Boehringer Ingelheim

Clinical Trial Protocol

Doc. No.: c01692098-04

BI Trial No.:	1280.15
BI Investigational Product:	Xentuzumab (BI 836845)
Title:	An open-label phase I dose escalation trial of weekly intravenous administrations of BI 836845 in Japanese patients with advanced solid tumours
Clinical Phase:	I
Clinical Trial Leader:	[redacted] Tel: [redacted] Fax: [redacted]
[redacted] **Investigator:**	[redacted] Tel: [redacted] Fax: [redacted]
Status:	Final Protocol (Revised Protocol (based on global amendment 2))
Version and Date:	**Version: 3.0** **Date: 29 Apr 2022**

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CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: Xentuzumab (BI 836845)			
Protocol date: 28 Feb 2014	**Trial number:** 1280.15		**Revision date:** 29 Apr 2022

Title of trial:	An open-label phase I dose escalation trial of weekly intravenous administrations of BI 836845 in Japanese patients with advanced solid tumours
[redacted]**investigator:**	[redacted]
Trial site:	[redacted]
Clinical phase:	I
Objectives:	• Identification of the maximum tolerated dose (MTD) of BI 836845 in Japanese patients with advanced solid tumours • Evaluation of safety, pharmacokinetics, pharmacodynamics, and anti-tumour activity
Methodology:	Open-label and dose escalation, followed by expansion cohort and rollover
No. of patients:	
total entered:	Maximum 24 (to identify the MTD and to conduct an expansion cohort if needed)
each treatment:	• Three (3) to 6 patients in 750 and 1000 mg dose cohort • Six (6) patients in 1400 mg dose cohort • Additional 6 patients as an expansion cohort if needed
Diagnosis:	Patients with advanced solid tumours
Main criteria for inclusion:	Patients with cytologically or histologically confirmed solid tumours that are refractory to standard therapy, for whom no standard therapy of proven efficacy exists, or who are not amenable to establish treatment options
Test product:	BI 836845
dose:	750, 1000, and 1400 mg
mode of admin.:	Weekly intravenous administrations over 1 hour
Duration of treatment:	• One treatment cycle consists of 21 days without discontinuation of study treatment. • The study treatment may be continued until patients meet any of the criteria for discontinuation.

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: Xentuzumab (BI 836845)			
Protocol date: 28 Feb 2014	**Trial number:** 1280.15		**Revision date:** 29 Apr 2022
Criteria for efficacy:	The following assessments will be performed according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 as other efficacy assessments • Objective response: number of patients whose best response is either complete response (CR) or partial response (PR) • Disease control: number of patients whose best response is either CR, PR, or stable disease (SD) • Duration of disease control: time from first disease control (CR, PR, or SD) to the time to progression or death		
Criteria for pharmacokinetics:	Pharmacokinetic profile of BI 836845		
Criteria for safety:	The following adverse events will mainly be evaluated according to Common Terminology Criteria for Adverse Events version 4.03 *The primary endpoint:* • MTD of BI 836845 in Japanese patients with advanced solid tumours (as identified by the number of patients with dose-limiting toxicities [DLTs]) *Other safety assessments:* • All adverse events • Laboratory tests • Eastern Cooperative Oncology Group (ECOG) performance status • Vital signs • Twelve (12)-lead electrocardiogram (ECG)		
Statistical methods:	Descriptive statistics		

FLOW CHART

Study period	**Screening**	**Treatment[a]**					
		Cycle 1			**Cycle 2**		
Visit		**1**	**2**	**3**	**1**	**2**	**3**
Day (day range)	**–28 to –1**	**1**	**8** (±1)	**15** (±1)	**1[b]**	**8** (±2)	**15** (±2)
Informed consent	X[1]				X[2]		
Demographics	X						
Medical history	X						
Inclusion and exclusion criteria	X	X[3]					
Physical examination	X	X			X		
Vital signs[4]	X	X	X	X	X	X	X
Body height	X						
Body weight	X				X		
ECOG performance status	X				X		
Pregnancy test[5]	X						
Tumour assessment (RECIST)[6]	X[7]						
Clinical tumour assessment	X				X		
Tumour markers[8]	X				X		
Twelve (12)-lead ECG[9]	X	X		X	X		
ECHO or MUGA[10]	X						
Pharmacogenomics and biobanking[11]		X					
Blood sampling for pharmacokinetics and biomarker analyses[12]		X	X	X	X	X	X
Blood sampling for anti-drug antibody assay		X			X		
Laboratory tests[13]	X	X	X	X	X	X	X
Endocrine assessments[14]	X	X[15]	X	X	X[15]		
BI 836845 administration		X	X	X	X	X	X
Adverse event	←			X			→
Concomitant therapy	←			X			→

Study period	**Treatment[a]**								
	Cycle 3			**Cycle 4**			**Cycle 5**		
Visit	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**
Day (day range)	**1[c]**	**8** (±2)	**15** (±2)	**1[c]**	**8** (±2)	**15** (±2)	**1[c]**	**8** (±2)	**15** (±2)
Physical examination	X			X			X		
Vital signs[4]	X	X	X	X	X	X	X	X	X
Body weight	X			X			X		
ECOG performance status	X			X			X		
Pregnancy test[5]	X						X		
Tumour assessment (RECIST)[6]	X						X		
Clinical tumour assessment	X			X			X		
Tumour markers[8]	X			X			X		
Twelve (12)-lead ECG[9]	X			X			X		
Blood sampling for pharmacokinetics and biomarker analyses[12]	X	X	X	X			X		
Blood sampling for anti-drug antibody assay	X			X			X		
Laboratory tests[13]	X	X	X	X			X		
BI 836845 administration	X	X	X	X	X	X	X	X	X
Adverse event	←				X				→
Concomitant therapy	←				X				→

Study period	**Treatment[a]**			**EOT[d,e]**	**FU1[f]**	**FU2[g]**
	Cycle 6 onwards					
Visit	**1**	**2**	**3**			
Day (day range)	**1[c]**	**8** (±2)	**15** (±2)		**42 after discontinuation** (+7)	**28 after FU1** (±4)
Physical examination	X			X	X[16]	
Vital signs[4]	X	X	X	X	X[16]	
Body weight	X			X		
ECOG performance status	X			X	X	
Pregnancy test[5]	(X)			X		
Tumour assessment (RECIST)[6]	(X)			X		
Clinical tumour assessment	X			X		
Tumour markers[8]	X			X		
Twelve (12)-lead ECG[9]	X			X		
Blood sampling for pharmacokinetics and biomarker analyses[12]				X[17]	X	
Blood sampling for anti-drug antibody assay				X	X	
Laboratory tests[13]	X			X	X	
Endocrine assessments[14]				X[18]		
BI 836845 administration	X	X	X			
Adverse event	←	X	→	X[19]	X[19,20]	X[20]
Concomitant therapy	←	X	→	X	X[21]	X[21]
Termination of trial medication				X[22]		
Patient status					X	X

a. One treatment cycle consists of 21 days without discontinuation of study treatment.
b. For the study treatment on Day 1 of Cycle 2, a window of +2 day is allowed.
c. For the study treatment on Day 1 of every cycle from Cycle 3, a window of ±2 day is allowed.
d. All assessments specified in the Flow Chart must be performed at the end of treatment (EOT) visit within 5 days after discontinuation of study treatment. If patient discontinuation of study treatment falls on a scheduled visit, EOT visit should be conducted instead of assessments at the scheduled visit.
e. At the time of all patients in the trial having sufficient data to answer the primary endpoint (see Section 5.2.1), patients continuing on study treatment will have the EOT assessments (except for blood collection for biomarker analyses) performed and then continue on study treatment into the rollover part with reduced clinical data collection.
f. The first follow-up (FU1) visit must be performed on 42 (a window of +7) days after the last administration of BI 836845.
g. The second follow-up (FU2) visit may be performed on 28 (a window of ±4) days after FU1 visit over the telephone if a visit at the trial site cannot be arranged. The visit will be skipped for patients conducted the rollover part.

1. Written informed consent must be obtained before any assessment at screening.
2. For patients who are willing to continue the study treatment after completion of Cycle 1, written informed re-consent must be obtained before study treatment on Visit 1 of Cycle 2.
3. The investigator confirms whether inclusion and exclusion criteria are still valid or not.
4. On administration day of every cycle, vital signs are performed at pre-infusion, during infusion (30 ± 5 minutes after start of infusion), and immediately before end of infusion. Further vital signs to be taken at any time if clinically indicated and/or after discontinuation of study treatment.
5. For women of child bearing potential, serum beta-human chorionic gonadotropin (β-hCG) is evaluated for pregnancy test at screening (within 7 days before start of study treatment), Visit 1 of every odd cycle, and EOT visit.
6. Tumour assessment is performed according to RECIST criteria version 1.1 by CT or MRI imaging at screening, end of Cycle 2 (before start of Cycle 3), end of Cycle 4 (before start of Cycle 5), and end of Cycle 6 (before start of Cycle 7). Thereafter, tumour assessment may be conducted every 3 cycles before start of Cycles 10, 13, 16, etc. Imaging may be performed within 7 days before start of the respective treatment cycle. The same radiographic procedure should be used throughout the cycle of trial. Tumour assessment may also be performed if the investigator considers it should be performed from the result of clinical tumour assessment.

7. Tumour assessment images taken within 28 days before start of Cycle 1 may be used as baseline scans where appropriate without the need to repeat scans during screening period.
8. The blood will be collected by the discretion of investigator at pre-infusion or post-infusion.
9. On Day 1 of Cycle 1, 12-lead electrocardiogram (ECG) is performed at pre-infusion, during infusion (30 ± 5 minutes after start of infusion), and immediately before end of infusion. ECG will be performed before infusion on Day 15 of Cycle 1 and Cycle 2 onwards during study treatment.
10. Echocardiography (ECHO) or multiple-gated acquisition scan (MUGA) must be assessed at screening. Further scans may be performed after start of study treatment if clinically indicated by the discretion of investigator.
11. The blood is collected at pre-infusion on Visit 1 of Cycle 1 for evaluating insulin-like growth factor binding protein (IGFBP)-3 promoter polymorphism evaluation (mandatory) and optional biobanking. At least 15 slides of tissue section prepared from the archived sample are required for analysing imprinting/methylation status of insulin-like growth factor (IGF)-2 (optional).
12. Blood sampling for pharmacokinetics and/or biomarker will be performed at the time points specified in Tables 10.1: 1, 10.1: 2 and 10.1: 3.
13. All laboratory parameters specified in Section 5.2.4 should be performed. The results from the previous laboratory test may be used on Visit 1 of each cycle if the examination was performed within 2 days before the visit. On another visits, the examinations will be performed before infusion. In case of adverse events related to laboratory abnormalities, adequate and more frequent evaluation will be performed at the discretion of the investigator.
14. All parameters specified in Section 5.2.7 should be performed using fasting plasma and serum samples.
15. Fasting plasma and serum samples may be collected within 7 days before Visit 1 of Cycle 1 and Visit 1 of Cycle 2.
16. Physical examination and vital signs at FU1 visit are optional.
17. Not applicable for patients who continue the study treatment into the rollover part regarding biomarker analyses
18. Fasting plasma and serum samples are collected where possible.
19. All adverse events (including deaths) occurring until 42 days after the last administration of BI 836845 will be collected and followed up until they have recovered or have been sufficiently characterised, unless the investigator and the sponsor agree not to pursue them further.
20. All adverse events (including death) occurring later than 42 days after the last administration of BI 836845 until end of the trial will also be collected and followed up until they have recovered or have been sufficiently characterised, unless the investigator and the sponsor agree not to pursue them further.
21. Concomitant therapies during follow-up period are only collected for cases where indicated for the treatment of adverse events
22. Not applicable for patients who continue the study treatment into the rollover part

FLOW CHART – ROLLOVER PART

Study period	**Treatment[a]** **Rollover**	**EOT[c]**	**FU1[d]**
Day (day range)	**Every 7 days[b]** (no limitation)		**42 after discontinuation** (+7)
Physical examination[1,2]	(X)	(X)	(X)
Vital signs[1,2]	(X)	(X)	(X)
Body weight[1,2]	(X)	(X)	
ECOG performance status[1]	(X)	(X)	(X)
Pregnancy test[1,3]	(X)	(X)	
Tumour assessment (RECIST)[1,4]	(X)	(X)	
Clinical tumour assessment[1,2]	(X)	(X)	
Twelve (12)-lead ECG[1,2]	(X)	(X)	
Laboratory tests[1,2,5]	(X)	(X)	
BI 836845 administration	X		
Adverse event[6]	X	X	X
Termination of trial medication		X	
Patient status			X

a. For patients who are willing to continue the study treatment in the rollover part, written informed re-consent must be obtained before the initial study treatment in the rollover part.
b. The investigator should make efforts to keep administration of BI 836845 at intervals of 7 days. However, weekly administration schedule can temporarily be accelerated, delayed or skipped due to administrative reasons at the discretion of the investigator.
c. EOT visit will be performed on the same day or after discontinuation of study treatment.
d. FU1 visit will be performed on 42 (a window of +7) days after the last administration of BI 836845.

1. These assessments are not mandatory and appropriately performed as per the standard of care at the study sites or at the discretion of investigator. Results should be recorded in the source data only, additional documentation in the electronic case report form (eCRF) is not required.
2. Only clinical relevant abnormalities are reported as adverse events.
3. For women of child bearing potential only
4. Tumour assessment is performed according to RECIST criteria version 1.1 by CT or MRI imaging. The same radiographic procedure should be used throughout the trial. Tumour assessment may also be performed if the investigator considers it should be performed from the result of clinical tumour assessment.
5. The site staff does not need to test for all laboratory parameters listed in Table 5.2.4: 1. In case of adverse events related to laboratory abnormalities, adequate and more frequent evaluation will be performed at the discretion of the investigator.
6. All adverse events (including deaths) occurring until 42 days after the last administration of BI 836845 will be collected.

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ABBREVIATIONS

ADA	anti-drug antibody
ADL	activities of daily living
AFP	alpha-fetoprotein
ALT (SGPT)	alanine aminotransferase
AST (SGOT)	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BLQ	below the lower limit of quantification
CA	cancer antigen
CEA	carcinoembryonic antigen
CK	creatine phosphokinase
CR	complete response
CRA	clinical research associate
CRO	contract research organisation
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Clinical Trial Leader
CTP	clinical trial protocol
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECHO	echocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid
ELISA	enzyme-linked immunosorbent assay
EOT	end of treatment
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FU1/FU2	the first follow-up/the second follow-up
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HbA_{1c}	haemoglobin A_{1c}
HED	human equivalent dose
HIV	human immunodeficiency virus
ICH–GCP	International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice
Ig	immunoglobulin
IGF	insulin-like growth factor
IGF-1R/IGF-2R	insulin-like growth factor-1 receptor/insulin-like growth factor-2 receptor
IGFBP	insulin-like growth factor binding protein
INR	international normalised ratio
IR	insulin receptor
IRB	Institutional Review Board

ISF	Investigator Site File
LHRH	luteinising hormone–releasing hormone
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTORC1	mammalian target of rapamycin complex 1
MUGA	multiple-gated acquisition scan
NC	not calculated
NCA	non-compartmental analysis
NOA	not analysed
NOP	no peak detectable
NOR	no valid result
NOS	no sample available
NSAIDs	nonsteroidal anti-inflammatory drugs
PAS	periodic acid–Schiff
PD	progressive disease
PK–PD	pharmacokinetic–pharmacodynamic
PR	partial response
PSA	prostate-specific antigen
q3w	on every 3 weeks
qw	weekly
RDC	remote data capture
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SD	stable disease
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TKI	tyrosine kinase inhibitor
TMF	Trial Master File
TSAP	Trial Statistical Analysis Plan
TSH	thyroid-stimulating hormone
ULN	upper limit of normal

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

The insulin-like growth factor (IGF) signalling system consists of ligands (IGF-1 and IGF-2), IGF-binding proteins (IGFBPs), and receptors (IGF-1 receptor [IGF-1R], IGF-2 receptor [IGF-2R] and insulin receptor [IR]). Evidence that targeting IGF may be useful in cancer treatment was first recognised decades ago. Research in IGF signalling has shown that it controls key cellular activities, including proliferation, growth, and survival and is often deregulated in neoplasia (R07-4212 and R10-5760).

There is experimental and clinical evidence that cancer cells express insulin and IGF receptors. Expression of IGF-1R or its ligand is increased in a variety of cancers, including lung, colon, prostate, breast, ovarian, liver cancer and sarcoma (R10-5759, R10-5756 and R10-5355). Therefore, the IGF system is a tempting target for anti-cancer drug development, and pharmacologic targeting strategies include inhibition of receptor function with anti-receptor antibodies or small molecule receptor tyrosine kinase inhibitors (TKIs; R10-5760, R10-5758, and R10-5757).

Most cancers express IGF-1 receptors, but there is evidence that autocrine and/or paracrine expression of ligands, particularly IGF-2, is deranged in neoplasm (R10-5355). In addition, the IGF-2 gene is an imprinted gene; loss of imprinting is one of several mechanisms leading to IGF-2 overexpression (R10-5694). For example, IGF-2 is the most overexpressed gene in colorectal cancer (R10-5355). Thus, targeting IGF-1 and IGF-2 may lead to a higher probability of response to a therapeutic strategy that may confer an advantage.

1.2 DRUG PROFILE

BI 836845 (xentuzumab as the generic name) is a fully human IgG1 monoclonal antibody (mAb) that binds to and neutralises the function of human IGF-1 and IGF-2. The BI 836845 molecule is composed of two heterodimers. Each of the heterodimers is composed of a heavy polypeptide chain of ~50 kDa (447 amino acids) and a light polypeptide chain of ~23 kDa (216 amino acids), and the four polypeptide chains of the antibody molecule are linked together by disulfide bonds. The heavy chains are glycosylated, and there are two binding sites for IGF-1 and IGF-2 per antibody molecule. The antibody has a molecular mass of approximately 146 kDa.

1.3 NON-CLINICAL INFORMATION

1.3.1 Pharmacology

BI 836845 binds with high affinity to IGF-1 and IGF-2, and potently neutralises the proliferative and prosurvival cellular signalling triggered by both proteins. Mode of action differentiation to IGF-1R-targeted mAbs was demonstrated, in particular through inhibition

of IGF-2-stimulated IR-A activation, an additional proliferative and prosurvival pathway not inhibited by IGF-1R-targeted mAbs. The growth of multiple cancer cell lines derived from different cancer types are inhibited by BI 836845. The combination potential of BI 836845 has been demonstrated using non-clinical models of Ewing's sarcoma. The viability of the RD-ES cell line was more effectively inhibited by the combination of BI 836845 and rapamycin than either agent alone. Studies also indicated that the mechanism for the improved efficacy of the combination is through BI 836845 inhibiting the increased IGF ligand signalling activity that is triggered when mammalian target of rapamycin complex 1 (mTORC1) is inhibited.

BI 836845 has a potent inhibitory effect on the IGF-1R phosphorylation potential (IGF bioactivity) of human plasma *ex vivo*. Due to its cross-reactivity to rat and Cynomolgus monkey IGF-1 and IGF-2, the pharmacodynamic effect of BI 836845 on IGF bioactivity in both these species was demonstrated using samples from 13-week toxicity studies. In both species, BI 836845 showed a clear and potent reduction in plasma IGF bioactivity for all doses tested (3.2–32 mg/kg human equivalent dose [HED]).

1.3.2 Toxicology

Safety Pharmacology (core battery) endpoints integrated in the 13-week toxicity study in Cynomolgus monkey (100% sequence homology of human IGF-1 and IGF-2) indicated no adverse cardiovascular, respiratory, or neurological effects of BI 836845.

Repeated intravenous administration in Cynomolgus monkey for 13 weeks and in rats (the second relevant species based on comparable binding affinity against IGF-1 and IGF-2) for up to 26 weeks led to a variety of dose-related and essentially reversible effects. The treatment-related changes included the body as a whole (growth retardation) in both species and liver functions, the haematolymphatic system, kidneys, bone, teeth, and ovaries in rats only.

Most if not all observed effects were attributable to the pharmacodynamic potential of BI 836845, i.e. reflecting the neutralisation of specific growth factors in these species during a phase of rapid body growth. Consequently, signs of general growth retardation, e.g. reduced body weight gain and body size were apparent in both species examined. The effects on the haematolymphatic system and liver function seen in the rat studies were considered to be below toxicological significance.

Glomerulopathy (periodic acid–Schiff [PAS]-positive granules in podocytes and dilated Bowman's spaces) was observed in individual rats (7–8 weeks old at the commencement of treatment) at all dose levels of the 13-week study, but not in those of the 26-week study (10–11 weeks old). This rat glomerulopathy is therefore considered an age-dependent change. As there were indications that IGF has a stronger effect on younger animals due to their steep growth curve until about Week 10, slightly older animals were used in the 26-week toxicity study. Also, the older animals did not show findings in bone and teeth. On the other hand, a higher incidence and severity of interstitial structures called 'persistent granulosa cell nests

within remnants of atretic follicles' were observed in the ovaries of rats at dosages of 20 and 200 mg/kg which was reversible after a 12-week recovery period. However, a number of follicles showed normal maturation, and the incidences of the different stages of the menstrual cycle were not affected.

The only effects noted in rats and Cynomolgus monkeys exposed similarly to rats were a dose-dependent reduction of body growth and alkaline phosphatase activity. Otherwise, young adult monkeys did not show any of the effects observed in rats although fully pharmacologically active doses were achieved in both species at all dose levels in terms of the reduced plasma IGF-1R phosphorylation activity (IGF bioactivity).

Furthermore, glucose levels, fructosamines, and haemoglobin A_{1c} (HbA_{1c}) were increased weakly in rats and in male Cynomolgus monkeys given 30 and 100 mg/kg (equivalent to 10 to 32 mg/kg HED).

1.4 CLINICAL INFORMATION

Boehringer Ingelheim is conducting the following two phase I trials with BI 836845 in patients with advanced solid tumours:

- Trial 1280.1: Investigating a weekly (qw) schedule in Taiwan
- Trial 1280.2: Investigating once every 3 weeks (q3w) schedule in the United Kingdom

At the cut-off date of July 10, 2013, a total of 81 patients were treated in two BI 836845 phase I dose-escalation trials.

A relevant biological dose for BI 836845 monotherapy in solid tumors was determined at 1000 mg qw, used as the recommended dose for further Phase II trials.

No relevant hyperglycaemia has been observed so far. BI 836845 was well tolerated, with no relevant non-specific side effects reported. The type and pattern of adverse events observed to date have generally been consistent with the underlying neoplastic conditions of patients enrolled on the study. The most common adverse events have been those pertaining to "General disorders", "Gastrointestinal disorders", "Respiratory, thoracic and mediastinal disorders" as well as "Investigations". The reported drug-related adverse events were mostly ranked Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or 2 until 1800 mg (qw schedule) and 3600 mg (q3w schedule) without any dose dependency. CTCAE grade 3 pulmonary haemorrhage was the only drug-related severe adverse event reported in 1280.1 trial. The adverse event declared a dose-limiting toxicity (DLT) and was considered drug-related by the investigator due to the timely relationship, as it occurred within 36 hours after first administration of the study drug at a dose of 450 mg weekly. As per the clinical trial protocol (CTP), 3 additional patients were therefore dosed at 450 mg (for a total of 6 patients), with no further DLTs observed at this or subsequent dose levels. Furthermore, a CT revealed a metastasis adjacent to the bronchus in which the haemorrhage had occurred.

No DLT was reported in 1280.2 trial. Given the safety profile of BI 836845 reported in 1280.1 and 1280.2 trials, sufficient tolerability with BI 836845 for patients is assured until 1800 mg (qw schedule) and 3600 mg (q3w schedule).

Maximum plasma concentrations of BI 836845 were observed at the end of infusion or shortly thereafter. After reaching the peak, plasma concentrations showed an at least biphasic decay with a terminal half-life in the order of 6 days. The estimated volume of distribution was about 5.8 L (approximately twice the plasma volume) and the total plasma clearance was about 30 mL/h. No deviations from dose-proportional pharmacokinetics have been observed in the dose range tested (10–1050 mg given qw schedule and 10–3600 mg given q3w schedule in 1280.1 and 1280.2 trials, respectively). Repeated qw dosing resulted in about 1.5-fold accumulation of BI 836845 plasma concentration at steady state, while only limited accumulation was observed after repeated q3w infusions.

A dose is considered biologically relevant when concentrations of free IGF-1 and free IGF-2 are considerably reduced over time. Free IGF-1 and free IGF-2 plasma concentrations are not measured in 1280.1 and 1280.2 trials. Therefore, a semimechanistic pharmacokinetic–pharmacodynamic (PK–PD) model was developed based on pharmacokinetics of BI 836845, measured pharmacodynamic biomarkers (i.e. plasma concentrations of total IGF-1, total IGF-2, and IGFBP-3), and literature applying a physiologically-based approach. This PK–PD model describes the pharmacokinetics of BI 836845 and interaction between BI 836845 and the different pharmacodynamic biomarkers, and allows the prediction of plasma concentrations of free IGF-1 and free IGF-2 over time. Simulations indicate that a qw dosing of 1000 mg reduces the population mean free IGF-1 concentration by more than 90% and in addition population mean free IGF-2 by 64% at trough steady-state relative to pre-treatment. This is considered as a relevant biological effect and a suitable dose to be taken forward.

Promising early efficacy signals have been observed with two confirmed partial responses (PRs) according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria in a patient with nasopharyngeal cancer (800 mg dose cohort given qw schedule) and a patient with a peripheral primitive neuroectodermal tumor/Ewing sarcoma (1050 mg dose cohort given qw schedule). Moreover, 12 out of 48 patients (1280.1 trial) and 4 out of 33 patients (1280.2 trial) confirmed stable diseases (SDs) have been observed in heavily pretreated patients suffering from advanced or metastatic solid tumours.

More detailed and updated information is provided in the latest version of Investigator's Brochure (c01690707).

2. RATIONALE, OBJECTIVES, AND BENEFIT–RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

As shown in Section 1.4, sufficient tolerability with BI 836845 for Caucasian and Asian patients with advanced solid tumours is assured until 1800 mg (qw schedule) and 3600 mg (q3w schedule). However, insight into tolerability with BI 836845 for Japanese patients with advanced solid tumours is not obtained yet.

This open-label dose escalation phase I trial, 1280.15, is the first administration of BI 836845 in Japanese patients with various types of advanced solid tumours. The rationale behind this study is to identify the maximum tolerated dose (MTD) of BI 836845 in Japanese patients with advanced solid tumours as weekly intravenous administration. Once the MTD will be identified, phase III trials will be planned to be conducted after tolerability with BI 836845 and combination drugs will be assured through the safety run-in cohort.

2.2 TRIAL OBJECTIVES

The objective of the trial is to identify the MTD of BI 836845 in Japanese patients with advanced solid tumours.

In case no MTD can be identified up to the highest dose tested in this trial, a relevant biological dose may be recommended based on all available data (safety, pharmacokinetics, pharmacodynamics, and efficacy).

Safety, pharmacokinetics, pharmacodynamics, and anti-tumour activity of BI 836845 will also be evaluated.

2.3 BENEFIT–RISK ASSESSMENT

Despite substantial improvements in cancer therapy, there is still a need for novel therapeutic agents.

Early evaluations of ongoing clinical trials of anti-IGF/IGF-1R agents as a single agent, as well as pharmacodynamic studies of BI 836845 on neoplastic cell lines, indicate the possibility of disease stabilisation, or tumour responses in a subset of patients with advanced and otherwise incurable cancers. In addition, targeting IGF-2, which is aberrantly overexpressed in certain cancers, with a ligand neutralising antibody such as BI 836845, may translate into an advantage over compounds further along in clinical development and which target the IGF-1R.

The non-clinical safety profile of BI 836845 in growing rats primarily has revealed that liver, peripheral blood/bone marrow, lymphoid organs, growing teeth, bone, kidneys, and the

ovaries are main target organs. There was full reversibility of effects except for alterations in kidney and teeth in the 13-week toxicity study. However, in the 26-week toxicity study, the findings in kidney and teeth were absent. The effects observed are mostly to be attributed to the direct pharmacological activity of BI 836845 and reflect the neutralisation of specific growth factors.

Experience to date with several anti-IGF-1 receptor antibodies or TKIs revealed that treatment may result in hyperglycaemia, which was rarely severe enough to cause cessation of treatment and often responded to metformin therapy. These findings were very rarely observed with BI 836845 monotherapy in phase I. Other observed adverse effects with anti-IGF-1R antibodies or TKIs included lethargy, anorexia, leukopenia, thrombocytopenia, elevated aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase, diarrhoea, and hyperuricaemia. In general, the observed adverse effects in single agent trials were moderate and not dose-limiting. Preliminary safety and efficacy data from 81 patients at the end of the dose escalation part of the first-in-human studies 1280.1 (qw schedule) and 1280.2 (q3w schedule) are available. A preliminary safety profile has been established and, overall, the safety data of BI 836845 in these trials is considered favourable.

The potential risks associated with BI 836845 are unknown in Japanese patients and unexpected or infrequent adverse events may occur in the clinical trial. The proposed trial will evaluate stepwise dose escalation of BI 836845, and the investigator should carefully be monitored the patients' safety during trial participation.

Although BI 836845 is a fully human antibody given intravenously, there may be potential for infusion reactions (e.g. infusion-related reactions, injection site reactions, immune system disorders) to occur. Such infusion reactions will be graded thoroughly and appropriate preventative and/or corrective actions implemented following the standard of care for such adverse events.

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

Together with the encouraging preliminary signs of anti-tumour activity observed (see Section 1.4 for details), this 1280.15 trial had warranted, until the negative efficacy results for BI 836845 in the placebo-controlled randomised Phase II 1280-0022 trial, continuation of clinical investigation of BI 836845 in patients with solid tumours. The 1280-0022 Phase II placebo-controlled, randomised trial recently completed primary endpoint analysis and showed no added benefit of BI 836845 compared to placebo, in patients with everolimus and exemestane backbone therapy, when treating trial participants with metastatic breast cancer, HR+, HER2– and non-visceral disease. No new safety signals were observed with the addition of BI 836845 to the everolimus and exemestane combination.

In consideration of these topline results of 1280-0022, as of 19 October, 2021, Boehringer Ingelheim recommended to immediately discontinue all BI 836845 treatments. As a consequence of the worsening in benefit-risk for BI 836845, Boehringer Ingelheim also

decided to terminate all oncology drug development for BI 836845 including the cessation of further manufacturing of investigational medicinal product BI 836845.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This trial is an open-label dose escalation phase I trial of BI 836845 in Japanese patients with various types of advanced solid tumours to identify the MTD, safety, pharmacokinetics, pharmacodynamics, and preliminary anti-tumour activity of BI 836845. Patients will be administered BI 836845 weekly and continued the study treatment every 21 days without discontinuation of study treatment.

Patients will be enrolled into the study at the time of obtaining written informed consent and will subsequently be assessed for the eligibility within a maximum 28 days screening period. Study treatment will be started after the investigator confirms the eligibility for the study treatment from Cycle 1 and will be continued until patients meet any of criteria for discontinuation, e.g. progressive disease (PD), undue toxicity, consent withdrawal (see Sections 3.3.4.1 and 3.3.4.2 for definition). One treatment cycle consists of 21 days. End of treatment (EOT) visit will be conducted within 5 days after patient discontinuation of study treatment. If patient discontinuation of study treatment falls on a scheduled visit, EOT visit should be conducted instead of assessments at the scheduled visit. Follow-up period will stop when once a patient has disease progression, is dead, is lost to follow-up, or has treatment with another anti-cancer drug, whichever occurs first, or patients have been willing to discontinue the trial. All adverse events will be collected and followed up according to Section 5.2.2.2.

At the time of all patients in the trial having sufficient data to answer the primary endpoint (see Section 5.2.1), patients continuing on study treatment will have the EOT assessments (except for blood collection for biomarker analyses) performed and then continue on study treatment into the rollover part with reduced clinical data collection. Clinical assessments and laboratory tests are not mandatory and appropriately performed as per the standard of care at the study sites or at the discretion of investigator, and only clinical relevant abnormalities are reported as adverse events according to Section 5.2.2.2. Results for the assessments and tests should be recorded in the source data only, additional documentation in the electronic case report form (eCRF) is not required.

A full clinical trial report will be written based upon the data before rollover part. At the end of the clinical trial, the data collected in the rollover part will be locked and the data may be summarised in an addendum of clinical trial report.

The trial will be supervised by the principal investigator specialised in the treatment of advanced solid tumours and experienced in phase I oncology trials. The trial site will have available all equipment necessary for dealing with any serious side effects and potential emergencies.

3.1.1 Administrative structure of the trial

The trial is sponsored by [redacted]

[redacted] will appoint a Clinical Trial Leader (CTL). CTL is responsible for coordinating the activities required in order to manage the trial in accordance with applicable regulations and internal standard operating procedures (SOPs), directing the clinical trial team in the preparation, conduct, and reporting of the trial, order the materials as needed for the trial, ensures appropriate training and information of clinical research associates (CRAs) and investigators.

Data management and statistical evaluation will be performed by [redacted] or a contract research organisation (CRO) appointed by [redacted] according to Boehringer Ingelheim SOPs. For these activities, a Trial Data Manager and a Trial Statistician will be appointed.

Tasks and functions assigned in order to organise, manage, and evaluate the trial will be defined according to Boehringer Ingelheim SOPs. A list of responsible persons and relevant local information (as protocol reference if applicable) are in the Investigator Site File (ISF) and the Trial Master File (TMF) document.

On-site monitoring will be performed by [redacted] or a CRO appointed by [redacted]

Electrocardiograms (ECGs) will be recorded by digital ECG machines and centrally evaluated by ERT, Inc. ECG machines at study sites can be used during the rollover part without data transfer and evaluation by the central ECG laboratory.

A principal investigator will be nominated to coordinate investigators at study site participating in this trial. Documents on participating (principal) investigators and other important participants, especially their curricula vitae, will be filed in the TMF.

The ISF document will be kept in print-out version at the sites as far as required by local regulation and Boehringer Ingelheim SOP. A copy of the ISF documents will be kept as an electronic TMF document according to Boehringer Ingelheim SOPs.

An external expert who is independent of the study sites (investigators) and the sponsor, with expertise in oncology clinical trials, will be assigned. The reviews by the assigned external expert ensure the adequacy of DLT evaluation and/or dose escalation which discussed and agreed between the study site (investigators) and the sponsor as an independent third party. In addition, an external expert can make recommendations to the sponsor regarding study continuation, amendment, or discontinuation as necessary when it is brought important safety information about the trial and/or investigational drug.

Details on handling of the trial supplies including responsible institutions are given in Sections 4.1.6, 4.1.7, and 4.1.8 of this CTP.

3.2 DISCUSSION OF TRIAL DESIGN

This trial follows a traditional 3 + 3 design with dose de-escalation in oncology phase I trials. Dose escalation, cohort expansion, or dose de-escalation will be decided after discussion and agreement with the principal investigator. Rationales for the initial dose and dose cohorts are described in Section 4.1.3.1.

3.3 SELECTION OF TRIAL POPULATION

Only patients with advanced solid tumours and maximum 18 patients evaluable for the primary endpoint will be entered. Number of evaluable patients to be entered in each dose cohort is described in Section 4.1.3.1. Additional 6 patients may also be entered as an expansion cohort to be recommended a relevant biological dose.

The trial will be conducted at 1 trial site [redacted].

A log of all patients enrolled into the trial (i.e. having given informed consent) will be maintained in the ISF at the trial site irrespective of whether they have been treated with BI 836845 or not.

3.3.1 Main diagnosis for study entry

Patients with cytologically or histologically confirmed solid tumours that are refractory to standard therapy, for whom no standard therapy of proven efficacy exists, or who are not amenable to establish treatment options.

3.3.2 Inclusion criteria

Patients who meet all of the following inclusion criteria by the judgment of investigator are eligible to receive the study treatment:

1. Patients with cytologically or histologically confirmed solid tumours that are refractory to standard therapy, for whom no standard therapy of proven efficacy exists, or who are not amenable to establish treatment options
2. Age ≥20 years old
3. Eastern Cooperative Oncology Group (ECOG) performance status (R01-0787) 0, 1, or 2
4. Written informed consent that is consistent with Good Clinical Practice (GCP) guidelines

3.3.3 Exclusion criteria

Patients for whom any of the following exclusion criteria apply by the judgment of investigator are not eligible to receive the study treatment:

1. Active infectious disease to be incompatible with the study treatment according to the CTP
2. Patients who do not have sufficient major organ function and meet any of the following test results at screening period
   - Cardiac left ventricular function with resting ejection fraction ≤50% as determined by echocardiography (ECHO) or multiple-gated acquisition scan (MUGA)
   - Absolute neutrophil count <1500/μL
   - Platelets <100 000/μL
   - Total bilirubin >1.5 × the upper limit of normal (ULN)
   - AST (SGOT) and/or ALT (SGPT) >2.5 × ULN (in case of known liver metastases, AST and/or ALT >5 × ULN)
   - Creatinine >1.5 × ULN
   - Haemoglobin <9 g/dL
   - HbA_{1c} ≥8% and fasting glucose >8.9 mmol/L (>160 mg/dL)
3. Serious illness or concomitant non-oncological disease including severe, acute, or chronic medical or psychiatric condition, or laboratory abnormality that may compromise the safety of the patient during the study, affect the patient's ability to complete the study, or interfere with interpretation of study results considered by the investigator to be incompatible with the study treatment according to the CTP
4. History of thrombosis (except tumour invading great vessels) within 1 year before start of study treatment or if concurrent anticoagulation required
5. Patients not recovered from any therapy-related toxicities from previous chemotherapies, hormonal therapies, immunotherapies, molecular-targeted therapies, or radiotherapies to CTCAE grade ≤1
6. Patients who have not recovered from any previous surgery and major surgery within the last 4 weeks before start of study treatment
7. Patients with untreated or symptomatic brain metastases. Patients with treated asymptomatic brain metastases may be eligible if there has been no change in brain disease status for at least 4 weeks before start of study treatment, no history of cerebral oedema or bleeding in the past 4 weeks before start of study treatment, and must be on a stable or reducing dose of dexamethasone. Anti-epileptic therapy will be allowed during the study treatment if the patient is stable on antiepileptic treatment for 4 weeks or more without adjustments before start of study treatment.
8. Patients who have been treated with any of the following within 4 weeks before start of study treatment: chemotherapies, immunotherapies, radiotherapies (within 2 weeks before start of study treatment for local palliative radiotherapies for the treatment of brain metastasis or extremities), biological therapies, molecular-targeted therapies, hormonal therapies for breast cancer within 2 weeks before start of study treatment (excluding luteinising hormone-releasing hormone [LHRH] agonists in prostate cancer or bisphosphonates), or treatment with other investigational drugs. Patients who have

completed the treatment with mitomycin C or nitrosoureas within 6 weeks before start of study treatment.
9. Patients who have used any investigational drug within 4 weeks before start of study treatment or who have planned concomitantly use with the trial.
10. Patients unable to comply with the CTP or unable to communicate or cooperate with the investigator
11. Active alcohol abuse or active drug abuse
12. Patients with unstable arrhythmias, unstable angina or severe obstructive pulmonary disease within the past 1 year.
13. Previous and concurrent other cancer (except for non-invasive and/or non-melanoma skin cancer, carcinoma *in situ* of the epithelium or mucosa, or mucosal gastric or colorectal cancer which has been curatively treated by endoscopic mucosal resection or endoscopic submucosal dissection). Other tumours treated curatively and with no evidence of recurrence for at least 5 years before enrolment into the trial is eligible.
14. Patients with uncontrolled diabetes mellitus
15. Female patients who are pregnant or who do not agree the interruption of breast feeding from start of study treatment within 4 months after the last study treatment. Female patients of child-bearing potential who have a positive serum pregnancy test within 7 days of enrolment in the trial. Females of child-bearing potential (premenopausal females) are defined as the females who observed menses within 12 months except for an alternative medical cause. Female patients who underwent an operation for sterilisation are excluded for this criterion.
16. Female patients of child-bearing potential or male patients who do not agree to use adequate contraception from start of study treatment within 4 months after the last study treatment. Combined oral contraceptives (approved in Japan), some intrauterine devices (approved in Japan), vasectomy since more than 2 months for male patients or for partners of female patients, etc. are accepted as contraception, and barrier methods of contraception are also accepted in so far as condom (approved in Japan) is used.
17. Known positive serology for human immunodeficiency virus (HIV). HIV testing is not mandatory.
18. History of relevant allergy or hypersensitivity to ingredients of BI 836845
19. Other patients judged ineligible for enrolment in the trial by the investigator

3.3.4 Removal of patients from therapy or assessments

Discontinuation of study treatment or discontinuation of the trial will be documented in the eCRF and the reason for discontinuation recorded and discussed in the clinical trial report if needed.

3.3.4.1 Criteria for discontinuation of study treatment in the trial for individual patients

Patients should discontinue the study treatment and initiate EOT and subsequent visits if any one of the following criteria is met:

- Patients who withdraw consent to further study treatment
- Patients who are no longer able to continue the study treatment (e.g. undue toxicity, pregnancy, surgery, concomitant diagnoses, concomitant therapies, administrative reasons) after discussion and agreement with the investigator and the sponsor
- Patients who developed PD by the discretion of investigator
- Patients who interrupt the study treatment more than 4 weeks as counted from the next planned treatment administration. If an interruption of more than 4 weeks is necessary and clinically justified, the patient may continue the study treatment after discussion and agreement between the investigator and the sponsor if there is documented clinical benefit (e.g., SD, disease control).
- Patients who require more than 2 dose reductions or dose reduction less than 500 mg throughout the study treatment

The EOT visit should be performed within 5 days after discontinuation of study treatment except for the rollover part. In case an adverse event is still ongoing at the time of discontinuation, every effort should be made to follow-up for the adverse event according to Section 5.2.2.2.

3.3.4.2 Criteria for discontinuation of the trial for individual patients

Patients should discontinue the trial if any one of the following criteria is met:

- Patients who withdraw consent to participation in the trial
- Significant non-compliance with the protocol requirements. Such patients may be discontinued the trial after discussion and agreement between the investigator and the sponsor.

3.3.4.3 Discontinuation of the trial by the sponsor

[redacted] reserves the right to discontinue the trial overall, or at a trial site, at any time for the following reasons:

- Failure to meet expected entry goals overall or at a trial site
- Emergence of any efficacy and/or safety information that could significantly affect continuation of trial: As described in Section 2.3 “BENEFIT–RISK ASSESSMENT”, Boehringer Ingelheim decided to terminate all oncology drug development for BI 836845 in consideration of.topline results of 1280-0022.
- Violation of GCP, the CTP, or the contract by the trial site or the investigator, disturbing the appropriate conduct of the trial.

The trial site will be reimbursed for reasonable expenses incurred in case of trial termination, except for cases relevant to the third bullet point above.

3.3.5 Replacement of patients

Patients will be replaced for the analysis of primary endpoint in cases of:

- Discontinuation during Cycle 1 for reasons other than DLT (e.g. withdrawal of informed consent because patients no longer wish to continue the study treatment or to participate in the trial)
- Patients who do not experience DLT but miss more than 1 visit during Cycle 1.
- Patients who are not evaluable with respect to DLT

Replacement of patients will be determined on a case by case basis and will only occur after discussion and agreement between the investigator and the sponsor.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

4.1.1 Identity of BI investigational product

Substance:	**BI 836845** (fully human mAb)
Pharmaceutical form:	Liquid formulation
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Route of administration:	Intravenous
Posology:	Infusion for over 1 hour. On Day 1 of Cycle 1, the duration of infusion may be extended to over 1 hour and up to a maximum of 3 hours in cases of CTCAE grade ≥2 infusion reactions.

Refer to the ISF for details of the preparation and handling regimen of BI 836845 including information on equipment, infusion procedure and process.

4.1.2 Method of assigning patients to treatment groups

A unique patient identification number will be assigned by the sponsor after the patient has signed the informed consent form. The number will represent the patient number that should be recorded on all eCRFs and correspondence regarding the patient. Once assigned, numbers for any screening failures, non-treated, non-evaluable, or discontinued patients will not be re-used.

Only in the case in which the investigator will confirm that patients have met all inclusion criteria and do not apply any exclusion criteria, the investigator will be able to register the patients (see Section 6.2.2 for details). The sponsor will assign the dose cohort for the registered patients.

4.1.3 Selection of doses in the trial

4.1.3.1 Initial dose and dose levels to be evaluated

Dose cohorts of BI 836845 to be evaluated are indicated in Table 4.1.3.1: 1. Actual number of evaluable patients to be entered will depend on the incidence of DLTs. To identify the MTD, 6 patients must enter the dose cohort. Dose escalation will proceed as outlined in Section 4.1.3.4 until the MTD or 1400 mg dose cohort has been reached. Additional 6 patients may also be entered as an expansion cohort to be recommended a relevant biological dose.

Table 4.1.3.1: 1 Dose cohorts and number of evaluable patients to be enrolled

Dose cohort	Number of evaluable patients
750 mg	3 to 6
1000 mg	3 to 6
1400 mg	6

As shown in Section 1.4, patients' tolerability was ensured until 1800 mg (qw schedule) and 3600 mg (q3w schedule) in 1280.1 and 1280.2 trials, respectively. Reported drug-related adverse events were mainly predictable and manageable. The rationale behind the starting dose of 750 mg is based on safety and efficacy results of 1280.1 and 1280.2 trials. Such a sufficient tolerability will be expected at 750 mg of BI 836845 in Japanese patients with advanced solid tumours. In addition, objective tumour response as PR was observed in Taiwanese patients who were treated in the close vicinity of the starting dose, 800 mg (see Section 1.4 for details).

After confirmation of sufficient tolerability in patients who are treated at 750 mg of BI 836845, the 1000 mg dose cohort will be opened. The dose of 1000 mg is an identified relevant biological dose which estimated to neutralise more than 90% for free IGF-1 and 64% for free IGF-2 in the blood from PK–PD modelling results. The 1400 mg dose cohort is also planned as a maximum dose because additional neutralisation of more than 2% for free IGF-1 and more than 7% for free IGF-2 are estimated at 1400 mg, and no effective neutralisation of free IGF-1 and free IGF-2 is expected more than 1400 mg.

4.1.3.2 Dose-limiting toxicities

For definition of a DLT, it is essential that patients are treated sufficiently according to supportive care standards, and baseline conditions, coexisting symptoms, and/or transient laboratory abnormalities of patients are also considered. A drug-related adverse event constitutes a DLT, if one of the following applies during Cycle 1:

Haematological toxicities:

- CTCAE grade 4 neutropenia (neutrophil counts of <500/µL) lasting 7 or more days
- Febrile neutropenia (neutrophil counts of <1000/µL with once observed a temperature of ≥38.3°C or a sustained temperature of ≥38.0°C for more than 1 hour)
- Infection with neutrophil counts of <1000/µL
- CTCAE grade 4 thrombocytopenia (platelet counts of <25 000/µL) or CTCAE grade 3 thrombocytopenia (platelet counts of <50 000–25 000/µL) associated with bleeding requiring platelet transfusion

Non-haematological toxicities:

- CTCAE grade 3 or 4 non-haematologic toxicity (except incompletely treated nausea, untreated vomiting, untreated diarrhoea, skin toxicity, fatigue, infusion reaction, electrolyte, hyperglycaemia, AST, or ALT). The following drug-related non-haematological toxicities should be defined as DLTs:
  - CTCAE grade ≥2 infusion reaction despite adequate pre-medication
  - CTCAE grade ≥2 nausea and/or vomiting persisting for 7 or more days despite antiemetic treatment
  - CTCAE grade ≥3 skin toxicity despite adequate supportive care measures for up to 14 days if it does not reach an improvement to grade ≤2
  - CTCAE grade ≥3 hyperglycaemia resistant to treatment with anti-diabetic agents
  - Any electrolyte CTCAE grade 3 adverse event which is refractory to optimal correction therapy
  - No recovery from a non-DLT CTCAE grade ≥3 toxicity to grade ≤1 within 14 days of administered dose
  - Sustained CTCAE grade 3 fatigue or asthenia for longer than 96 hours associated with deterioration of ECOG performance status

It is understood that also other drug-related adverse events (CTCAE grade 2) may carry the potential to be significant enough to necessitate treatment interruption or discontinuation, and as such qualify as DLT. Such adverse events will be required the confirmation after thorough discussion between the investigator and the sponsor on a case-by-case basis.

All adverse events which are determined as DLTs occurring during Cycle 2 or later (DLT-equivalent adverse events) will also be considered during evaluation of the overall safety in the trial.

All DLTs and DLT-equivalent adverse events have to immediately be reported to the sponsor. DLTs and DLT-equivalent adverse events must be determined after discussion and agreement with the investigator and the sponsor. The sponsor may ask for the opinion of the assigned external expert if needed.

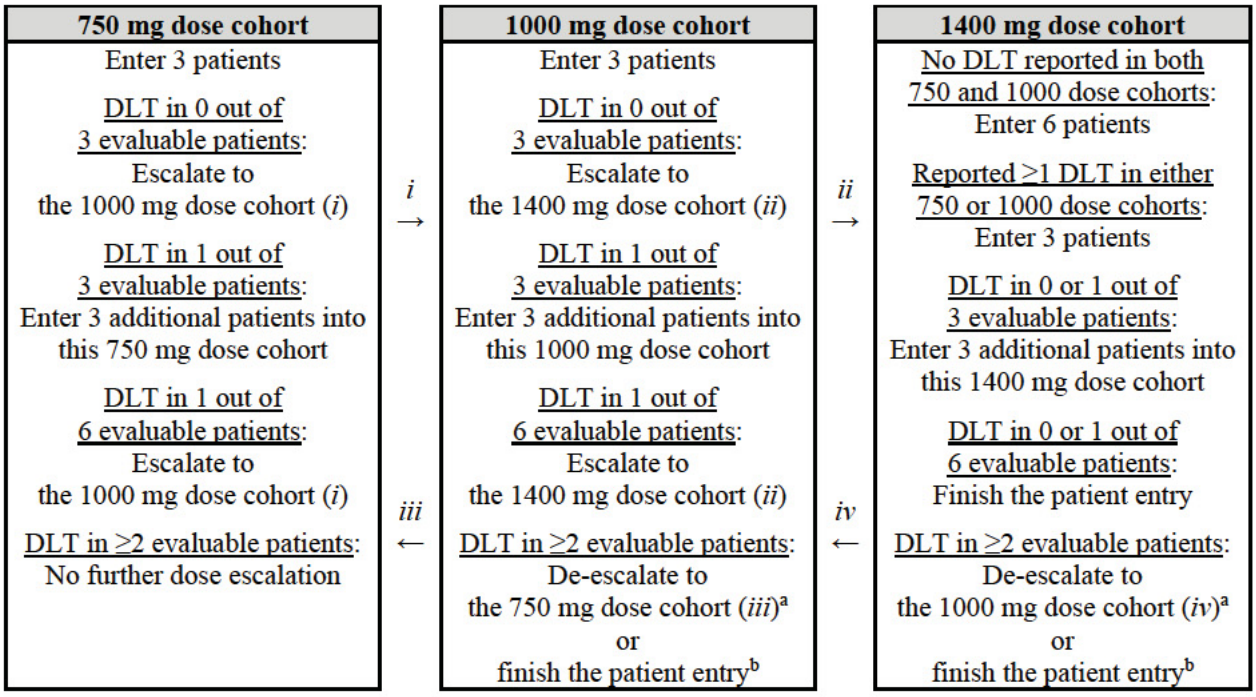
4.1.3.3 Maximum tolerated dose

The MTD of BI 836845 is the highest dose tested with DLT occurring in not over 1 out of 6 evaluable patients.

In case the MTD will not be reached until 1400 mg, it will be deemed as a sufficient tolerability in Japanese patients with advanced solid tumours at 1400 mg.

4.1.3.4 Dose escalation, cohort expansion, and/or dose de-escalation

Dose escalation, cohort expansion, and/or dose de-escalation will be performed as summarised in Figure 4.1.3.4: 1.



a. Three (3) evaluable patients will be entered into the de-escalated dose cohort. It cannot be decided the dose re-escalation from the de-escalated dose cohort.
b. Patient entry will be finished if 6 evaluable patients have already been entered into the de-escalated dose cohort.

Figure 4.1.3.4: 1 Criteria for dose escalation, cohort expansion, and dose de-escalation

In case no MTD can be identified up to the highest dose tested in this trial, additional 6 patients may also be entered as an expansion cohort to be recommended a relevant biological dose.

Dose escalation, cohort expansion, or dose de-escalation must be decided after discussion and agreement with the principal investigator and the sponsor based on the incidence of all reported DLTs. The sponsor may ask for the opinion of the assigned external expert if the investigator or the sponsor considers this to be needed.

4.1.3.5 Initiation of study treatment with BI 836845 for the next cycle (Cycle 2 onwards)

Except for the rollover part, patients who met all of the following criteria on the first day planned to initiate the study treatment of next cycle will continue the study treatment and will perform the assessments defined for Day 1 of next cycle.

- Recovery of drug-related haematological adverse events to CTCAE grade ≤2 or baseline
- Recovery of drug-related non-haematological adverse events to CTCAE grade ≤1 or baseline (except for alopecia, skin hyperpigmentation, incompletely treated nausea, untreated vomiting, untreated diarrhoea, skin toxicity, fatigue, infusion reaction, electrolyte, hyperglycaemia, AST, or ALT)
- Absence of any other discontinuation criteria (see Section 3.3.4)
- Written re-consent for the participation of repeated study treatment from Cycle 2 (only before start of Cycle 2)

Patients who are not eligible for continuing the study treatment will discontinue the study treatment and will be assessed at EOT visit.

4.1.3.6 Dose reduction

If patients develop a DLT or a DLT-equivalent adverse event, the study treatment will be resumed at a reduced dose after the DLT or the DLT-equivalent adverse event has recovered to baseline or CTCAE grade ≤1. However, study treatment should not be resumed and the patient should discontinue the study treatment if any of the criteria in Section 3.3.4 are met.

Only 2 dose reductions will be permitted according to Table 4.1.3.6: 1. If dose reductions are required 3 times throughout the study treatment or dose reduction less than 500 mg, the patient should be discontinued the study treatment.

Table 4.1.3.6: 1 Dose reduction scheme

Starting dose	Assigned dose after the first dose reduction	Assigned dose after the second dose reduction
750 mg	500 mg	Patient discontinuation
1000 mg	750 mg	500 mg
1400 mg	1000 mg	750 mg

4.1.3.7 Dose interruption

The study treatment in a patient may be interrupted at any time when there is concern about the patients' safety after discussion and agreement with the investigator and the sponsor. In

case patients develop a DLT or a DLT-equivalent adverse event, see Section 4.1.3.6 for details.

During drug interruption, the scheduled BI 836845 administration will be missed and will not be retrospectively administered. All the other scheduled assessments shall be performed as described in the Flow Chart. Patients should discontinue the study treatment when the duration of dose interruption exceeds 4 weeks as counted from the next planned treatment administration according to Section 3.3.4.1.

4.1.3.8 Initiation of rollover part

At the time of all patients in the trial having sufficient data to answer the primary endpoint (see Section 5.2.1), patients continuing on study treatment will have the EOT assessments (except for blood collection for biomarker analyses) performed and then continue on study treatment into the rollover part with reduced clinical data collection.

The investigator should make efforts to keep administration of BI 836845 at intervals of 7 days. However, weekly administration schedule can temporarily be accelerated, delayed or skipped due to administrative reasons at the discretion of the investigator.

4.1.4 Drug assignment and administration of doses for each patient

A method of drug assignment for patients is described in Section 4.1.2.

BI 836845 will be administered intravenously over 1 hour with repeated administration weekly until patients meet any of criteria for discontinuation (see Section 3.3.4 for definition) as per the Flow Chart. Infusion duration on Day 1 of Cycle 1 may be extended to over 1 hour and up to a maximum of 3 hours in cases of CTCAE grade ≥2 infusion reactions (see Section 4.2.1.1 for grading and management of infusion reactions). **An infusion duration of less than 1 hour must be avoided because mannitol is used in the formulation of BI 836845.**

Patients will be treated at the assigned dose during the study treatment unless patients are required the dose reduction (see Section 4.1.3.6 for definition). Intra-patient dose escalation will not be allowed.

In case of a delay of infusion, the reason and the exact time of deviation must be recorded in the eCRF because the accuracy of this information is crucial for the proper evaluation and appraisal of pharmacokinetics and other data. In case of a drug interruption, the reason must be recorded in the eCRF. Administration status is not recorded in the eCRF during the rollover part.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Not applicable because it is an open-label trial

4.1.5.2 Procedures for emergency unblinding

Not applicable because it is an open-label trial

4.1.6 Packaging, labelling, and re-supply

BI 836845 drug supplies will be provided from [redacted]

For details of packaging and the description of the label as well as the process for resupply of investigational drug, see the ISF.

4.1.7 Storage conditions

BI 836845 will be stored in the original packaging at the temperature stated on the drug label.

4.1.8 Drug accountability

Drug supplies which will be provided by the sponsor must be kept in a secure and limited access storage area in the hospital pharmacy. Where necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature according to the ISF.

The investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the CTP by the Institutional Review Board (IRB)
- Availability of a signed and dated clinical trial contract between the sponsor and the Head of Trial Centre
- Approval/notification of the regulatory authority, e.g. competent authority
- Availability of the curriculum vitae of the principal investigator
- Availability of a signed and dated CTP or immediately imminent signing of the CTP

The investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the trial site, the use by each patient, and the return of unused products.

These records will include dates, quantities, batch/serial numbers, expiry ('use-by') dates, and medication numbers. The investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the sponsor.

At the time of return of unused products, the investigational drug storage manager must verify that all unused drug supplies have been returned.

Upon completion of the trial, the investigational storage manager submits to the sponsor a copy of the investigational drug dispensing and return log. When submitting the copy, the investigational drug storage manager should exercise caution to preserve the anonymity of patients' names.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatments

Rescue medication to reverse the effects of BI 836845 is not available. Potential side effects of BI 836845 should be treated symptomatically.

Symptomatic treatments of tumour-associated symptoms are allowed. Concomitant medications and/or concomitant therapies to provide adequate supportive care may be given as clinically necessary. Patients should receive full supportive care including transfusions of blood and blood products, antibiotics, analgesia etc., according to local practice or guidelines where appropriate. Anti-emetic medication should be prescribed according to local practice.

Precaution should be taken to avoid extravasation. Patients should be asked to report any pain or burning at the site of injection immediately. If extravasation is suspected, the infusion should be stopped immediately. Treatment should be initiated according to local practice.

All concomitant and concomitant therapies should be recorded in the eCRF except during the rollover part. Trade name and indication of concomitant therapies will be documented. If patients receive parenteral nutrition during the trial, the components need not be specified in detail and should just be indicated as "parenteral nutrition" and the form be completed. If a patient requires anaesthesia, it will be sufficient to indicate "anaesthesia" without specifying the details.

If surgery is considered necessary for the patient, whenever possible, at least 7 days should elapse after the last dose of BI 836845 before surgery is performed. Treatment can be resumed from 12 days after surgery.

4.2.1.1 Management and grading of infusion reactions

The investigational drug infusions should always be administered in a hospital environment and under close supervision of the medically qualified staff member with immediate availability of full resuscitation facilities.

Infusion reactions may occur during infusion with BI 836845 and include pyrexia, chills, rigors, dyspnoea, urticaria, bronchospasm, hypotension, and hypertension. **A 1-hour observation period is recommended following each infusion.** Mild to moderate infusion reactions may be managed with a slower infusion rate and prophylactic antihistamines for subsequent dosing. Severe reactions require immediate interruption of infusion. The details are summarised in Table 4.2.1.1: 1. The grading of hypersensitivity reactions will be according to CTCAE version 4.03.

Table 4.2.1.1: 1 Infusion reaction management

Intensity for infusion reaction	Management
CTCAE grade 1 or 2	In the event of a mild to moderate CTCAE grade 1 or 2 non-allergic infusion reaction, the infusion rate should be reduced by 50%. Once the adverse event has resolved, the investigator should wait and deliver the infusion at the reduced rate for another 30 minutes. If tolerated, the infusion rate may then be increased to the next close rate on the patient's infusion schedule. In case of a CTCAE grade 2 adverse event that requires therapy (e.g. antihistamines, nonsteroidal anti-inflammatory drugs [NSAIDs], steroids, narcotics, intravenous fluids) or infusion interruption and resolves promptly the infusion may also be restarted at half of the infusion rate at the time of onset of the infusion reaction.
CTCAE grade 3	For Patients experiencing CTCAE grade 3 infusion reaction, infusion should be interrupted immediately and patients should receive aggressive symptomatic treatment. Only after all the symptoms have disappeared the infusion should be started. The infusion rate at restart should be half of the infusion rate at the time of onset of the infusion reaction.
CTCAE grade 4	For patients experiencing CTCAE grade 4 infusion reaction such as anaphylaxis during an infusion should have infusion immediately stopped and receive appropriate treatment including use of resuscitation medications and/or equipment that must be available. Such patients should be discontinued the study treatment and should be followed up.

The infusion reactions should be treated symptomatically as judged clinically relevant by the investigator. For symptomatic treatment of infusion reactions: hydrocortisone, antihistamines such as chlorpheniramine accompanied by an antipyretic/analgesic, and/or a bronchodilator is recommended.

4.2.1.2 Management of hyperglycaemia

In case of hyperglycaemia treatment should follow standard and local guidelines and may include oral antidiabetics such as metformin. The appropriate expert advice should be considered in the management of hyperglycaemia. When treatment with the investigational drug is discontinued, the need for further antidiabetic treatment has to be evaluated depending on the blood glucose levels of the patient.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The use of concomitant drugs for prophylactic purpose is prohibited to prevent the expression of drug-related adverse events. Additional experimental anti-cancer treatment and/or standard chemotherapy, immunotherapy, hormone treatment, with the exception of megestrol acetate and LHRH analogues, is not allowed during the trial.

For symptom control palliative radiotherapy may be permitted after discussion and agreement with the investigator and the sponsor on a case-by-case basis (e.g. for bone metastases). The impact of any palliative radiotherapy on tumour assessments must be documented.

Any concomitant medication should be reduced to the clinically necessary minimum on the days of BI 836845 infusion.

4.2.2.2 Restrictions on diet and life style

No restrictions on diet and lifestyle apply to the trial.

4.3 TREATMENT COMPLIANCE

BI 836845 will be administered by infusion over 1 hour in accordance with the CTP under supervision of the investigator or delegated study personnel.

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY

Although this trial will primarily aim to identify the MTD of BI 836845 in Japanese patients with advanced solid tumours, preliminary anti-tumour activity will also be assessed by tumour measurement and clinical evaluation. Tumour assessments should be performed following every 2 cycles of study treatment up to the end of Cycle 6, and thereafter every 3 cycles.

5.1.1 Endpoints of efficacy

Other efficacy assessments:

[redacted]

5.1.2 Assessment of efficacy

[redacted]

5.2 SAFETY

5.2.1 Endpoints of safety

The primary endpoint:

- MTD of BI 836845 in Japanese patients with advanced solid tumours (as identified by the number of patients with DLTs)

Other safety assessments:

- All adverse events
- Laboratory tests
- ECOG performance status
- Vital signs
- Twelve (12)-lead electrocardiogram (ECG)

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

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

Serious adverse event

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

An adverse event which possibly leads to disability will be handled as “deemed serious for any other reason” and reported as an SAE.

Patients may be hospitalised during selected phases of the trial for administrative reasons. These hospitalisations for administrative reasons and other hospitalisations as described below need not be reported as SAEs. The events not considered to be SAEs are

hospitalisations for the: routine treatment or monitoring of the underlying disease, not associated with any deterioration in condition; treatment, which was elective or already planned at the screening visit, for a pre-existing condition that is unrelated to the indication under study and did not worsen; admission to a hospital or other institution for general care, not associated with any deterioration in condition; treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission or; admission to hospice for respite care.

Intensity of adverse event

The intensity of adverse events should be classified and recorded according to CTCAE version 4.03 in the eCRF.

When no CTCAE grading is available for a specific adverse event, the intensity of the AE should be judged based on the following:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self care ADL
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to adverse event

Causal relationship of adverse event

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, and confounding factors such as concomitant medication, concomitant diseases, and relevant history. Assessment of causal relationship should be recorded in the eCRFs. The reason for the decision on causal relationship needs to be provided in the eCRFs.

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

Worsening of underlying disease or other pre-existing conditions

Worsening of the underlying disease or of other pre-existing conditions will be recorded as an adverse event or a SAE in the eCRF.

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

Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an adverse event or SAE in the eCRF if they are judged clinically relevant by the investigator.

Adverse events of special interests

DLTs and DLT-equivalent adverse events (see Section 4.1.3.2 for definition), and DILI are defined as "adverse events of special interests". Adverse events of special interests are to be reported in an expedited manner similar to SAE even if they do not meet any of the seriousness criteria (see Section 5.2.2.2 for details).

If a DLT or a DLT-equivalent adverse event is observed, or the investigator determines any DILI is related to the study treatment, the administration of the investigational drug and/or application of concomitant therapy must be managed according to Sections 4.1.3.5, 4.1.3.6, and 4.2.

The DILI is defined as followings:

- For patients with normal liver function (ALT, AST, and bilirubin within normal limits) at baseline:
  An elevation of AST and/or ALT ≥3 × ULN combined with an elevation of bilirubin ≥2 × ULN measured in the same blood draw sample
- For patients with impaired function tests (AST and/or ALT >ULN) at baseline:
  An elevation of transaminase ≥ (baseline + 4 × ULN) combined with an elevation of total bilirubin ≥2 × ULN measured in the same blood draw sample

Patients showing these laboratory abnormalities need to be followed up according to Appendix 10.3.2 of this CTP and the "DILI checklist" provided in the ISF. Patients with abnormal liver function tests must have their abnormalities and the etiology documented in detail as baseline conditions. Every effort should be made to explain possible deteriorations of baseline conditions.

Other significant adverse events

Other significant adverse events are defined any adverse event caused by discontinuation of study treatment and/or dose reduction.

5.2.2.2 Adverse event and serious adverse event reporting

All adverse events, serious and non-serious, occurring during any cycle of the trial (i.e. from signing the informed consent onwards through the follow-up period) will be collected, documented, and reported to the sponsor by the investigator on the appropriate eCRFs and/or SAE reporting forms. Reporting will be done according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the ISF.

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

The investigator also has the responsibility to report all adverse events (including deaths) occurring within obtaining written informed consent and 42 days after the last administration of BI 836845 will be collected. Any adverse events or SAEs reported to the sponsor during this phase must be documented in the safety database.

Except for the rollover part, all adverse events (including death) occurring later than 42 days after the last administration of BI 836845 until end of the trial will also be collected. Any adverse events or SAEs reported to the sponsor during this phase must be documented in the safety database.

Except for the rollover part, all adverse events, including those persisting after end of study treatment must be followed up until recovery to CTCAE grade ≤1 or baseline condition or, in case of persistence, sufficient characterisation of the toxic effects has been achieved and the investigator and the sponsor agree not to pursue them further.

If not stipulated differently in the ISF, the investigator must report the following adverse events immediately (within 24 hours or the next business day whichever is shorter) to the sponsor:

1. If using paper process SAE form via telephone/fax or
2. If available for the trial, using the remote data capture (RDC) or electronic data capture (EDC)

SAEs as well as non-serious adverse events occurring at the same time as an SAE and/or which are medically related to the SAE(s) and adverse events of special interests must be reported as SAEs. With receipt of any further information to these events, a follow-up SAE report has to be provided. SAEs and non-serious adverse events must include a causal relationship assessment made by the investigator. This information must be also reported immediately to the head of the trial site.

Boehringer Ingelheim has set up a list of adverse events which are defined to be always serious. In order to support the investigator with the identification of these "always serious adverse events", if a non-serious adverse event is identified to be serious per definition by Boehringer Ingelheim, a query will be raised. The investigator must verify the description

and seriousness of the adverse event. If the event description is correct, the item "serious" needs to be ticked and an SAE has to be reported in expedited fashion following the same procedure as above. The list of these adverse events can be found via the RDC/EDC environment.

With receipt of any further information to these adverse events, a follow-up SAE report has to be provided. SAEs and non-serious adverse events must include a causal relationship assessment made by the investigator. This information must also be reported immediately to the head of the trial site.

The SAE form is to be forwarded to the defined unique entry point identified for the Drug Safety Department of [redacted] (contact details will be provided in the ISF). This immediate report is required irrespective of whether the investigational product has been administered or not and irrespective of causal relationship. It also applies if new information to existing SAEs or protocol-specified adverse events of special interests becomes available.

Pregnancy

In rare cases, pregnancy might occur in clinical trials. Once a female patient has been enrolled into the clinical trial, after having taken study medication, the investigator must report immediately any drug exposure during pregnancy to the sponsor. As well as once a male patient has been enrolled into the clinical trial, after having taken study medication, the investigator must report immediately any drug exposure during pregnancy for the male patient's partner to the sponsor. Drug exposure during pregnancy has to be reported immediately (within 24 hours or next business day whichever is shorter) to the defined unique entry point for SAE forms of the Drug Safety Department of [redacted] (contact details will be provided in the ISF). The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up. In the absence of an adverse events or SAE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B).

5.2.3 Dose-limiting toxicity and maximum tolerated dose

See Sections 4.1.3.2 and 4.1.3.3 for definitions of DLTs and the MTD, respectively.

5.2.4 Assessment of safety laboratory parameters

Laboratory tests specified in Table 5.2.4: 1 will be assessed at the visits indicated in the Flow Chart. The results from the previous laboratory test may be used on Visit 1 of each cycle if the examination was performed within 2 days before the visit. At another visits, the

examinations will be performed before infusion. The site staff does not need to test for all laboratory parameters listed in Table 5.2.4: 1 and to enter the test results in the eCRF during the rollover part. In case of adverse events related to laboratory abnormalities, adequate and more frequent evaluation will be performed at the discretion of the investigator.

Table 5.2.4: 1 Laboratory parameters

Category	Test name
Haematology:	Red blood cell count, haemoglobin, white blood cell count and differential, reticulocytes, and platelets
Biochemistry:	Glucose, sodium, potassium, calcium, creatinine, AST, ALT, alkaline phosphatase, lactate dehydrogenase, bilirubin (total and direct), urea or blood urea nitrogen, total protein, uric acid, lipase, amylase, creatine phosphokinase (CK). In case of pathological CK, further evaluation (e.g., by troponin assays, CK-MM, CK-MB, ECG examination) should be performed and the findings documented. Glomerular filtration rate (GFR) will be calculated by the Cockcroft–Gault formula (see Appendix 10.2) utilising serum creatinine values and recorded in the eCRF.
Coagulation:	Prothrombin time, international normalised ratio (INR) where therapeutically indicated, and activated partial thromboplastin time
Urinalysis:	pH, glucose, erythrocytes, leukocytes, protein, nitrite will be analysed by dipstick (semi-quantitative measurements: –, ±, +, ++, +++). In case of abnormal findings, further evaluation should be performed and the findings documented.

5.2.5 Electrocardiogram

A standard 12-lead resting ECG will be performed at the time points specified in the Flow Chart. ECG must be performed pre-infusion, during infusion (after 30 ± 5 minutes) and immediately before end of infusion on Day 1 of Cycle 1. ECG will be performed before infusion on Day 15 of Cycle 1 and Cycle 2 onwards during study treatment.

5.2.6 Left ventricular ejection fraction

Left ventricular ejection fraction (LVEF) as measured by ECHO or MUGA scan must be assessed at screening. Further scans may be performed after start of study treatment if clinically indicated by the discretion of investigator. The same method of measurement should be used throughout the trial.

ECHO should be performed to assess the LVEF by referring the standard guidelines of the American Society of Echocardiography (R06-1414). MUGA is recommended as a non-invasive method for the assessment of diseases of the heart muscle. It is used for the monitoring of the ejection fraction of the cardiac ventricles, especially the LVEF.

5.2.7 Endocrine Assessments

Fasting plasma and serum samples (where possible at EOT visit) should be collected from patients for determination of the following as per the time points specified in the Flow Chart:

- Glucose
- Insulin
- Thyroid-stimulating hormone (TSH)
- Human growth hormone
- HbA_{1c}
- C-peptide

Fasting plasma and serum samples may be collected within 7 days before Visit 1 of Cycle 1 and Visit 1 of Cycle 2.

Further samples may be taken throughout the trial where required and deemed appropriate by the investigator. All analyses are to be performed by the local clinical laboratory.

5.2.8 Assessment of vital signs and physical examination

Vital signs (blood pressure, pulse, respiratory rate after 2 minutes supine rest, and temperature) will be recorded at the screening visit and at the time points specified in the Flow Chart. On administration day of every cycle except for the rollover part, vital signs are performed at pre-infusion, during infusion (30 ± 5 minutes after start of infusion), and immediately before end of infusion. Further vital signs to be taken at any time if clinically indicated and/or after discontinuation of administration.

A physical examination will be performed at screening and at the time points specified in the Flow Chart. The physical examination should include a thorough cardiopulmonary examination, an examination of the regional lymph nodes, an examination of the abdomen and an assessment of the mental and neurological status. Additional symptoms which have not been reported during a previous examination should be clarified. A physician or a clinical research coordinator should perform this examination. Measurement of height (in cm) and body weight (in kg) and the evaluation of the ECOG performance status will be performed at the time points specified in the Flow Chart.

5.2.9 Pregnancy testing

Beta-human chorionic gonadotropin (β-hCG) testing in serum will be performed as outlined in the Flow Chart at screening (within 7 days before start of study treatment), Visit 1 of every odd cycle, and at the EOT visit except for the rollover part. Methods and duration of contraception indicated in the latest subject information should be applied. Should a woman

become pregnant or suspect she is pregnant while participating in the trial, she should inform her treating physician immediately.

5.3 OTHER

5.3.1 Demographic and cancer history

Demographics (e.g. sex, birth date, race) and baseline conditions will be collected during the screening visit.

Cancer history will also be obtained as many as possible.

- The type of cancer including the histological subtype and molecular markers if applicable or available (e.g., *EGFR* mutation status, *KRAS*/*BRAF* mutation status)
- The primary tumour site
- The month and year of first histological diagnosis
- The differentiation grade (not specified, undifferentiated, poorly-differentiated, moderately-differentiated, and well-differentiated).
- The TNM stage of the tumour obtained at screening visit of the trial including the number and location of metastatic sites
- Previous surgeries
- Number and type of previously administered chemotherapies, immunotherapies, hormonal therapies, molecular-targeted therapies, and biological therapies including specification of the treatment protocol and name of treatment
- The best response (CR, PR, SD, PD, or unknown)

5.3.2 Medical history and concomitant therapies

Relevant symptoms due to underlying disease, pre-existing diseases, and/or the treatments present at screening will be recorded in patients' eCRFs.

Any changes of concomitant therapies from baseline to treat such symptoms will be recorded in patients' eCRFs except for the rollover part.

[redacted]

[redacted]

5.3.4 Pharmacogenomic evaluation

To allow for pharmacogenomic analyses, 2 blood samples will be asked.

The first blood sample of 2 mL will be collected in an EDTA tube from all patients on Day 1 of Cycle 1 and will be stored at –20ºC or below at Boehringer Ingelheim. It will be used for DNA extraction and subsequent genotyping of polymorphisms in the IGF pathway, including e.g. IGF-binding proteins, like IGFBP-3. In addition, analysis of the DNA sample may be performed in an effort to identify genetic factors predisposing to adverse events. With regard to the sample, the patient's blood sample and the extracted DNA can be disposed in response to the patient's request after the patient withdraws informed consent for pharmacogenomics.

The second blood sample (8.5 mL blood in PAXgene tubes, DNA banking sample) will be stored at –20ºC or below at Boehringer Ingelheim for 15 years after the end of the clinical trial or until there is no more material available for tests. The stored DNA may be analysed at a later time to identify whether there are other genetic factors that could contribute to a better therapeutic outcome or a higher risk of developing drug-related adverse events. The second sample will be taken and stored after separate written informed consent is given. Storage as well as retrieval and analysis of banked samples take place in a strictly controlled environment. With regard to the sample, the patient's blood sample and the extracted DNA can be disposed in response to the patient's request after the patient withdraws informed consent for pharmacogenomics until 3 months after archive of clinical trial report in the trial. After the samples are anonymised at the instant of 3 months after archive of clinical trial report, the samples cannot be disposed unless consent withdrawal. The first and second blood sample will be disposed after the clinical trial report is archived and after reaching the maximum allowed storage duration, respectively.

Both blood samples will be disposed as clinical waste no way to trace back to the identity of the donor.

Collection of the first sample is a mandatory part of the CTP, whereas the collection of the second sample is voluntary.

If possible, tissue slides cut from archival formalin-fixed paraffin-embedded (FFPE) tumour tissue will be obtained from initial diagnostic surgery. If tissue is available from more than 1 occasion, the latest obtained tissue should be used wherever possible. Participation in this pharmacogenomic investigation for archived tissue sample is voluntary and not a prerequisite for participation in the study. The tissue sample will be stored for 15 years after the end of the clinical trial or until there is no more material available for tests at 4–25ºC at CRO which is delegated the pharmacogenomics tests of the sample. The tissue will be analysed for mRNA expression of IGF pathway related genes, e.g. tumour IGF-1 and IGF-2. For these analyses, tumour tissue slide sets from FFPE tumour samples must contain a minimum of 15 slides (RNase-free preparation). Further mutations/deletions in genes relevant for response or resistance, e.g. in genes belonging to the PI3K family and in PTEN, and imprinting/methylation status of IGF-2 will be explored. In an effort to fully understand mechanisms of drug effect, mutation and gene expression analyses may be extended to other important oncogenes or tumour-related genes. With regard to the sample, the patient's tissue sample can be disposed in response to the patient's request after the patient withdraws informed consent for pharmacogenomics. The tissue sample will be disposed after the clinical trial report is archived as clinical waste no way to trace back to the identity of the donor.

The results of pharmacogenomics tests will not be disclosed to patients because they are exploratory analysis which is not validated for diagnostic use. This analysis may be performed at a later point in time, and the results may be reported in a separate report.

5.4 APPROPRIATENESS OF MEASUREMENTS

The RECIST version 1.1 (R09-0262) to be used for evaluation of tumour response are well-established and scientifically accepted. The CTCAE version 4.03 (R10-4848) are commonly used in the assessment of adverse events in cancer patients.

All measurements performed during the trial will be to identify the MTD, and to evaluate the safety, pharmacokinetics, pharmacodynamics and preliminary anti-tumour activity of BI 836845 for the trial.

The scheduled assessments are to monitor drug-induced changes in respect to vital signs, laboratory tests, and ECG. Tumour evaluations are necessary for determination of tumour response to treatment and possible pharmacodynamic effects. Biomarker analyses are necessary for correlation with therapeutic outcome. Immunogenicity testing will detect any anti-drug antibody reactions as a result of infusion of BI 836845.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Pharmacokinetic samples will be collected at the time points specified in Tables 10.1: 1, 10.1: 2, and 10.1: 3.

5.5.1 Pharmacokinetic endpoints

5.5.2 Methods of sample collection

The exact time and date of sampling, and drug administration (except for the rollover part) are to be recorded in the eCRF.

At the time points specified in the Flow Chart and in Appendix 10.1, the blood samples will be taken for determination of BI 836845 plasma concentrations using EDTA as an anticoagulant. For quantification of BI 836845, at least 2 mL of blood will be taken.

Details about blood sample collection, preparation of EDTA-anticoagulated plasma samples, storage, and shipment will be provided in a sample handling manual.

[redacted]

5.6 BIOMARKERS FOR EVALUATING PHARMACODYNAMICS

This trial includes biomarkers that are measured and evaluated by an explorative objective. These assessments are hypothesis generating and will be used to expand our understanding of the disease and investigational drug.

The following biomarkers will be analysed in samples collected from patients entered into the trial:

- Total IGF-1, total IGF-2, and IGFBP-3 in the serum
- IGF bioactivity in the heparinised plasma

As medical knowledge in this field is constantly evolving, other blood biomarkers that come to be known as potentially relevant prognostic and/or predictive markers of treatment response may also be explored via available blood. For this purpose leftover biomarker samples will be stored beyond end of the study for a maximum of 15 years. Biomarkers that come to be known or emerge as not relevant during the trial may not be analysed.

5.6.1 Endpoints based on biomarkers

Biomarker analysis is exploratory, and no endpoint will be based on biomarkers.

5.6.2 Method of sample collection

Details about blood sample collection, preparation of plasma and serum samples, required tubes, labelling of tubes, storage and shipment (frequency and addresses) will be provided in the sample handling manual.

5.6.4 Tumour markers

In case of applicable tumour markers of the underlying disease (e.g. CA 15-3, CA-125, CEA, PSA, AFP), the blood sample will be obtained pre-dose and post dose at the discretion of the investigator. Sample type specification, sampling procedure, and sample collection will follow the local standard. Analysis will be performed at the trial site.

5.7 PHARMACOKINETIC–PHARMACODYNAMIC RELATIONSHIP

No formal analysis of a PK–PD relationship is planned in the trial.

If the data suggest a PK–PD relationship of special parameters (e.g. IGF-1 concentration, IGF-2 concentration, IGFBP-3 concentration, phosphorylation of IGF-1R), a detailed analysis may be performed.

Correlation between drug concentration and response may be investigated if adequate appropriate data are available. In addition, exploratory correlation may also be investigated between drug concentration and adverse events.

Data may also be used to develop PK–PD models using nonlinear mixed effect modelling techniques, if feasible. For this purpose data may also be combined with data from other trials. Modelling activities will be planned and documented separately according to internal and external guidelines and SOP.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Visit schedule of the trial should be conducted in the order as summarised below:

1. Written informed consent
2. Screening visit
3. Registration for eligible patients
4. Study treatment during Cycle 1
5. Eligibility assessment for continuing the study treatment of next cycle
6. Continuation of study treatment during the next cycle if eligible until discontinuation of study treatment
7. Rollover part: Continuation of study treatment until discontinuation after having sufficient data to answer the primary endpoint
8. EOT visit if ineligible for the study treatment
9. Follow-up visits

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Patients will visit as specified in the Flow Chart. If patients could not visit on a scheduled day, the actual date of conducting planned investigation or evaluation will be recorded with the reason why patients could not visit on the scheduled day.

6.2.1 Screening period

Written informed consent must be obtained before any trial-specific evaluation is performed as part of screening and the trial overall.

After obtaining written informed consent, patients will attend a screening visit between Day –28 and –1 before receiving their initial study treatment. Patients will be assessed for the eligibility during the screening visit by evaluating all assessments specified in the Flow Chart.

Patients who meet all of the inclusion criteria (see Section 3.3.2) and do not apply any of the exclusion criteria (see Section 3.3.3) are eligible for participation and can be registered in the trial by the discretion of investigator.

6.2.2 Patient registration

Patient must be registered in the trial as soon as possible after the investigator confirmed the patient eligibility for the study treatment. Procedures for the patient registration are listed as follows:

- The investigator or clinical research coordinator will document the necessary details in a patient registration form and facsimile the form to the registration centre at [redacted]
- The registration centre will confirm all contents of patient registration form and judge whether the patient is eligible to participate in the trial and then facsimile the form describing the result of judgement to the trial site.

6.2.3 Treatment period

All assessments and evaluations must be performed before infusion of BI 836845 except for a part of vital signs, ECG measurements, and pharmacokinetic blood samplings (see Flow Chart).

The investigator confirms whether inclusion and exclusion criteria are still valid or not before study treatment on Visit 1 of Cycle 1. For patients who are willing to continue the study treatment after completion of Cycle 1, written informed re-consent must be obtained before study treatment on Visit 1 of Cycle 2.

All planned visit dates are programmed from the start of Day 1 of Cycle 1. If a visit is missed, there will be no re-scheduling. If a patient should attend the trial site between the "missed" and the next scheduled visit, the missed visit assessments should be performed. The current date and the reason for the delay must be recorded in the medical records. All subsequent visits should adhere to the scheduled visits for all cycles of treatment period.

The treatment period of the trial will continue for an indeterminate number of cycles until any one of discontinuation criteria (see Section 3.3.4.1) is met, and then the EOT visit must be performed. The end of treatment period will be the last day of study treatment.

6.2.3.1 Rollover part

At the time of all patients in the trial having sufficient data to answer the primary endpoint (see Section 5.2.1), patients continuing on study treatment will have the EOT assessments (except for blood collection for biomarker analyses) performed and then continue on study treatment into the rollover part with reduced clinical data collection. For patients who are willing to continue the study treatment in the rollover part, written informed re-consent must be obtained before the initial study treatment in the rollover part. After initiation of the rollover part, the investigator should make efforts to keep administration of BI 836845 at intervals of 7 days. However, weekly administration schedule can temporarily be accelerated, delayed or skipped due to administrative reasons at the discretion of the investigator. Clinical assessments and laboratory tests are not mandatory and appropriately performed as per the standard of care at the study sites or at the discretion of investigator, and only clinical relevant abnormalities are reported as adverse events according to Section 5.2.2.2. Results for the assessments and tests should be recorded in the source data only, additional documentation in the eCRF is not required.

6.2.4 End of Treatment

EOT visit must be performed within 5 days after discontinuation of study treatment. If patient discontinuation of study treatment falls on a scheduled visit, EOT visit should be conducted instead of assessments at the scheduled visit. In the rollover part, EOT visit will be performed on the same day or after discontinuation of study treatment. The investigator must confirm sufficient recovery from drug-related adverse events before patients will receive the next anti-cancer therapy between EOT visit and the first follow-up (FU1) visit.

6.2.5 Follow-up period

The FU1 visit must be performed 42 (a window of +7) days after the last administration of BI 836845.

Patients are also followed up at the second follow-up (FU2) on 28 (a window of ±4) days after FU1 visit. This FU2 visit may be performed over the telephone if a visit at the trial site cannot be arranged.

FU2 visits will be skipped for patients conducted the rollover part.

6.3 END OF THE WHOLE TRIAL

The trial will be considered completed as soon as the last patient has completed follow-up period. In case no MTD can be identified up to the highest dose tested in this trial, the sponsor will determine whether an expansion cohort will be conducted or not.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

This trial follows a traditional 3 + 3 design with dose de-escalation in oncology phase I trials. All planned analyses will be descriptive and no statistical model will be used in analyses.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The analyses in this trial are descriptive and exploratory. No formal statistical tests will be performed.

7.3 PLANNED ANALYSES

All patients who received at least one dose of BI 836845 will be included in the analyses.

7.3.1 Primary analyses

The objective of this study is to identify the MTD (for definition of MTD, see Section 4.1.3.3) of BI 836845. In order to identify the MTD, the number of patients who are observed DLTs at each dose level will be presented.

7.3.2 Secondary analyses

7.3.3 Safety analyses

The following measures will indicate how well BI 836845 is tolerated:

- Adverse events of special interest

- Adverse events leading to dose reduction
- Adverse events leading to discontinuation of study treatment
- The overall incidence and intensity of AEs according to Common Terminology Criteria, CTCAE version 4.03 (R10-4848) as well as relatedness of Adverse events to treatment
- SAEs
- Causes of death
- Vital signs
- Change from baseline for all laboratory tests
- ECOG performance status
- ECG

Frequency distributions, descriptive statistics and listings will be used to examine these variables.

Adverse event data from the first cycle will be presented separately. All data collected during the study will be assigned to a study period (e.g. screening, on-treatment, follow-up etc.) and be presented by BI 836845 dose level. Details will be provided in the TSAP.

7.3.4 Interim analyses

No interim analyses are planned.

If considered necessary, as soon as the MTD is identified, an evaluation of the safety and efficacy aspects may be performed via a snapshot of the data base. Results of this evaluation will be documented and stored. If applicable such an analysis will be defined in more detail in the TSAP.

7.3.5 Pharmacokinetic analyses

7.3.6 Pharmacodynamic analyses

Pharmacodynamic parameters, as described in Section 5.6, will be analysed using an explorative approach to determine whether given biomarkers can be used as potential signals for efficacy with BI 836845.

7.3.7 Pharmacogenomic analyses

The exploratory pharmacogenetic analysis will investigate the association between genetic factors and response or resistance. All statistical analysis performed will be considered hypothesis generating in scope.

7.4 HANDLING OF MISSING DATA

No imputation will be performed on missing efficacy data.

Missing baseline laboratory values will be imputed by the respective values from the screening visit.

7.4.1 Plasma concentration–time profiles

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

7.4.2 Pharmacokinetic assessment

7.5 RANDOMISATION

No randomisation will be performed. Patients will be assigned into dose cohorts which are determined according to Section 4.1.3.4 by order of admission into the trial.

7.6 DETERMINATION OF SAMPLE SIZE

The trial will be based on a traditional 3 + 3 design which is generally applied in oncology phase I trials to identify the MTD (see Section 4.1.3.3), where cohorts of 3 to 6 patients will be entered sequentially into escalating dose tiers. Maximum 18 patients evaluable for the MTD of BI 836845 will be enrolled when no patient is replaced because of early discontinuation (see Section 3.3.5). If the expansion cohort will be conducted, additional 6 patients will be entered.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for GCP (ICH–GCP) and relevant Boehringer Ingelheim SOPs and the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997. Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/ICH–GCP and the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997).

The rights of the investigator/trial site and of the sponsor with regard to publication of the results of this trial are described in the trial site's contract. As a general rule, no trial results should be published prior to finalisation of the clinical trial report.

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

8.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB 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 must give a full explanation to trial patients by using the patient information form, which is prepared avoiding the use of technical terms and expressions. The patient is given sufficient time to consider participation in the trial. The investigator obtains written consent of the patient's own free will with the informed consent form after confirming that he patient understands the contents. The investigator 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.

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

The patient must be informed that his/her medical records may be examined by authorised monitors (CTL/CRA) or Clinical Quality Assurance auditors appointed by [redacted] by appropriate IRB members, and by inspectors from regulatory authorities.

8.2 DATA QUALITY ASSURANCE

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

8.3 RECORDS

eCRFs for individual patients will be provided by the sponsor via RDC/EDC. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

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

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

For eCRFs, all data must be derived from source documents.

8.3.2 Direct access to source data and documents

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

8.3.3 Storage of records

Storage period of records

Trial site:
The trial site must retain the source documents and essential documents for a period defined by the Japanese GCP regulation and the trial site's contract with the sponsor.

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

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore, a unique reference document for the evaluation of listedness needs to be provided. For the BI 836845, this will be the current version of the Investigator's Brochure. The current versions of these reference documents are to be provided in the ISF. No adverse events are classified as listed for matching placebo, study design, or invasive procedures.

8.4.2 Expedited reporting to health authorities and IRBs

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

8.5 STATEMENT OF CONFIDENTIALITY

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

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

8.6 COMPLETION OF TRIAL

When the trial is completed, the principal investigator should inform the head of the trial site of the completion in writing, and the head of the trial site should promptly inform the IRB and sponsor of the completion in writing.

8.7 PROTOCOL VIOLATIONS

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

8.8 COMPENSATION AVAILABLE TO THE PATIENT IN THE EVENT OF TRIAL RELATED INJURY

In the event of health injury associated with this trial, the sponsor is responsible for compensation based on the contract signed by the trial site.

9. REFERENCES

9.1 PUBLISHED REFERENCES

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9.2 UNPUBLISHED REFERENCES

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10. APPENDICES

10.1 SAMPLING TIME POINTS FOR PHARMACOKINETICS AND BIOMARKERS

Table 10.1: 1 Blood sampling scheme for Cycle 1

Cycle	Visit	Day	Time point	eCRF time/ planned time	Plasma BI 836845	ADA	Total IGF-1 and total IGF-2	IGFBP-3	IGF-1R phosphory-lation
1	1	1	Pre-dose	–0:05	X	X	X	X	X
			Start of BI 836845 infusion	*0:00*					
			Immediately before end of infusion	1:00	X				X
			2:00	2:00	X				
			3:00–5:00	4:00	X				
			6:00–8:00	7:00	X				
		2	23:00–25:00	24:00	X		X		X
	2	8 ± 1	Pre-dose, 144:00–192:00	168:00	X		X		X
			Immediately before end of infusion	169:00	X				X
	3	15 ± 1	Pre-dose, 312:00–360:00	336:00	X		X		X
			Immediately before end of infusion	337:00	X				X

Table 10.1: 2 Blood sampling scheme for Cycles 2 and 3

Cycle	Visit	Day	Time point	eCRF time/ planned time	Plasma BI 836845	ADA	Total IGF-1 and total IGF-2	IGF-1R phosphory-lation
2	1	1	Pre-dose	–0:05	X	X	X	X
			Start of BI 836845 infusion	*0:00*				
			Immediately before end of infusion	1:00	X			X
	2	8 ± 2	Pre-dose, 120:00–216:00	168:00	X		X	X
			Immediately before end of infusion	169:00	X			X
	3	15 ± 2	Pre-dose, 288:00–384:00	336:00	X		X	X
			Immediately before end of infusion	337:00	X			X
3	1	1	Pre-dose	–0:05	X	X	X	X
			Start of BI 836845 infusion	*0:00*				
			Immediately before end of infusion	1:00	X			X
			2:00	2:00	X			
			3:00–5:00	4:00	X			
			6:00–8:00	7:00	X			
		2	23:00–25:00	24:00	X		X	X
	2	8 ± 2	Pre-dose, 120:00–216:00	168:00	X		X	X
			Immediately before end of infusion	169:00	X			X
	3	15 ± 2	Pre-dose, 288:00–384:00	336:00	X		X	X
			Immediately before end of infusion	337:00	X			X

Table 10.1: 3 Blood sampling scheme for Cycle 4 onwards

Cycle	Visit	Day	Time point	eCRF time/ planned time	Plasma BI 836845	ADA	Total IGF-1 and total IGF-2
4	1	1	Pre-dose	–0:05	X	X	X
			Start of BI 836845 infusion	*0:00*			
			Immediately before end of infusion	1:00	X		
5	1	1	Pre-dose	–0:05	X	X	X
			Start of BI 836845 infusion	*0:00*			
			Immediately before end of infusion	1:00	X		

Study period	Plasma BI 836845	ADA	Total IGF-1 and total IGF-2	IGF-1R phosphory-lation
EOT (not applied for the rollover part)	X	X	X[1]	X[1]
FU1 (not applied for the rollover part)	X	X	X	X

1. Not applicable for patients who continue the study treatment into the rollover part

If the infusion duration deviates from the scheduled time, the exact start and end times should be recorded. If the infusion stops in between, the stop time and the time when it is started again need to be documented. If the duration of infusion is prolonged or shortened, all following time points of pharmacokinetic and biomarker sampling should be adapted to the time when the infusion has ended.

10.2 COCKCROFT–GAULT FORMULA

The Cockcroft–Gault formula is commonly used to calculate GFR and is the recommended formula to calculate GFR in the trial.

$$\text{GFR} = \frac{(140 - \text{age}) \times \text{weight} \times \text{Fs}}{\text{serum creatinine} \times 72}$$

GFR (mL/min), age (years), weight (kg), serum creatinine (mg/dL), Fs is a correction Factor for Sex: in males Fs = 1, in females Fs = 0.85

10.3 CLINICAL EVALUATION OF LIVER INJURY

10.3.1 Introduction

Alterations of liver laboratory parameters, as described in Section 5.2.2.1 (adverse events of special interests), are to be further evaluated using the following procedures.

10.3.2 Procedures

Repeat the following lab tests: ALT, AST, and bilirubin (total and direct) – within 48 to 72 hours. If ALT and/or AST ≥3 × ULN combined with an elevation of total bilirubin ≥2 × ULN are confirmed, results of the laboratory parameters described below must be made available to the investigator and to Boehringer Ingelheim as soon as possible.

In addition,

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

and report these via the eCRF (except for the rollover part).

Clinical chemistry:
alkaline phosphatase, albumin, PT or INR, CK, CK-MB, coeruloplasmin, α-1 antitrypsin, transferrin, amylase, lipase, fasting glucose, cholesterol, triglycerides

Serology:
Hepatitis A (Anti-IgM, Anti-IgG), Hepatitis B (HBsAg, Anti-HBs, DNA), Hepatitis C (Anti-HCV, RNA if Anti-HCV positive), Hepatitis D (Anti-IgM, Anti-IgG), Hepatitis E (Anti-HEV, Anti-HEV IgM, RNA if Anti-HEV IgM positive), Anti-Smooth Muscle antibody (titer), Anti-nuclear antibody (titer), Anti-LKM (liver-kidney microsomes) antibody, Anti-mitochondrial antibody
<project dependent: Epstein Barr Virus (VCA IgG, VCA IgM), cytomegalovirus (IgG, IgM), herpes simplex virus (IgG, IgM), varicella (IgG, IgM), parvovirus (IgG, IgM), toxoplasmosis (IgG, IgM)>

Hormones, tumour marker:
TSH

Haematology:
Thrombocytes, eosinophils

- Provide abdominal ultrasound to rule out biliary tract, pancreatic or intrahpeatic pathology, e.g. bile duct stones or neoplasm.
- Initiate close observation of subjects by repeat testing of ALT, AST, and total bilirubin (with fractionation by total and direct) at least weekly until the laboratory ALT and/or AST abnormalities stabilise or return to normal, then according to the protocol. Depending on further laboratory changes, additional parameters identified e.g. by reflex testing will be followed up based on medical judgement and GCP.

11 DESCRIPTION OF GLOBAL AMENDMENT

11.1 GLOBAL AMENDMENT 1

Number of global amendment		1
Date of CTP revision		04 Jul 2019
BI Trial number		1280.15
BI Investigational Product		Xentuzumab (BI 836845)
Title of protocol		An open-label phase I dose escalation trial of weekly intravenous administrations of BI 836845 in Japanese patients with advanced solid tumours
To be implemented only after approval of the IRB		☒
To be implemented immediately in order to eliminate hazard - IRB to be notified of change with request for approval		☐
Can be implemented without IRB approval as changes involve logistical or administrative aspects only		☐
Section to be changed **Description of change** **Rationale for change**		Throughout the Clinical Trial Protocol Changes by amendment of Clinical Trial Protocol Update version number, revision date etc.
Section to be changed **Description of change** **Rationale for change**		Synopsis Section 1.2 – DRUG PROFILE Addition of ‘xentuzumab’ Decide the generic name of BI 836845
Section to be changed **Description of change** **Rationale for change**		Synopsis Section 3.1.1 – Administrative structure of the trial Section 8.1 – STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT Changes of organisation and role names Re-organisation of sponsor

Section to be changed **Description of change** **Rationale for change**		Synopsis – Methodology FLOW CHART FLOW CHART – ROLLOVER PART Section 3 – DESCRIPTION OF DESIGN AND TRIAL POPULATION Section 4 – TREATMENTS Section 5 – VARIABLES AND THEIR ASSESSMENT Section 6 – INVESTIGATIONAL PLAN Table 10.1: 3 – Blood sampling scheme for Cycle 4 onwards Appendix 10.3.2 – Procedures Addition of rollover part Add procedures regarding rollover part
Section to be changed **Description of change** **Rationale for change**		Section 1.4 – CLINICAL INFORMATION Section 9.2 – UNPUBLISHED REFERENCES Change of description regarding Investigator's Brochure and the reference Refer the latest version of Investigator's Brochure
Section to be changed **Description of change** **Rationale for change**		Section 3.1 – OVERALL TRIAL DESIGN AND PLAN Section 7.3.4 – Interim analyses Addition regarding clinical trial report and change of interim analysis plan Clarify the procedure
Section to be changed **Description of change** **Rationale for change**		Section 3.1.1 – Administrative structure of the trial Section 4.1.3.1 – Initial dose and dose levels to be evaluated Section 5.2.2.2 – Adverse event and serious adverse event reporting Section 5.2.5 – Electrocardiogram Section 5.3.4 - Pharmacogenomic evaluation Section 8.3 – RECORDS Optimisation of terminology Change systems using in this trial. Adopt adequate terminologies

11.2 GLOBAL AMENDMENT 2

Number of global amendment		2
Date of CTP revision		29 Apr 2022
BI Trial number		1280.15
BI Investigational Product		Xentuzumab (BI 836845)
Title of protocol		An open-label phase I dose escalation trial of weekly intravenous administrations of BI 836845 in Japanese patients with advanced solid tumours
To be implemented only after approval of the IRB		☒
To be implemented immediately in order to eliminate hazard - IRB to be notified of change with request for approval		☐
Can be implemented without IRB approval as changes involve logistical or administrative aspects only		☐
Section to be changed **Description of change** **Rationale for change**		Section 2.3 – BENEFIT–RISK ASSESSMENT Update of risk-benefit evaluation in consideration of topline results of 1280-0022 trial Clarify the reason for termination of BI 836845 clinical development and cessation of further BI 836845 manufacturing
Section to be changed **Description of change** **Rationale for change**		Section 3.3.4.3 – Discontinuation of the trial by the sponsor Update of information that significantly affect continuation of trial Clarify the sponsor's decision
Section to be changed **Description of change** **Rationale for change**		Section 5.2.9 – Pregnancy testing Modification of information on methods and duration of contraception Refer to the latest subject information for updated appropriate methods and duration of contraception