/or signs of PD will be recorded on the AE page in the eCRF. If signs and symptoms of "disease progression" / "progressive disease (PD)" / "relapse" / "resistant disease" of the patient's underlying malignancy meet the standard seriousness criteria, they will additionally be reported on the BI SAE form and SAE reporting procedures will be followed.

Exempted events are reviewed at appropriate intervals by sponsor following a pre-specified review plan.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Actual date and clock time of drug administration and exact time points of blood sampling will be documented in the CRFs by the medical personnel. The actual drug administration times and sampling times will be used for determination of pharmacokinetic parameters.

5.3.1 Assessment of pharmacokinetics

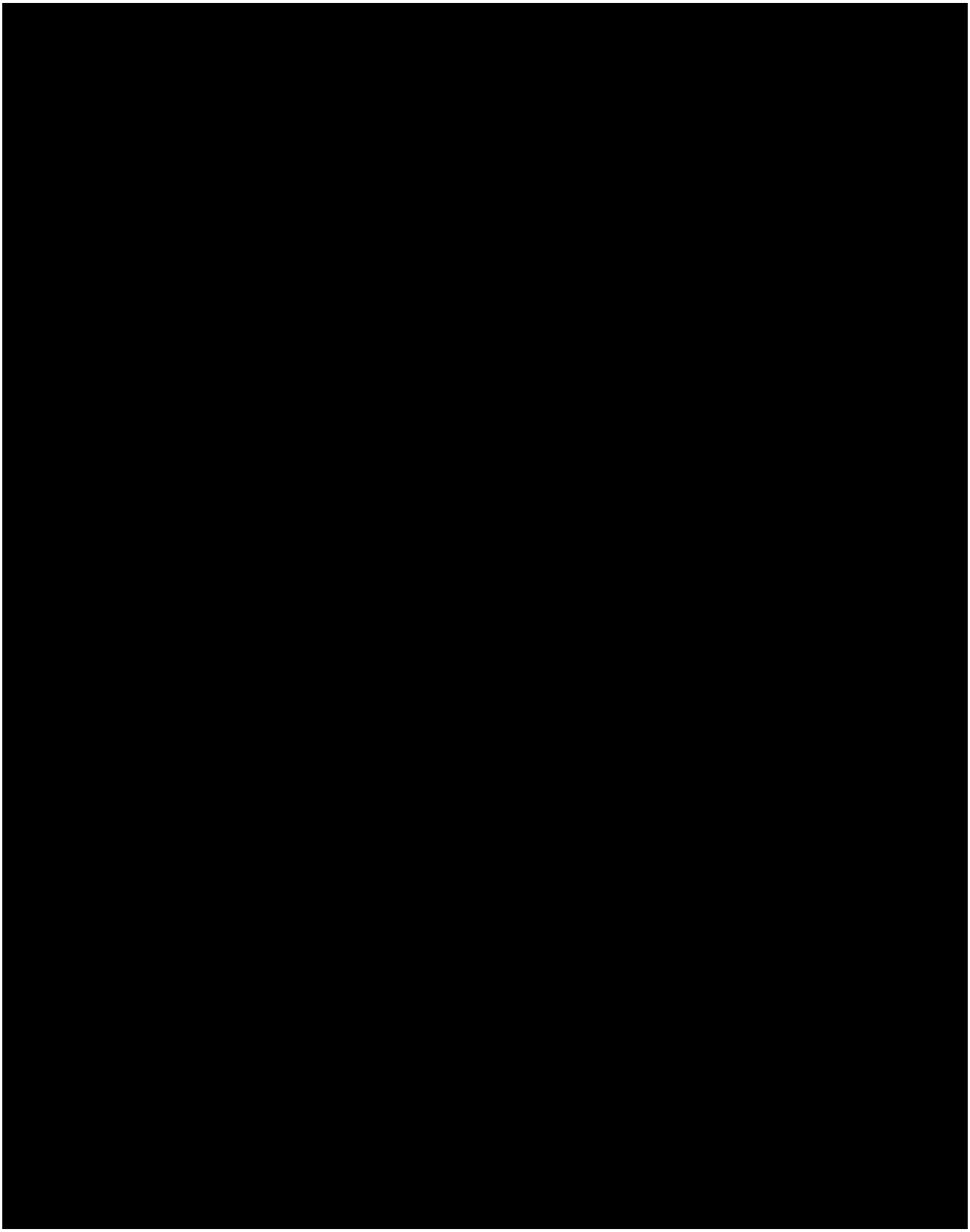
Pharmacokinetic profiles of BI 836880 (Part I and II) and BI 754091 (Part II) in plasma will be investigated after the first, second and fourth infusion cycle in Part I and the first and after the fourth infusion cycle in Part II. Standard plasma PK parameters as specified in Sections 2.1.3 and 2.2 will be calculated. Pharmacokinetic data may additionally be analyzed using population pharmacokinetic approaches. 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 standard operating procedure (SOP). Exploratory pharmacokinetic analyses can be performed as necessary for safety review. 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 interim and final results may therefore occur.

5.3.2 Methods of sample collection

The time points for collection of PK samples are given in Appendix 10.4. For quantification of analyte concentrations, approximately 3 mL of blood will be taken from a forearm vein into a blood drawing tube for each drug administered at the time points listed in the Appendix 10.4. Details of the sample collection, preparation, storage and shipment are described in the laboratory manual.

After completion of the trial the plasma samples may be used for further methodological investigations, e.g. for stability testing. However, only data related to the analyte and/or its metabolite(s) including anti-drug antibodies (if applicable) will be generated by these additional investigations. The study samples will be discarded after completion of the

additional investigations but not later than 5 years upon the final study report has been signed.



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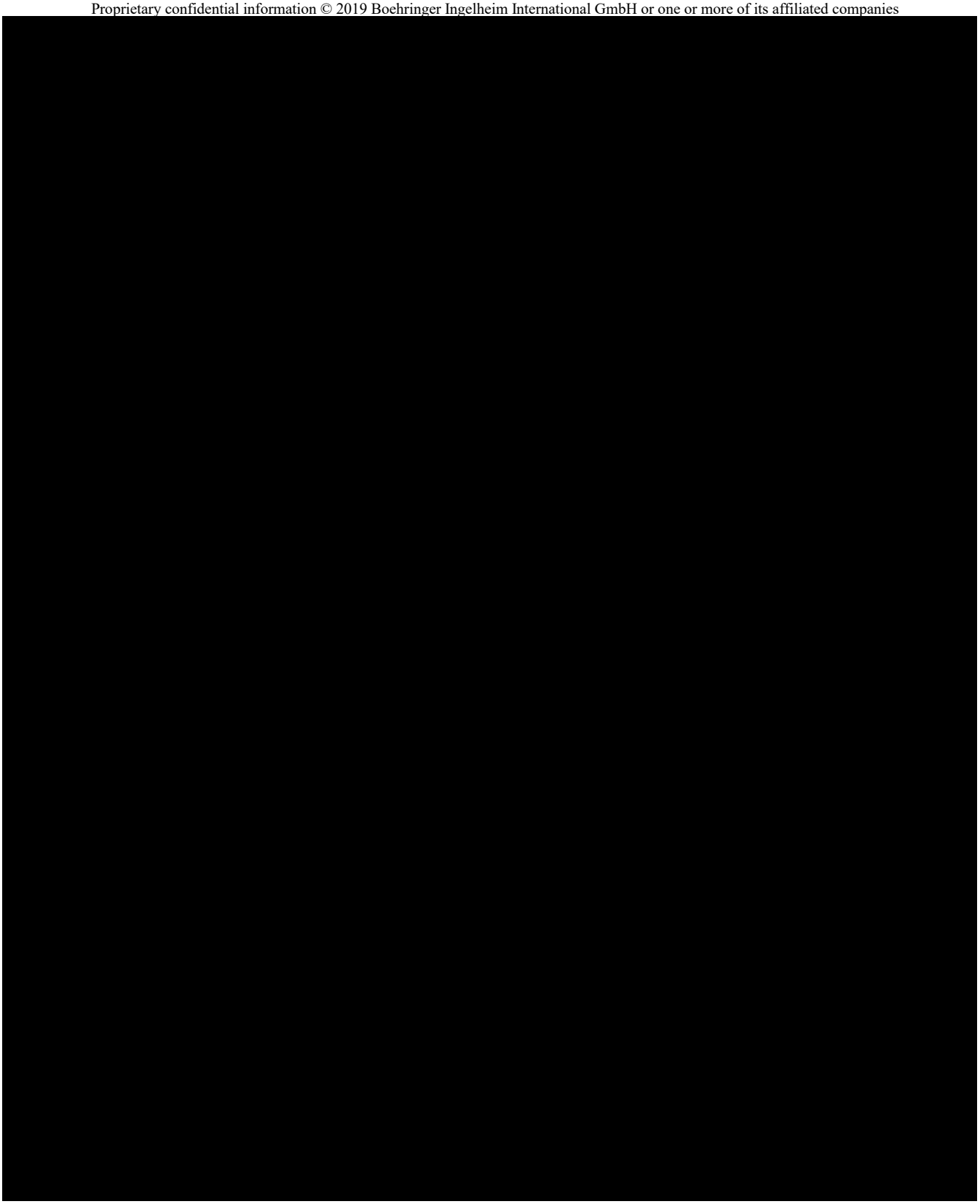

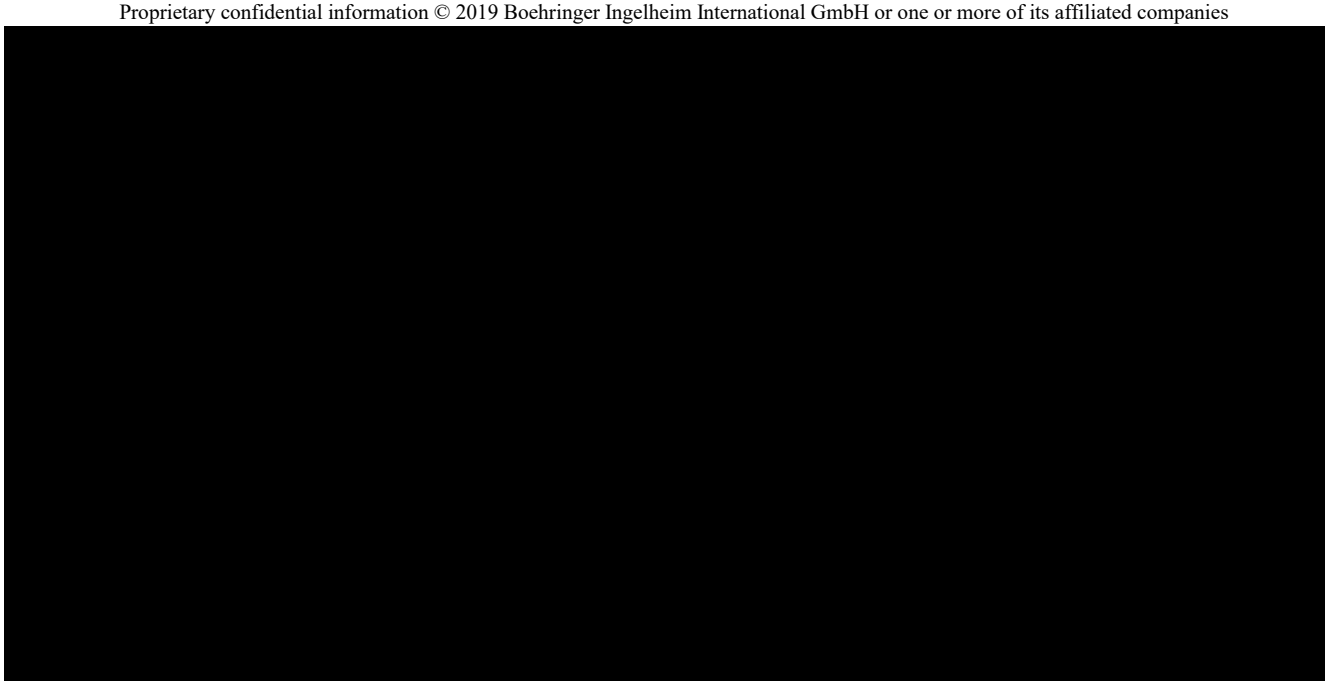

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine pharmacokinetic and pharmacodynamic parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an intravenously administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Sections 2.1.3, 2.2, and 5.3 are generally used assessments of drug exposure. The biomarkers and pharmacodynamic parameters and measurements outlined in Section 5.4 are of exploratory nature only. The determination of the immunogenic response before or during treatment with NBEs is generally applied to monitor immunogenicity risks.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

All patients should adhere to the visit schedule as specified in the Flow Chart. In case a patient misses a visit within one treatment cycle and the patient belatedly reports to the investigator between the missed and the next scheduled visit, the delayed visit should be scheduled as soon as possible and documented with the actual date and the reason for the delayed visit. The next visit, should still take place at the time it was originally scheduled in this treatment cycle. In case the day of treatment administration (visit 1 of a cycle) is delayed, all subsequent visits of a cycle will be recalculated based on the actual date of treatment of the delayed cycle.

During the treatment phase, patients are required to be hospitalized under close surveillance with access to intensive care for at least 48 hours after the first administration of trial medication(s) to allow close monitoring for infusion-related reactions or other adverse events and availability of patients for PK visits. After good tolerability of the first cycle of trial medication, 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 may shorten the duration of surveillance to 8 hours for cycles 2, 3 and 4 (PK samples included) and at investigator's discretion for further cycles.

If pathological laboratory values or other issues require an additional unscheduled visit, a new eCRF page will be created for the unscheduled visit. At the unscheduled visit, it is sufficient to record only the clinical relevant labs/examinations performed.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

The investigations as outlined in the Flow Chart will be performed at the respective visits. 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 the subsections of Section 5.2.

Procedure for collection of blood samples for PK, [redacted] are given in Sections 5.3 and 5.4.
A more detailed overview of collection of blood samples for PK, [redacted] is given in Appendix 10.4.

6.2.1 Screening and run-in period(s)

Screening Period
The examinations required for the screening visit may be conducted within a time interval specified in the Flow Chart. Prior to any other study related procedure, written informed consent must be obtained from the patient.

Baseline Conditions
Demographics (sex, birth date, race, and ethnicity where allowed), information on tobacco and alcohol use, and baseline conditions will be collected during the screening visit.

Medical History of cancer:
History of the patient's cancer will be obtained. The type of cancer, the date of the first histological diagnosis (month and year may be sufficient), and the primary tumour site will be reported on the eCRF. The differentiation grade (not specified, undifferentiated, poorly differentiated, moderately differentiated, well differentiated) obtained at the time of diagnosis and the location of metastatic sites as well as the stage according to the tumour, (lymph) node, and metastasis (TNM) classification will be provided as obtained at diagnosis and at trial screening. Previous surgeries will be reported.

Previously administered chemotherapy, tyrosine kinase inhibitor treatment, vaccine therapy, antibodies therapy, immune therapy, and hormone therapy will be reported, including start and end dates (month and year may be sufficient), as well as whether therapy was given as neoadjuvant, adjuvant, or palliative therapy. The date of tumour progression after previous lines of treatment will be recorded, if known.

Baseline information relevant to the disease history such as PD-L1 expression level, microsatellite instability (MSI), and tumour mutation burden (TMB) information will be collected in eCRF where available.

Other Medical History:
Past diseases and/or concomitant diagnoses relevant to patient's safety during the trial as judged by the Investigator will be recorded in eCRF.

Concomitant Medications:
Past medications relevant to patient's safety during the trial as judged by the Investigator will be recorded in eCRF. From the date of signature of the ICF, all concomitant medications will be recorded

6.2.2 Treatment period(s)

Please refer to the Flow Chart for a detailed presentation of each visit during the treatment period.

6.2.3 Follow-up period and trial completion

6.2.3.1 End of treatment (EoT) visit

The EoT visit will be performed as soon as possible but no later than 7 days after permanent discontinuation of the trial medication for any reason or e.g. when the Investigator decided with the patient to permanently discontinue the trial medication or became aware that the trial medication had been terminated.

The assessments of the EoT visit will then be performed instead of at the next planned visit.

If the patient finishes active treatment without having PD, tumour assessment/imaging must be performed at the time of EoT, unless it has been done within the past 4 weeks.

6.2.3.2 Safety follow-up visit

The safety follow-up visit is performed 42 (+3) days after the last administration of trial medication(s). The information collected at this visit must include all new AEs that occurred after the EoT visit, and a follow-up of AEs ongoing at EoT.

A patient will be considered as having completed the trial when any of the following applies:

- Completion of safety follow-up visit
- Lost to follow-up
- Withdrawal to be followed-up
- Death

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

7.1.1 Statistical design – Part I (BI 836880 monotherapy dose finding part)

Part I of the trial will be designed as an open label study. The objective of the design is to determine the MTD defined as the highest dose with less than 25% risk of the true DLT rate being equal or above 0.33 (EWOC criterion). The part I dose-finding will be guided by a Bayesian 2-parameter logistic regression model with overdose control (R13-4806; R13-4803).

The model is formulated as follows:

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

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

π_d represents the probability of having a DLT in the MTD evaluation period at dose d, d* = 720 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.

The estimated probability of a DLT at each dose level from the model will be summarized using the following intervals:

Underdosing: [0.00, 0.16)
Targeted toxicity: [0.16, 0.33)
Over toxicity: [0.33, 1.00]

The BLRM-recommended dose for the next cohort is the level with the highest posterior probability of the DLT rate falling in the target interval [0.16, 0.33] among the doses fulfilling EWOC. Applying the EWOC criterion it should be unlikely (<25% posterior probability) that the DLT rate at that dose will exceed 0.33.

The MTD may be considered reached if one of the following criteria is fulfilled:
1. The posterior probability of the true DLT rate in the target interval [0.16 – 0.33] of the MTD is above 0.5, OR
2. At least 9 patients have been treated in this part, of which at least 6 at the MTD.

The SMC may recommend stopping the dose finding phase after the criterion for MTD is fulfilled. Further patients may be included to confirm this MTD estimate. If no DLT is observed at a dose of which the efficacy is considered sufficient, the SMC may decide to include additional number of patients at this dose level and to declare this dose as the dose recommended for further testing.

Since a Bayesian approach is applied, a prior distribution $f(\theta)$ for the unknown parameter vector θ needs to be specified.

The prior distribution for θ will be specified as a mixture of two bivariate normal distributions,
$f(\theta) = a_1 f_1(\theta) + a_2 f_2(\theta)$
with
a_i, i = 1, 2 the prior mixture weights ($a_1 + a_2 = 1$)
and
$f_i(\theta) = MVN(\mu_i, \Sigma_i)$
the multivariate normal distribution of the i-th component with mean vector μ_i and covariance matrix Σ_i, where

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

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:
To determine the prior distribution for θ, a meta-analytic predictive (MAP) approach will be used. Toxicity information on BI 836880 from the 1336-0001 is available. Exact details on the derivation of the prior distributions and on the evaluation of the model using hypothetical data scenarios and operating characteristics are provided in the statistical appendix, i.e., Section 10.5.1, a brief description is given here.
The historical data for 1336-0001 phase I as of 20 July2018 can be found in Table 7.1.1: 1.

Table 7.1.1: 1 Historical data from 1336-0001 as of 20 July2018

Dose BI 836880 (mg)	N of patients treated	N of patients with DLTs during MTD evaluation period
40	2	0
120	2	0
360	2	0
720	17	0
1000	5	1

The following steps were performed to derive the prior distribution for θ:

- The MAP prior was derived using the information in Table 7.1.1: 1 allowing for moderate to substantial between-trial heterogeneity. This mixture component was assigned 90% mixture weight.
- A second, weakly informative component was added with 10% mixture weight. The weakly informative prior was derived to reflect a prior assumption that the median DLT rate at the starting dose of 360 mg would equal 10% and median DLT rate at 720 mg would equal 60%.

The prior distributions are given in Table 7.1.1: 2. The corresponding prior probabilities of a DLT at different doses and the corresponding probability of underdosing, targeted dosing, and overdosing are shown in Table 7.1.1: 3.

Table 7.1.1: 2 Prior distribution

Parameter	Means, standard deviations, correlation	Mixture weight
θ: component 1	(-2.263,0.116), (0.677,0.946), -0.076	0.9
θ: component 2	(0.405, 1.323), (2,1), 0	0.1

Table 7.1.1: 3 Prior probabilities of DLTs

Dose	Probability of true DLT rate in					Quantiles		
	[0,0.16)	[0.16,0.33)	[0.33,1]	Mean	StD	2.5%	50%	97.5%
360 mg	0.925	0.049	0.026	0.069	0.109	0.000	0.041	0.336
720 mg	0.751	0.169	0.080	0.154	0.176	0.027	0.100	0.844

The prior may be updated once the trial has started in case new data that can be used will be available. The prior that is used for each BLRM analysis for the SMC meetings will be documented in the SMC minutes, the prior used for the final analysis will be documented in the Trial Statistical Analysis Plan (TSAP).

7.1.2 Statistical design – Part II (BI 836880 and BI 754091 combination dose finding)

Part II of the trial will be performed as an open label single arm study. The primary objective of the design is also to determine the MTD in Japanese patients of BI 836880 in combination with BI 754091. To determine the MTD, patients are entered sequentially into escalating dose cohorts. The dose-finding will be guided by a Bayesian 5-parameter logistic regression model with overdose control. The model is defined as follows. Let $\pi_{1,d1}$ be the probability of having a DLT when giving dose d_1 of BI 836880 as monotherapy, and $\pi_{2,d2}$ the probability of having a DLT when giving dose d_2 of the combination partner BI 754091 as monotherapy, respectively. A logistic regression model is used to model the dose-toxicity relationship for each component individually:
BI 836880 part:

$$\text{logit}(\pi_{1,d1}) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$$

BI 754091 part:

$$\text{logit}(\pi_{2,d2}) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*)$$

where logit(π) = log(π /(1- π)), the reference doses d_1*=500 mg and d_2*=240 mg are set for BI 836880 and BI 754091, respectively.

Assuming no toxicity interaction between the two compounds, the probability of a DLT when giving the combination of dose d_1, d_2 is obtained as

$$\pi^0_{12,d1,d2} = \pi_{1,d1} + \pi_{2,d2} - \pi_{1,d1}\pi_{2,d2}$$

with corresponding odds

$$\text{odds}(\pi^0_{12,d1,d2}) = \pi^0_{12,d1,d2} /(1- \pi^0_{12,d1,d2})$$

In order to account for a potential positive (higher toxicity than expected under independence) or negative (lower toxicity than expected under independence) interaction between BI 836880 and BI 754091, a dose-dependent interaction term $-\infty<\eta<\infty$ is introduced to the model by the following definition:

$$\text{odds}(\pi_{12,d1,d2}) = \text{odds}(\pi^0_{12,d1,d2}) \exp(\eta\, d_1/d_1^*\, d_2/d_2^*)$$

and $\pi_{12,d1,d2}$ is used in the likelihood

$$r_{d1,d2} \sim \text{Binomial}(n_{d1,d2},\pi_{12,d1,d2})$$

where $r_{d1,d2}$ denotes the variable describing the observed number of DLTs from $n_{d1,d2}$ patients at the dose combination d_1, d_2.

Since a Bayesian approach is applied, prior distributions f for each of the parameter vectors θ_1=(log(α_1),log(β_1)), θ_2=(log(α_2),log(β_2)) and for the interaction term η need to be specified.

The prior distributions for θ_1 and θ_2 will be specified as mixtures of two multivariate normal distributions, i.e.
$f(\theta_k) = a_{1,k}\, f_1(\theta_k) + a_{2,k}\, f_2(\theta_k)$
with
$a_{1,k}$, $a_{2,k}$ the prior mixture weights, k=1,2 and
$f_i(\theta_k) = \text{MVN}(\mu_{ik}, \Sigma_{ik})$ (k=1,2),
the multivariate normal distribution of the i-th component with mean vector μ_{ik} and covariance matrix Σ_{ik}, where

$$\Sigma_{ik} = \begin{pmatrix} \sigma^2_{ik,11} & \sigma_{ik,11}\sigma_{ik,22}\rho_{ik} \\ \sigma_{ik,11}\sigma_{ik,22}\rho_{ik} & \sigma^2_{ik,22} \end{pmatrix}$$

Mixture prior distributions have the advantage that they allow for specification of different logistic dose-toxicity curves, therefore making the prior more robust.
A meta-analytic approach will be used for the prior specification of η.

The estimated probability $\pi_{12,d1,d2}$ of a DLT at each dose combination d_1, d_2 from the model will be summarised using the following intervals:
Under dosing: [0.00, 0.16)
Targeted toxicity: [0.16, 0.33)
Over dosing: [0.33, 1.00]

The BLRM-recommended dose for the next cohort is the level with the highest posterior probability of the DLT rate falling in the target interval [0.16, 0.33) among the doses fulfilling EWOC. Applying the EWOC criterion it should be unlikely (<25% posterior probability) that the DLT rate at that dose will exceed 0.33.
As described The MTD may be considered to be reached if one of the following criteria is fulfilled:

1. The posterior probability of the true DLT rate in the target interval [0.16 – 0.33) of the MTD is above 0.5, OR
2. At least 9 patients have been treated in the study, of which at least 6 at the MTD.

Prior derivation:
To determine the prior distributions for θ_1, θ_2 and η a meta-analytic predictive (MAP) approach will be used. Toxicity information on BI 836880 monotherapy from the study 1336-0001, and the Part 1 of this study, toxicity information on BI 754091 monotherapy from the studies 1381-0001 and 1381-0004, and toxicity information on the combination of BI 836880 and BI 754091 from study 1336-0011 will be incorporated. Exact details on the evaluation of the model using hypothetical data scenarios and operating characteristics are provided in the statistical appendix; a brief description is given here.

The historical data for BI 836880 can be found in Table 7.1.1: 1. For BI 754091, the historical data can be found in Tables 7.1.2: 2 and 7.1.2: 3. Expected historical data for the combination of BI 836880 and BI 754091 can be found in Table 7.1.2: 4. Since data from 1336-0012 Part 1 and 1336-0011 were not yet available by the time of finalization of the CTP, data as is might be observed in future in these trials will be used as dummy data. This dummy data will be replaced by actual data as soon as it becomes available. Whenever BLRM calculations are performed for Part 2 of 1336-0012, all available information will be used and the resulting prior distribution will be documented.

Table 7.1.2: 1 Hypothetical data expected from 1336-0012 part 1

Dose BI 836880 (mg)	N of patients treated	N of patients with DLTs during MTD evaluation period
360	6	1
720	3	2

Table 7.1.2: 2 Preliminary data from 1381-0001

Dose BI 754091 (mg)	N of patients treated	N of patients with DLTs during MTD evaluation period
80	3	0
240	34	0
400	3	0

Table 7.1.2: 3 Preliminary data from 1381-0004

Dose BI 754091 (mg)	N of patients treated	N of patients with DLTs during MTD evaluation period
240	6	0

Table 7.1.2: 4 Hypothetical data expected from 1336-0011

Dose BI 836880 (mg) / BI 754091 (mg)	N of patients treated	N of patients with DLTs during MTD evaluation period
360 / 240	1	1
500 / 240	0	0
720 / 240	0	0

The following steps were performed to derive the prior distribution for Part 2:

1) The meta-analytic predictive prior was derived for both compounds and for the interaction parameter η using the information in Tables 7.1.2: 1 – 7.1.2: 4, allowing for moderate to substantial between-trial heterogeneity, tau parameters are assumed to be normally distributed with mean log(0.25) and SD log(2)/1.96. See a reference (R18-3210) for details on the MAP prior. These prior components were assigned 90% mixture weight for both compounds.
2) A second, weakly informative prior component was added with the same mean values as the MAP prior, standard deviation (2, 1) and correlation 0. This mixture component was assigned 10% mixture weight

The resulting parameters of the prior distributions for four combination levels, i.e., (120/240, 360/240, 500/240, 720/240), are given in Table 7.1.2: 5. The corresponding prior probabilities of a DLT at different dose combinations and the corresponding probabilities of under toxicity, targeted toxicity and over toxicity are shown in Table 7.1.2: 6. As can be seen from Table 7.1.2: 6, the dose combination 120 mg BI 836880 and 240 mg BI 754091 has prior probability of over toxicity below 25%. It fulfils the overdose criterion and is therefore a suitable starting dose combination.

Table 7.1.2: 5 Prior Distribution

Parameter	Prior distributions Means, standard deviations, correlation	Mixture weight
$\log(\alpha_1)$, $\log(\beta_1)$: component 1	(-1.877,-0.574), (0.983, 0.893), -0.145	0.9
$\log(\alpha_1)$, $\log(\beta_1)$: component 2	(-1.877,-0.574), (2,1), 0	0.1
$\log(\alpha_2)$, $\log(\beta_2)$: component 1	(-1.500, 1,213), (1.070, 1.034), 0.387	0.9
$\log(\alpha_2)$, $\log(\beta_2)$: component 2	(-1.500, 1,213), (2,1), 0	0.1
η	0.466, 0.989	N/A

Table 7.1.2: 6 Prior probabilities of DLTs

Dose (mg)	Dose (mg)	Probability of true DLT rate in			Descriptive statistics				
BI 836880	BI 754091	[0,0.16)	[0.16,0.33)	[0.33,1]	Mean	SD	2.5%	50%	97.5%
120	240	0.486	0.327	0.187	0.209	0.162	0.023	0.165	0.637
360	240	0.280	0.311	0.409	0.318	0.213	0.035	0.273	0.814
500	240	0.134	0.213	0.653	0.468	0.255	0.059	0.454	0.933
720	240	0.077	0.100	0.822	0.680	0.299	0.065	0.774	1.000

The prior will be updated once the trial has started in case new data that can be used will be available. The prior that is used for each BLRM analysis for the SMC meetings will be documented in the SMC minutes, the prior used for the final analysis will be documented in the TSAP.

7.2 NULL AND ALTERNATIVE HYPOTHESES

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

7.3 PLANNED ANALYSES

No per protocol set will be used in the analysis. However, important protocol deviations will be summarised. The TSAP will specify the important protocol deviations in detail.

For the determination of the MTD, only MTD evaluable patients will be considered. For the analysis of secondary and further endpoints, all patients in the treated set (i.e. patients treated with at least one dose of trial medication) will be included in the analysis. Any other analysis sets will be defined in the TSAP.

7.3.1 General considerations

Treated set includes all patients who were treated with at least one dose of trial medication. The pharmacokinetic parameters listed in Sections 2.1.3 and 2.2.2 will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' (001-MCS-36-472). PK analyses will be performed using validated software programs, normally, Phoenix WinNonlin [redacted] with applications validated for the respective purpose. Graphs and tables will be generated using validated customised [redacted] macros or appropriate graphic software.

7.3.2 Primary endpoint analyses

In order to identify the MTD, the number of patients with DLTs during the MTD evaluation period of Part I and Part II at each dose level must be presented. Patients who discontinue during the first treatment course for reasons other than DLTs will be excluded from the determination of MTD.

In addition, the number of patients with DLTs that occurred during the entire treatment period will be also summarised.

7.3.3 Secondary endpoint analyses

Please refer to Section 2.1.3 for PK related secondary endpoints. Details on the statistical inference for PK parameters, e.g., dose proportionality using C_{max} and AUC_{0-504h} of BI 836880 in case of more than 3 dose level tested, will be specified in the TSAP.

[redacted]

7.3.5 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the REP, a period of 42 days after the last dose of trial medication, will be assigned to the on-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, i.e. all adverse events occurring between start of treatment and end of the REP. 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 MedDRA at database lock.

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 summarised. 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.

7.3.6 Interim Analyses

No formal interim analysis is foreseen.
The sponsor will continuously monitor the safety. The dose escalation design foresees that the sponsor and the SMC perform regular safety evaluations. These evaluations will be unblinded to dose.
If considered necessary, an evaluation of the efficacy and 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.

Regarding exploratory PK analysis, please refer Section 5.3.1.

7.4 HANDLING OF MISSING DATA

In general, no imputation will be performed on missing efficacy data. Detailed censoring rules will be specified in the TSAP. 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 AEs, with particular emphasis on potential DLTs. For partial or missing AE onset and/or end dates, BI internal rules will be followed (see Reference Document 001-MCG-156_RD-01 "Handling of missing and incomplete AE dates").
Handling of missing PK data will be performed according to the relevant SOP of the Sponsor (001-MCS-36-472_RD-01).

7.5 RANDOMISATION

No randomisation will be performed.

7.6 DETERMINATION OF SAMPLE SIZE

No formal statistical power calculations of sample size were performed. Approximately 9 patients for Part I are expected, and approximately 15 patients for Part II are expected. As

more patients might be needed based on the recommendation of the SMC and the actual number of cohorts tested.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

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 Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as "protocol deviation".

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

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. 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 finalisation of the Clinical Trial Report. In exceptional cases, data may be published before the clinical trial report as long as this is discussed and agreed to by the investigators and the sponsor.

The certificate of insurance cover is made available to the investigator and the patients, and is stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB/IEC and CA according to national and international regulations. The same applies for the implementation of changes introduced by amendments. Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative."

The investigator or delegate must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible.

The patient must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.
Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.
The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.
Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.
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

CRFs for individual patients will be provided by the sponsor. For drug accountability, refer to Section 4.1.12.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. Changes to the data should be traceable (audit trail).
Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least one documented attempt to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

Copies of source documents necessary for tumour assessment will be provided to an authorised vendor. Before sending or uploading those copies, the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents.
If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.
For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of patient's participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The investigator /institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

Trial site(s):
The trial site(s) must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).
Sponsor:

The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

Exemptions from expedited reporting are described in Section 5.2.9.2.4.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the World Health Organisation (WHO) GCP handbook.
Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:
Personalised 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 at the site 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.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, biobanking and future use of biological samples and clinical data, in particular

- Sample and data usage has to be in accordance with the separate biobanking informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data
- Samples and/or data may be transferred to third parties and other countries as specified in the biobanking ICF

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.
The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed").

The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of suspected unexpected serious adverse reactions (SUSARs) occurring with the trial medication until 30 days after LPLT at their site. **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.
Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.
Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim.

A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

A SMC composed of participating investigators and members of the BI trial team will be established to review individual and aggregated safety and efficacy data at regular intervals to determine the safety profile, risk/benefit ratio, recommend next dose level/does escalation/de-escalation/modification/next cohort size, and appropriateness of further enrolment.
Details of the SMC responsibilities and procedures are described in the SMC charter.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF. The investigators will have access to the BI clinical trial portal (Clinergize) to facilitate document exchange and maintain electronic ISF.

BI has appointed a Clinical Trial Leader (CT Leader), 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,
- ensure appropriate training and information of Clinical Trial Managers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a CRO with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

Data Management will be done by BI or a vendor according to BI SOPs.
Statistical Evaluation will be done by BI according to BI SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.
A central laboratory service, a central imaging collection service, and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual and Central Laboratory Manual, available in the ISF.

9. REFERENCES

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10. APPENDICES

10.1 IMMUNE-RELATED ADVERSE EVENTS OF SPECIAL INTEREST

Table 10.1: 1 Immune-related adverse events of special interest

This table defines immune-related AEs that must be reported as AESIs if they occur after exposure to BI 754091.

Immune-related adverse events of special interest
Pneumonitis (report as AESI if an irAE is ≥ Grade 2)
• Acute interstitial pneumonitis • Interstitial lung disease • Pneumonitis
Colitis (report as AESI if an irAE is ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)
• Intestinal obstruction • Colitis • Colitis microscopic • Enterocolitis • Enterocolitis haemorrhagic • Gastrointestinal perforation • Necrotizing colitis • Diarrhea
Endocrine (report as AESI if an irAE is ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)
• Adrenal insufficiency • Hyperthyroidism • Hypophysitis • Hypopituitarism • Hypothyroidism • Thyroid disorder • Thyroiditis • Hyperglycaemia, if ≥ Grade 3 and associated with ketosis or metabolic acidosis
Endocrine (report as AESI for any grade)
• Type 1 diabetes mellitus (if new onset)

Immune-related adverse events of special interest
Hematologic (report as AESI if an irAE is ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)
• Autoimmune haemolytic anaemia • Aplastic anaemia • Thrombotic thrombocytopenic purpura • Idiopathic (or immune) thrombocytopenia purpura • Disseminated intravascular coagulation • Haemolytic-uraemic syndrome • Any Grade 4 anaemia regardless of underlying mechanism
Hepatic (report as AESI if an irAE is ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat the AE**)**
• Hepatitis • Autoimmune hepatitis • Transaminase elevations (ALT and/or AST)
Infusion Reactions (report as AESI for any grade)
• Allergic reaction • Anaphylaxis • Cytokine release syndrome • Serum sickness • Infusion reactions • Infusion-like reactions
Neurologic (report as AESI for any grade)
• Autoimmune neuropathy • Guillain-Barre syndrome • Demyelinating polyneuropathy • Myasthenic syndrome
Ocular (report as AESI if an irAE is ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)
• Uveitis • Iritis

Immune-related adverse events of special interest
Renal (report as AESI if an irAE is ≥ Grade 2)
• Nephritis • Nephritis autoimmune • Renal failure • Renal failure acute • Creatinine elevations (report as an irAE if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)
Skin (report as AESI for any grade)
• Dermatitis exfoliative • Erythema multiforme • Stevens-Johnson syndrome • Toxic epidermal necrolysis
Skin (report as AESI if an irAE is ≥ Grade 3)
• Pruritus • Rash • Rash generalized • Rash maculopapular • Any rash considered clinically significant in the physician's judgment
Other (report as AESI for any grade)
• Myocarditis • Pancreatitis • Pericarditis • Any other Grade 3 event that is considered immune-related by the physician

10.2 MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS (PART II ONLY)

Management of immune-related adverse event toxicities associated with anti-PD-1 mAbs are presented below. **BI 754091 should be permanently discontinued for Grade 3-4 pneumonitis, Grade 3-4 adrenal insufficiency, Grade 4 diabetes mellitus, any grade encephalitis, Grade 4 hypophysitis, Grade 4 rash, Grade 3-4 or recurrent colitis of any grade, any recurrent Grade 3-4 AE, transaminase increased >5 times ULN or total bilirubin >3 times ULN (unless unequivocally attributably to another cause), inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2-3 AEs that do not recover to Grade 1 or less within 12 weeks.**

- Pneumonitis:
    - For Grade 2 events, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
    - For Grade 3-4 events immediately treat with i.v. steroids. Administer additional anti-inflammatory measures, as needed.
    - BI 754091 should be permanently discontinued for Grade 3-4 pneumonitis, inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2 AEs that do not recover to Grade 1 or less within 12 weeks.
- Diarrhoea/Colitis:

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhoea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

- All subjects who experience diarrhoea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via i.v. infusion. For Grade 2 or higher diarrhoea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For Grade 2 diarrhoea/colitis that persists greater than 3 days, administer oral corticosteroids.
- For Grade 3 or 4 diarrhoea that persists >1 week, treat with i.v. steroids followed by high-dose oral steroids.
- For Grade 3 or 4 colitis, or recurrent colitis of any grade, permanently discontinue BI 754091, and immediately treat with i.v. steroids followed by high-dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days.
- BI 754091 should be permanently discontinued for Grade 3-4 or recurrent colitis of any grade, inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2-3 AEs that do not recover to Grade 1 or less within 12 weeks.

- Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis) Grade 3, or ≥ Grade 3 hyperglycaemia, if associated with ketosis (ketonuria) or metabolic acidosis

  - For Type 1 diabetes mellitus Grade 3-4 or Grade 3-4 hyperglycaemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycaemia associated with metabolic acidosis or ketonuria.
    - Evaluate subjects with serum glucose and a metabolic panel, urine ketones, glycosylated haemoglobin, and C-peptide.
  - BI 754091 should be permanently discontinued for Grade 4 diabetes mellitus, any recurrent Grade 3 AE or persistent Grade 2-3 AE that does not recover to Grade 1 or less within 12 weeks.
- Hypophysitis:
  - For Grade 2 events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For Grade 3 events, treat with an initial dose of i.v. corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For Grade 4 events, permanently discontinue BI 754091, and treat with an initial dose of i.v. corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - BI 754091 should be permanently discontinued for Grade 4 hypophysitis, any recurrent Grade 3 AE, inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2-3 AEs that do not recover to Grade 1 or less within 12 weeks.
- Hyperthyroidism or Hypothyroidism:
  Thyroid disorders can occur at any time during treatment. Monitor subjects for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
  - For Grade 2 hyperthyroidism events (and Grade 3-4 hypothyroidism):
    - In hyperthyroidism, nonselective beta-blockers (e.g., propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.
  - For Grade 3-4 hyperthyroidism
    - Treat with an initial dose of i.v. corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - BI 754091 should be permanently discontinued for any recurrent Grade 3-4 AE, inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2-3 AEs that do not recover to Grade 1 or less within 12 weeks.

- Hepatic:
  - For Grade 2 events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with i.v. or oral corticosteroids
  - For Grade 3-4 events, treat with i.v. corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 28 days.
  - BI 754091 should be permanently discontinued for any recurrent Grade 3-4 AE, transaminase increases >5 times ULN or total bilirubin >3 times ULN (unless unequivocally attributably to another cause), inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2-3 AEs that do not recover to Grade 1 or less within 12 weeks.
- Renal failure or nephritis:
  - For Grade 2 events, treat with corticosteroids.
  - For Grade 3-4 events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days.
  - BI 754091 should be permanently discontinued for any recurrent Grade 3-4 AE, inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2-3 AEs that do not recover to Grade 1 or less within 12 weeks.
- Adrenal insufficiency:
  - BI 754091 should be permanently discontinued for Grade 3-4 adrenal insufficiency or persistent Grade 2 AEs that do not recover to Grade 1 or less within 12 weeks.
- Rash:
  - BI 754091 should be permanently discontinued for Grade 4 rash, any recurrent Grade 3 AE or persistent Grade 2-3 AEs that do not recover to Grade 1 or less within 12 weeks.
- Encephalitis:
  - BI 754091 should be permanently discontinued for any grade encephalitis.
- Infusion reactions:
  Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

10.3 BLOOD PRESSURE MEASUREMENT PROCEDURE

Blood pressure measurements should be performed on the same arm and, if possible, by the same person. The machines or devices to be used for blood pressure measurement should be certified. The machines to be used for blood pressure measurement should be certified. 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.

In case of a suspected “white coat effect” it is recommended to repeat the measurement in a pleasant condition after sufficient rest. Values from self-blood pressure measurement (SBPM) communicated from patient to investigator is not considered valuable for study related decisions.

10.4 TIME SCHEDULE FOR PHARMACOKINETIC (PK), [redacted] BLOOD SAMPLING

Table 10.4: 1 Time schedule for PK, [redacted] blood sampling for Part I

Cycle	Visit	Day	Time Point	CRF Time / planned time (hh:min)	PK: BI 836880	[redacted]
1, 2	1	1	Before start of BI 836880 infusion	-0:05	X	
			Start of BI 836880 infusion	0:00		
			Immediately after end of infusion*	1:00**	X	
			0.5h after the end of infusion	1:30	X	
			1.5h after the end of infusion	2:30	X	
			3.5h after the end of infusion	4:30	X	
			6.5h after the end of infusion	7:30	X	
	2a	2	24h after the start of infusion	24:00	X	
	2b	3	48h after the start of infusion	48:00	X	
	3	8	7 days after start of infusion	168:00	X	
	4	15	14 days after start of infusion	336:00	X	
3	1	1	Before start of BI 836880 infusion	-0:05	X	
			Start of BI 836880 infusion	0:00		
			Immediately after end of infusion*	1:00**	X	
	2a	2	24h after the start of infusion	24:00	X	
4	1	1	Before start of BI 836880 infusion	-0:05	X	
			Start of BI 836880 infusion	0:00		
			Immediately after end of infusion*	1:00**	X	
			0.5h after the end of infusion	1:30	X	
			1.5h after the end of infusion	2:30	X	

Cycle	Visit	Day	Time Point	CRF Time / planned time (hh:min)	PK: BI 836880	[redacted]
			3.5h after the end of infusion	4:30	X	
			6.5h after the end of infusion	7:30	X	
	2a	2	24h after the start of infusion	24:00	X	
	3	8	7 days after start of infusion	168:00	X	
	4	15	14 days after start of infusion	336:00	X	
5-12	1	1	Before start of BI 836880 infusion	-0:05	X	
			Start of BI 836880 infusion	0:00		
EoT					X	
Safety follow-up					X	

* within 5 min after the end of infusion

** PTM of 1:00 according to an infusion duration of 60 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.

Table 10.4: 2 Time schedule for PK, [redacted] blood sampling for Part II

Cycle	Visit	Day	Time Point	CRF Time / planned time (hh:min)	PK BI 836880 BI 754091	[redacted]
1	1	1	Before start of BI 754091 infusion	-0:05	X	
			Start of BI 754091 infusion	0:00		
			After end of BI 754091 infusion	1:00*	X	
			Start of BI 836880 infusion	1:15		
			After end of BI 836880 infusion	2:15*	X	
			6 hours after start of BI 754091infusion (3:45 after end of BI 836880 if	6:00	X	

Cycle	Visit	Day	Time Point	CRF Time / planned time (hh:min)	PK BI 836880 BI 754091
			no infusion delay)		
	2a	2	24h after start of BI 754091 infusion	24:00	X
	3	8	7 days after start of BI 754091 infusion	168:00	X
	4	15	14 days after start of BI 754091 infusion	336:00	X
2, 3	1	1	Before start of BI 754091 infusion	-0:05	X
			Start of BI 754091 infusion	0:00	
			After end of BI 754091 infusion	1:00*	X
			Start of BI 836880 infusion	1:15	
			After end of BI 836880 infusion	2:15*	X
4	1	1	Before start of BI 754091 infusion	-0:05	X
			Start of BI 754091 infusion	0:00	
			After end of BI 754091 infusion	1:00*	X
			Start of BI 836880 infusion	1:15	
			After end of BI 836880 infusion	2:15*	X
			6 hours after start of BI 754091 infusion (3:45 after end of BI 836880 if no infusion delay)	6:00	X
	2a	2	24h after start of BI 754091 infusion	24:00	X
	3	8	7 days after start of BI 754091	168:00	X

Cycle	Visit	Day	Time Point	CRF Time / planned time (hh:min)	PK BI 836880 BI 754091
			infusion		
	4	15	14 days after start of BI 754091 infusion	336:00	X
5, 6	1	1	Before start of BI 754091 infusion	-0:05	X
			Start of BI 754091 infusion	0:00	
			After end of BI 754091 infusion	1:00*	X
			Start of BI 836880 infusion	1:15	
			After end of BI 836880 infusion	2:15*	X
7-12	1	1	Before start of BI 754091 infusion	-0:05	X
EoT					X
Safety follow-up					X

* within 5 min after the end of infusion

10.5 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. The simulations for scenarios and operating characteristics were produced using R version 3.4.2.

10.5.1 Part I (BI 836880 monotherapy dose finding part)

Hypothetical data scenarios

Hypothetical data scenarios are shown in Table 10.5.1: 1. These scenarios reflect potential on-study data constellations and related escalation as allowed by the model. 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.

For example, scenario 1 represents the case that no DLT is observed in the first three patients at the starting dose of 360 mg. In this case, the next optimal dose, i.e. the dose with the highest probability of being in the target interval, is 720 mg. Similarly scenario 4 represents the case where no DLTs are observed, and the next optimal dose recommended is 720 mg according to BLRM since no higher dose is available.

Scenarios 5 illustrates the case where low dose cohorts have no DLT and the highest dose level 720 mg/kg has 1 DLT, in such cases, BLRM would continue to assign patients on 720 mg/kg,

In scenario 6, two DLT is observed already in the patient. In this case, the model recommends de-escalation to 360 mg.

Table 10.5.1: 1 Hypothetical data scenarios

Scenario	Dose (mg)	# DLT	# Pat	Current Dose: P(OD)	Next Recommended Dose	Next Dose		
						P(UD)	P(TD)	P(OD)
1	360	0	3	0.005	720	0.728	0.213	0.059
2	360	1	3	0.052	720	0.406	0.416	0.179
3	360	2	3	0.241	360	0.350	0.410	0.241
4	360 720	0 0	3 3	0.016	720	0.831	0.152	0.016
5	360 720	0 1	3 3	0.093	720	0.561	0.346	0.093

6	360 720	0 2	3 3	0.319	360	0.865	0.114	0.021

Operating characteristics

Operating characteristics are a way to assess the long-run behaviour of a model by illustrating the precision of the design in estimating the MTD. 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 10.5.1: 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 means
- Scenario 2: high-toxicity scenario
- Scenario 3: low-toxicity scenario
- Scenario 4: non-logistic dose-toxicity scenario
- Scenario 5: low-toxicity followed by high-toxicity
- Scenario 6: super high-toxicity scenario

Table 10.5.1: 2 Assumed true dose-toxicity scenarios

Scenario		Dose (mg)	
		360	720
1 (Prior)	P(DLT)	0.069	0.154
2 (High Tox)		0.321	0.500
3 (Low Tox)		0.039	0.180
4 (Non-Logistic)		0.280	0.360
5 (Low-High)		0.180	0.317
6 (Super High Tox)		0.580	0.769

* Additional dose level 1250mg added (assumed true tox probability of 0.444, 0.603, 0.250, 0.380 and 0.600 under scenarios 1-5 respectively) to allow R code to run. For scenario 6, additional dose level 120mg added (assumed true tox probability of 0.26) to allow R code to run.

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 10.5.1: 3.

Table 10.5.1: 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	72.6	0.0	25.7	1.7	11.4(3-24)	2.3(1-8)
2	0.0	40.5	19.3	40.2	8.3(3-27)	3.4(1-10)
3	10.9	88.4	0.0	0.7	11.7(3-33)	1.8(1-6)
4	0.0	29.7	44.9	25.4	9.3(3-24)	3.0(1-12)
5	0.0	83.3	5.3	11.4	10.3(3-21)	3.1(1-8)
6	0.0	46.4	11.6	42.0	8.7(3-18)	4.1(2-9)

In Scenario 1, which reflects the case that the true dose-toxicity is aligned with prior means, 72. 6% of the simulated trials declared a dose as MTD with true DLT rate under the targeted dose range, since there is no dose with assumed true toxicity probability in the target interval, therefore it is logical that none of the trials declares a MTD with true tox probability in the target interval. In many cases the model chooses that dose as MTD that is closest to the target interval, this is 720mg with assumed tox probability of 0.154, since 0.154 is very close to the target interval.

Scenario 2 (high-toxicity scenario) shows, that when the true DLT rate is high, i.e. the majority dose levels with true DLT rate above the target interval, 40.5% of the simulated trials declared a dose as MTD with true DLT rate in the targeted dose range. The starting dose has already >32.1% 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 (40.2%) 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.

Scenarios 3 and 5 show that when the true DLT rate is low and low-high, most of the simulated trials declared a dose as MTD with true DLT rate in the targeted dose range.

Scenario 4 shows, that when the true DLT rate is non-logistic, then more likely the model will declare a overdose as MTD.

Scenario 6 shows that when the true DLT rate is super high, 42% of simulated trials stopped, since none of the doses is considered tolerable anymore. This is an expected situation for a super high-toxicity scenario.

The mean patient numbers range from 8.3 patients (Scenario 2) to 11.7 (Scenario 3) during the simulation. This shows that the planned maximum of 9 patients is reasonable.

In summary, the considered data scenarios show a reasonable behaviour of the model and the operating characteristics demonstrate a good precision of MTD determination.

10.5.2 Part II (BI 836880 and BI 754091 combination dose finding)

Hypothetical data scenarios

Hypothetical data scenarios are shown in Table 10.5.2: 1. These scenarios reflect potential on-study data constellations and related escalation as allowed by the model. For each scenario, the probability of overdose for the current dose combination, as well as the next potential dose combination and related probabilities of under-dosing, target dose, and over-dosing are shown.

Table 10.5.2: 1 Hypothetical data scenarios

Scenario	Dose (mg)	# DLT	# Pat	Current Dose: P(OD)	Next Recommended Dose	Next Dose		
						P(UD)	P(TD)	P(OD)
1	120/240	0	3	0.054	360/240	0.413	0.339	0.248
2	120/240	1	3	0.228	120/240	0.336	0.436	0.228
3	120/240	2	3	0.528	NA	NA	NA	NA
4	120/240 360/240	0 0	3 3	0.085	360/240	0.609	0.306	0.085
5	120/240 360/240	0 1	3 3	0.295	120/240	0.627	0.324	0.049
6	120/240 360/240	0 2	3 3	0.602	120/240	0.408	0.440	0.152

For example, scenario 1 represents the case that no DLT is observed in the first three patients at the starting dose combination of 120/240 mg/kg. In this case, the next optimal dose combination, i.e. the dose combination with the highest probability of being in the target interval, is the next dose combination, i.e., 360/240 mg/kg. Scenarios 5 illustrates the case where low dose combination cohorts have no DLT and the highest dose combination level 360/240 mg/kg has 1 DLT, in such cases, BLRM would de-escalate and put patients on 120/240 mg/kg, In scenarios 3, two DLT is observed already in the patient. In this case, the model recommends stopping the trial because of high overdose probabilities.

Operating characteristics

Operating characteristics are a way to assess the long-run behaviour of a model by illustrating the precision of the design in estimating the MTD. Under an assumed true dose-toxicity curve, metrics such as the probability of recommending a dose combination with true DLT rate in the target interval can be approximated via simulation. Table 10.5.2: 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 means
- Scenario 2: high-toxicity scenario
- Scenario 3: low-toxicity scenario
- Scenario 4: non-logistic dose-toxicity scenario
- Scenario 5: low-toxicity followed by high-toxicity
- Scenario 6: super high-toxicity scenario

Table 10.5.2: 2 Assumed true dose-toxicity scenarios

Scenario		Dose (mg)		
		120/240	360/240	720/240
1 (Prior)	P(DLT)	0.209	0.318	0.680
2 (High Tox)		0.291	0.327	0.516
3 (Low Tox)		0.054	0.128	0.190
4 (Non-Logistic)		0.145	0.290	0.505
5 (Low-High)		0.128	0.169	0.550
6 (Super High Tox)		0.489	0.580	0.769

Table 10.5.2: 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	5.9	76.9	3.8	13.4	11.9 (3-30)	3.3 (1-10)
2	0.0	64.6	9.5	25.9	10.3 (3-30)	3.4 (1-11)
3	68.1	29.2	0.0	2.7	14.6 (3-42)	1.8 (0-8)
4	66.3	7.5	20.8	5.4	11.8 (3-27)	2.8 (1-9)
5	62.2	10.6	23.4	3.8	11.9 (3-27)	2.7 (1-7)

6	0.0	24.4	26.5	49.1	11.0 (3-27)	4.3 (1-10)

In scenario 1, which reflects the case that the true dose-toxicity is aligned with prior means, 76.9% of the simulated trials declared a dose as MTD with true DLT rate in the targeted dose range.

In Scenario 2 (high-toxicity scenario), 64.6% of the simulated trials declared a dose as MTD with true DLT rate in the targeted dose range.

In Scenarios 1 and 2, the starting dose has already >12.0% 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 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 assumed dose-toxocity scenarios.

In Scenarios 3-5, there is/are one or two dose(s) with assumed true toxicity probability in the underdosing interval [0.00, 0.16), in some cases the model chooses that dose as MTD that is closest to the target interval, which results in certain percentage of trials with an MTD with true DLT rate in underdosing interval.

Scenario 6 shows that when the true DLT rate is super high, 49.1% of simulated trials stopped, since none of the doses is considered tolerable anymore. This is an expected situation for a super high-toxicity scenario.

The mean patient numbers range from 10.3 patients (Scenario 2) to 14.6 (Scenario 3) during simulation. This shows that the planned maximum of 12 patients is reasonable.

In summary, the considered data scenarios show a reasonable behaviour of the model and the operating characteristics demonstrate a good precision of MTD determination.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		28 Mar 2019
EudraCT number **EU number**		Not applicable
BI Trial number		1336-0012
BI Investigational Medicinal Product(s)		BI 836880 and BI 754091
Title of protocol		An open label, Phase I study of BI 836880 monotherapy and combination therapy of BI 836880 and BI 754091 in Japanese patients with advanced solid tumours
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Clinical Trial Protocol Synopsis – Trial site(s)
Description of change		Multi-centre trial conducted in **Japan** ~~Asia~~
Rationale for change		Clarification
Section to be changed		Clinical Trial Protocol Synopsis – Total number of patients treated Clinical Trial Protocol Synopsis – Number of patients on each treatment
Description of change		Approximately **24** ~~21~~
Rationale for change		A buffer of 3 patients was added for the possibility of adding extra number of patients for DLTs or other reasons.
Section to be changed		Flow Chart and Section 5.2.3 Vital signs
Description of change		Arterial oxygen saturation (SpO_2) was added as a part of vital signs measurements.
Rationale for change		For early detection of potential interstitial lung diseases.
Section to be changed		Flow Chart and Section 5.2.7 Chest X-ray
Description of change		Regular Chest X-ray testing was added.
Rationale for change		For early detection of potential interstitial lung diseases.
Section to be changed		Flow Chart
Description of change		Footnote b is modified: Safety laboratory assessments including haematology, clinical biochemistry, and urinalysis

		will be performed locally. If screening laboratory assessments, ~~and,~~ pregnancy testing, **and chest X-ray are** performed within ~~72 hours of~~ **3 days before** initiation of treatment, they do not need to be repeated on Cycle 1 Day 1. Refer to Section 5.2 for additional details.
Rationale for change		Clarification
Section to be changed		1.1 Medical background
Description of change		The following description in the fourth paragraph was deleted: Studies in mice have shown that Ang2, a ligand of the Tie2 receptor, controls vascular remodelling 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 tumour vessel plasticity, allowing vessels to respond to VEGF and FGF2 (R12-3834).
Rationale for change		It was found to be redundant.
Section to be changed		1.3 Rationale for performing the trial
Description of change		In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking (please see Section **5.5** ~~5.4~~)
Rationale for change		Correction of error
Section to be changed		1.4.1 Benefits
Description of change		This trial is for patients with **advanced cancer and for whom there are** no therapy options of proven efficacy, or who are not amenable to **currently available** standard therapies. ~~The investigational agent~~ BI 836880 is an investigational antiangiogenic agent **and BI 754091 is an investigational immune checkpoint inhibitor**. There are many antiangiogenic agents already approved to treat **various types of** cancer**.** ~~and by~~ **Similarly there are many immune checkpoint inhibitors approved in various types of cancers. By** participating in this trial and receiving study medication(s) **either as monotherapy or in combination**, patients **with advanced cancer** may have a better chance to delay ~~in~~ tumour progression, compared with no anti-cancer treatment.

		Based on the mode of action of BI 836880 and BI 754091, published and internal preclinical data, and available clinical data, it is anticipated that **treatment with this** ~~the~~ combination will **potentially improve response rate with** ~~increase the anti tumour efficacy resulting in an increase in response rate with~~ prolonged duration of response as compared to each monotherapy.
Rationale for change		Clarification
Section to be changed		Table 1.4.2:1 Potential risks, their rationale, and mitigation strategy
Description of change		Summary of data, rationale for the risk of hypertension in BI 836880: This is a class effect ~~AE~~ and has been identified as ~~a side effect~~ **an expected AE in this trial**. Summary of data, rationale for the risk of thromboembolic events in BI 836880: This is a class effect **and expected AE with antiangiogenics** ~~AE~~. Mitigation strategy for immune-related adverse events (irAEs) in BI 754091: Recommendations for the management of irAEs are provided. **Investigators** involved in **this trial have experience in managing irAE and sites have facilities. A 48-hour hospitalisation with access to intensive care is mandated for all patients after the first study drug administration to secure the patient safety.**
Rationale for change		Clarification
Section to be changed		1.4.3 Discussion
Description of change		Both BI 836880 and BI 754091 are currently tested in early phase clinical trials **as monotherapy and as a combination**. …. !" #$%%&'()*+, &-&./&0/1&*&$223'**+, &1%.".#*'&*.3345! 678669 ,.*+,' &# %3"3*+,'&2(3' ." :3%0."&*.3";.*+ 5! <=>9?@ *32&*.,"*#.*+ &1-&":,1 3' %,*&#*&*&":,') &/*+3$A%3".*3'."A 34&1-,'#, ,-,"*# .# ;&"&"*,1BC.-," *+, $"%,* %,1.:&/ ",,1 34 *+,#, 2&*.,"*#*+,', .# &:&#, 43' 23*,"*.&/ 0,",4.* 344,',1 0(*+.#'3-,/ %31, 34&:*.3";.*+

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Rationale for change		Clarification
Section to be changed		3.3.3 Exclusion criteria
Description of change		21. Women who are pregnant, nursing, or who plan to become pregnant while in the trial. Female patients of childbearing potential must have a negative urine or serum pregnancy test within ~~72 hours~~**3 days** prior to taking study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the patient to be eligible. **Women who are nursing can be enrolled if they stop nursing. In this case, the patient cannot resume nursing even after discontinuation of study treatment.**
Rationale for change		Clarification
Section to be changed		4.1.6 Dose modifications
Description of change		Updated: Before initiating a new treatment cycle, the actual health status will be assessed according to Flow Chart and described in Section 5.2. To continue treatment with further cycles, all of the following **retreatment** criteria must be met: Added: **If a patient develops an interstitial lung disease, the treatment has to be discontinued**
Rationale for change		In response to the PMDA's review, the first paragraph was updated for clarification. The discontinuation criteria for interstitial lung diseases were also added in response to a PMDA's review comment.
Section to be changed		4.1.7 Dose limiting toxicities
Description of change		The following exception from a DLT criterion of ≥G3 non-haematologic toxicities was removed: ~~o Grade 3 infusion related reaction which can be controlled by appropriate medication according to investigator's decision, and the subsequent infusion will not be delayed for more than two weeks~~
Rationale for change		In response to the PMDA's review, BI is going to handle G3 Infusion related reactions regardless of the controllability

Section to be changed		5.3.2 Methods of sample collection
Description of change		After completion of the trial the plasma ~~and urine~~ samples may be used for further methodological investigations, e.g. for stability testing. However, only data related to the analyte and/or its metabolite(s) including anti-drug antibodies (if applicable) will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years upon the final study report has been signed.
Rationale for change		Correction of error

[redacted]

Section to be changed		7.1.2 Statistical design – Part II (BI 836880 and BI 754091 combination dose finding)
Description of change		A sentence in the 12th paragraph was updated as follows: Since data from 1336-0012 Part 1 and **1336-0011** ~~1336-0012~~ were not yet available by the time of finalization of the CTP, data as is might be observed in future in these trials will be used as dummy data.
Rationale for change		Correction of error
Section to be changed		7.1.2 Statistical design – Part II (BI 836880 and BI 754091 combination dose finding)
Description of change		The title of tables 7.1.2: 2 and 7.1.2: 3 was updated as follows: Table 7.1.2: 2 **Preliminary data** ~~Hypothetical data expected~~ from 1381-0001 Table 7.1.2: 3 **Preliminary data** ~~Hypothetical data expected~~ from 1381-0004
Rationale for change		Clarification
Section to be changed		7.6 Determination of sample size
Description of change		No formal statistical power calculations of sample size were performed. Approximately 9 patients for Part I are expected, And approximately **15**~~12~~

		patients for Part II are expected. **As** ~~Fewer or~~ more patients might be needed based on the recommendation of the SMC and the actual number of cohorts tested.
Rationale for change		A buffer of 3 patients was added for the possibility of adding extra number of patients for DLTs or other reasons.
Section to be changed		8.3 Records
Description of change		CRFs for individual patients will be provided by the sponsor. For drug accountability, refer to Section **4.1.12** ~~4.1.13~~
Rationale for change		Correction of error

11.2 GLOBAL AMENDMENT 2

Date of amendment		21 Aug 2019
EudraCT number **EU number**		Not applicable
BI Trial number		1336-0012
BI Investigational Medicinal Product(s)		BI 836880 and BI 754091
Title of protocol		An open label, Phase I study of BI 836880 monotherapy and combination therapy of BI 836880 and BI 754091 in Japanese patients with advanced solid tumours
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		4.1.5 Drug assignment and administration of doses for each patient
Description of change		The duration of infusion should not be prolonged to more than 6 hours for BI 836880, and more than **3**~~2~~ hours for BI 754091.
Rationale for change		Update according to the latest result of in-use stability test for BI 754091.
Section to be changed		4.1.6 Dose modifications
Description of change		Administration of trial drugs has to be stopped temporarily in case of a DLT (see Section 4.1.7). Patients may resume the treatment only after recovery from DLT to at least fulfil retreatment criteria. **The future dose of BI 836880 must be a tested dose which is one dose level below the dose received by the patient.** The dose level for

		treatment resumption should be as prescribed in Table 4.1.6: 1. Treatment has to be discontinued in case the DLT is not reversible.
Rationale for change		Clarification
Section to be changed		4.1.6 Dose modifications
Description of change		**Dose reduction for BI 754091 is not allowed. The dose of BI 754091 may be delayed for a patient for one cycle, plus an additional 3 weeks, because of AEs following discussion with the sponsor.** **In combination treatment arms, both drugs (BI 836880 and BI 754091) will be stopped, paused, or re-exposed together unless an AE can be attributed to either BI 836880 or BI 754091. Only if a causal relationship to one trial drug can be unequivocally established, the other trial drug may be continued.** ~~In case of irAEs which meets the criteria in Section 10.2, dose level of BI 754091 can be reduced according to~~ Table 4.1.6: 2~~.~~ ~~Table 4.1.6:2 Dose reduction recommendations for BI 754091~~
Rationale for change		Correction: Dose reduction recommendation for BI 754091 is removed to follow the determination at the project. Clarification of recommendation on combination treatment in Part II.
Section to be changed		5.2.3 Vital signs
Description of change		At days of administration blood pressure and **pulse**~~heart~~ rate will be evaluated at the following time points:
Rationale for change		Correction
Section to be changed		5.2.9.1.4 Adverse events of special interest
Description of change		Infusion-related reactions In the event of an infusion-related reaction ≤ Grade 2, ~~the infusion rate of study drug(s) may be decreased by 50% or interrupted until resolution of the event and re-initiated~~ **the infusion should be temporarily stopped. Upon recovery, it should be infused at 50% of the initial rate until completion of the infusion. In patients experiencing infusion-related reactions ≤ Grade**

		2, subsequent infusions may be administered at 50% of the initial rate.
Rationale for change		Correction to be consistent with descriptions in Section 4.1.5.
Section to be changed		7.1.1 Statistical design – Part I (BI 836880 monotherapy dose finding part)
Description of change		The estimated probability of a DLT at each dose level from the model will be summarized using the following intervals: Underdosing: [0.00, 0.16)~~]~~ Targeted toxicity: [0.16, 0.33)~~]~~ Over toxicity: [0.33, 1.00]
Rationale for change		Correction of typographical error
Section to be changed		7.1.2 Statistical design – Part II (BI 836880 and BI 754091 combination dose finding)
Description of change		The resulting parameters of the prior distributions for four combination levels, i.e., (120/240, 360/240, 500/240, 720/240), are given in Table 7.1.2: 5. The corresponding prior probabilities of a DLT at different dose combinations ~~(with the consideration of BLRM simulation, BI754091 80 and 400 mg are included and they will not be tested in patients. More details about simulation are included in Section 10.5.2)~~ and the corresponding probabilities of under toxicity, targeted toxicity and over toxicity are shown in Table 7.1.2: 6.
Rationale for change		Updated according to removal of dose reduction recommendation and keep fixed dose for BI 754091
Section to be changed		7.1.2 Statistical design – Part II (BI 836880 and BI 754091 combination dose finding)
Description of change		Removal of the 1st and 3rd tables (tables for BI 754091 80 mg and 400 mg) from Table 7.1.2: 6
Rationale for change		Updated according to removal of dose reduction recommendation and keep fixed dose for BI 754091
Section to be changed		10.5.2 Part II (BI 836880 and BI 754091 combination dose finding)
Description of change		Removal of the 1st and 3rd tables (tables for BI 754091 80 mg and 400 mg) from Table 10.5.2:2

Rationale for change		Updated according to removal of dose reduction recommendation and keep fixed dose for BI 754091

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
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