CLINICAL TRIAL PROTOCOL

	Document Number:	c18134159-05
EudraCT No.:	2017-002945-31	
BI Trial No.:	1401-0001	
BI Investigational Product(s):	BI 905677	
Title:	An open-label, Phase I trial to determine the maximum-tolerated dose and investigate safety, pharmacokinetics and efficacy of BI 905677 administered intravenously in patients with advanced solid tumours	
Lay Title:	This study aims to find and test a safe dose of BI 905677 in patients with different types of cancer (solid tumours)	
Clinical Phase:	Phase I	
Trial Clinical Monitor:	[redacted] Tel: +[redacted]	
Coordinating Investigator:	[redacted] Tel +[redacted] Fax +[redacted]	
Status:	Final Protocol (Revised Protocol (based on Global Amendment 3))	
Version and Date:	**Version: 4.0**	**Date: 02 August 2018**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Finished product name	Not applicable
Active ingredient name:	BI 905677
Protocol date	31 January 2018
Revision date	02 August 2018 (Global Amendment 3)
Trial number	1401-0001
Title of trial:	An open-label, Phase I trial to determine the maximum-tolerated dose and investigate safety, pharmacokinetics and efficacy of BI 905677 administered intravenously in patients with advanced solid tumours
Coordinating Investigator:	[redacted] Tel [redacted] Fax
Trial site(s):	Multi-centre trial
Clinical phase:	I
Objective(s):	The primary objective of this trial is to determine the maximum tolerated dose (MTD) of BI 905677 given as an intravenous infusion and to determine the recommended dose and dosing schedule for further trials in the development of BI 905677.
Methodology:	Open-label, single arm, dose escalation of BI 905677
Number of patients entered:	Up to 60
Number of patients on each treatment:	Two dose escalation schedules with approximately 30 patients on each schedule
Diagnosis :	Patients with histologically or cytologically confirmed advanced, unresectable and/or metastatic solid tumours who are either refractory after standard therapy for the disease or for whom standard therapy is not appropriate. Patients must also have exhausted treatment options known to prolong survival for their disease.
Main in- and exclusion criteria	• Histologically or cytologically confirmed diagnosis of an advanced, unresectable and/or metastatic non-haematologic malignancy. Patient must have measurable or evaluable lesions (according to RECIST 1.1). • Patient who has failed conventional treatment or for whom no therapy of proven efficacy exists or who is not eligible for established treatment options. Patient must have exhausted

	treatment options known to prolong survival for their disease. • Patient willing to undergo mandatory skin biopsy at the timepoints specified in the protocol. • Eastern Cooperative Oncology Group score of 0 or 1. • Adequate hepatic, renal and bone marrow function • Recovered from any previous therapy-related toxicity to ≤ CTCAE Grade 1 at start of treatment (except for alopecia and stable sensory neuropathy which must be ≤ CTCAE Grade 2). • At least 18 years of age at the time of consent or over the legal age of consent in countries where that is greater than 18 years. • Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial. • Life expectancy ≥ 3 months at the start of treatment in the opinion of the investigator.
Test product(s):	BI 905677
dose:	The starting dose will be: Schedule A – 0.05 mg/kg every 3 weeks Schedule B – starting dose to be determined based on safety information and schedule A MTD. Drug administration every 2 weeks (Day 1 and Day 15 of 4 week cycle)
mode of administration:	Intravenous infusion
Comparator products:	Not applicable
Duration of treatment:	Patients may continue on treatment for unlimited cycles, until disease progression or other criteria for stopping treatment are met
Endpoints	Primary endpoints; • The maximum tolerated dose (MTD) of BI 905677 which will be assessed based on the number of patients experiencing Dose Limiting Toxicities (DLTs), graded according to CTCAE Version 5.0, in the first cycle of treatment (3 weeks in Schedule A and 4 weeks in Schedule B). Separate MTDs will be determined for Schedule A and Schedule B. • Number of patients experiencing adverse events (AEs) during the entire treatment period Secondary endpoints; • The following pharmacokinetic (PK) parameters of BI 905677 will be evaluated after the first administration of BI 905677 (if feasible):

	○ C_{max}: maximum measured concentration of BI 905677 in serum after first infusion ○ AUC_{0-tz}: area under the serum concentration-time curve over the time interval from 0 to the last measured time point (t_z)
Safety criteria:	Incidence and severity of adverse events graded according to the common terminology criteria for adverse events (CTCAE, version 5.0), incidence of dose limiting toxicities, laboratory parameters, physical examination, vital signs, ECOG performance status, ECG, ophthalmology, bone biomarkers and densitometry.
Statistical methods:	Dose escalation guided by a Bayesian Logistic Regression Model (BLRM) with overdose control that will be fitted to binary toxicity outcomes. The estimate of parameters will be updated as data are accumulated using the BLRM. At the end of the dose escalation, the toxicity probability at each dose level will be calculated to determine an estimate of the MTD. All endpoints will be analysed descriptively.

FLOWCHART

SCHEDULE A; CYCLE DURATION = 3 WEEKS

Trial Period	**Screening**	**Treatment Cycles* (1 Cycle = 21 Days)**				**End of Treatment (EOT)**	**Follow-up****
Timing	**1-28 days prior to first dose**	**Day 1*****	**Day 4******** ±1 day 48-96 hours after dosing	**Day 8** ±1 day	**Day 15** ±2 days	**Within 7 days of EOT decision*********	**42-49 days after last dose**
Informed consent	X						
Review of in-/exclusion criteria	X						
Demographics and smoking/alcohol history	X						
Medical History	X						
Physical Examination	X	X				X	X
ECOG Performance Status	X	X				X	X
Vital Signs	X	X[a]		X	X	X	X
12 lead-electrocardiogram (ECG)	X	X[b]		X[b]		X	
Safety laboratory blood tests and urinalysis	X	X		X[c]	X[c]	X[c]	X[d]
Vitamin D blood test	X	X[e]				X	
Pregnancy test[f]	X	X				X	
Bone densitometry	X	Every 12 weeks (± 7 days) from start of treatment until EOT				X[g]	
Ophthalmologic assesment	X	Repeated if clinically indicated – see section 5.2.5.4					
Height	X						
Weight	X	X				X	
Tumour Assessment	X[h]	Every 6 weeks (± 7 days) from start of treatment until documented progression[i]					
Skin Biopsy	X[j]	X[j]	X[j]				
Blood sample for bone biomarkers		X[k]				X	
Blood samples for cytokine release testing		X[l]					
Blood samples for Pharmacokinetics		X[m]	X[m]	X[m]	X[m]	X[m]	X[m]
Blood sample for anti-drug antibodies (ADAs)		X				X	X
Assess eligibility for further treatment		X[n]					
BI 905677 Infusion[o]		X					
Adverse events	X	X	X	X	X	X	X
Concomitant Therapies	X	X	X	X	X	X	X
Completion of patient participation							X

* Patients may continue on treatment for unlimited cycles, until criteria for stopping treatment are met (see Section 3.3.4)
** Wherever possible the follow-up visit must be performed in person, but if the investigator judges appropriate, follow-up information may be collected by telephone.
*** Cycle 1 Day 1 assessments (Physical examination, ECOG performance status, vital signs, ECG, safety laboratory blood tests, urinalysis, pregnancy test, weight) do not need to be performed if done within 2 calendar days (during the Screening visit) and in the opinion of the investigator a repeat is not required. In this case the latest value prior to start of treatment will be considered the baseline.
**** Cycle 1 and Cycle 2 only
***** If the decision to permanently discontinue trial treatment is taken during a scheduled visit, the EOT visit should be performed instead of the scheduled visit.

a	See section 5.2.2 for details of vital signs measurement on day of infusion
b	ECG required on Day 8 of Cycle 1 but not on Day 8 of Cycle 2 and subsequent cycles. For detailed schedule, refer to Appendix 10.2.
c	In case of haematological toxicity of Grade 4 a complete blood count has to be performed at least twice per week until improvement to a lower grade.
d	Safety laboratory tests and urinalysis at follow-up are optional and at the discretion of the investigator.
e	Vitamin D will be tested on Day 1 of every third cycle (i.e. Cycle 3 Day 1, Cycle 6 Day 1)
f	Pregnancy test is only required for women of childbearing potential. See Section 3.3.2 for further details.
g	Bone densitometry at the EOT visit is not required if bone densitometry has been performed within the previous 4 weeks.
h	Tumour assessments performed prior to informed consent as part of routine clinical practice will be accepted if they meet the requirements of the protocol and are performed within the Screening visit window.
i	Tumour assessment should be performed every 6 weeks calculated from start of treatment until documented progression. In the event of early discontinuation or an interruption/delay to treatment, wherever possible the tumour assessment schedule should not be changed. See Section 5.1.1 for further details.
j	Skin biopsy is mandatory for all patients who start treatment after certain criteria are met – see Section 5.4. A total of two skin biopsies are required. The first skin biopsy may be obtained any time prior to the first dose. A second skin biopsy sample will be obtained within 48-96 hours of receiving treatment in Cycle 2. See Section 5.4 for further details.
k	Bone biomarkers will be assessed on Cycle 1 Day 1, Cycle 2 Day 1 and then on Day 1 of every odd-numbered cycle.
l	For detailed schedule, refer to Appendix 10.2
m	For detailed PK sampling schedule, refer to Appendix 10.2. PK sampling on Day 8 and Day 15 is only required in Cycles 1-4.
n	Assessment of eligibility for further treatment is required prior to dosing on Day 1 of each cycle from Cycle 2 onwards.
o	Patients will be monitored for cytokine release syndrome for 6 hours after the first three administrations of BI 905677 and for 3 hours following subsequent administrations if the previous administrations were well-tolerated. See Section 5.2.5.3 for details.

SCHEDULE B; CYCLE DURATION = 4 WEEKS

Trial Period	**Screening**	**Treatment Cycles*(1 Cycle = 28 Days)**					**End of Treatment (EOT)**	**Follow-up****
Timing	**1-28 days prior to first dose**	**Day 1*****	**Day 4******** ±1 day 48-96 hours after dosing	**Day 8** ±1 days	**Day 15** ±1 day	**Day 22** ±1 days	**Within 7 days of EOT decision** ******	**42-49 days after last dose**
Informed consent	X							
Review of in-/exclusion criteria	X							
Demographics and smoking/alcohol history	X							
Medical History	X							
Physical Examination	X	X			X		X	X
ECOG Performance Status	X	X					X	X
Vital Signs	X	X[a]		X	X[a]	X	X	X
12 lead-electrocardiogram (ECG)	X	X[b]		X[b]	X[b]		X	
Safety laboratory blood tests and urinalysis	X	X		X[c]	X[c]	X[c]	X[c]	X[d]
Vitamin D blood test	X	X[e]					X	
Pregnancy test[f]	X	X					X	
Bone densitometry	X	Every 12 (± 7 days) weeks from start of treatment until EOT					X[g]	
Ophthalmologic assessment	X	Repeated if clinically indicated – see section 5.2.5.4						
Height	X							
Weight	X	X			X		X	
Tumour Assessment	X[h]	Every 8 weeks (± 7 days) from start of treatment until documented progression[i]						
Skin Biopsy	X[j]	X[j]	X[j]					
Blood sample for bone biomarkers		X[k]					X	
Blood samples for cytokine release testing		X[l]			X[l]			
Blood samples for Pharmacokinetics		X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]
Blood sample for anti-drug antibodies (ADAs)		X			X[n]		X	X
Assess eligibility for further treatment		X[o]			X[o]			
BI 905677 Infusion[p]		X			X			
Adverse events	X	X	X	X	X	X	X	X
Concomitant Therapies	X	X	X	X	X	X	X	X
Completion of patient participation								X

* Patients may continue on treatment for unlimited cycles, until criteria for stopping treatment are met (see Section 3.3.4)

** Wherever possible the follow-up visit must be performed in person, but if the investigator judges appropriate, follow-up information may be collected by telephone.
*** Cycle 1 Day 1 assessments (Physical examination, ECOG performance status, vital signs, ECG, safety laboratory blood tests, urinalysis, pregnancy test, weight) do not need to be performed if done within 2 calendar days (during the Screening visit) and in the opinion of the investigator a repeat is not required. In this case the latest value prior to start of treatment will be considered the baseline.
**** Cycle 1 and Cycle 2 only
***** If the decision to permanently discontinue trial treatment is taken during a scheduled visit, the EOT visit should be performed instead of the scheduled visit.

a	See section 5.2.2 for details of vital signs measurement on day of infusion
b	ECG required on Day 8 and 15 of Cycle 1 but not on Day 8 and 15 of Cycle 2 and subsequent cycles. For detailed schedule, refer to Appendix 10.3.
c	In case of haematological toxicity of Grade 4 a complete blood count has to be performed at least twice per week until improvement to a lower grade.
d	Safety laboratory tests and urinalysis at follow-up are optional and at the discretion of the investigator.
e	Vitamin D will be tested on Day 1 of every third cycle (i.e. Cycle 3 Day 1, Cycle 6 Day 1)
f	Pregnancy test is only required for women of childbearing potential. See Section 3.3.2 for further details.
g	Bone densitometry at the EOT visit is not required if bone densitometry has been performed within the previous 4 weeks.
h	Tumour assessments performed prior to informed consent as part of routine clinical practice will be accepted if they meet the requirements of the protocol and are performed within the Screening visit window.
i	Tumour assessment should be performed every 8 weeks calculated from start of treatment until documented progression. In the event of early discontinuation or an interruption/delay to treatment, wherever possible the tumour assessment schedule should not be changed. See Section 5.1.1 for further details.
j	Skin biopsy is mandatory for all patients who start treatment after certain criteria are met – see Section 5.4. A total of two skin biopsies are required. The first skin biopsy may be obtained any time prior to the first dose. A second skin biopsy sample will be obtained within 48-96 hours of receiving treatment in Cycle 2. See Section 5.4 for further details.
k	Bone biomarkers will be assessed on Cycle 1 Day 1, on Cycle 2 Day 1 and then on Day 1 of every odd-numbered cycle.
l	For detailed schedule, refer to Appendix 10.3.
m	For detailed PK sampling schedule, refer to Appendix 10.3. PK sampling on Day 8 and Day 22 is only required in Cycles 1-4. PK sampling on Day 15 is only required in Cycles 1-6.
n	Blood sample for ADAs is only required on Day 15 of Cycle 1 and Cycle 2. For detailed schedule, refer to Appendix 10.3.
o	Assessment of eligibility for further treatment is required prior to dosing on Day 1 and Day 15 of each cycle from Cycle 1 Day 15 onwards.
p	Patients will be monitored for cytokine release syndrome for 6 hours after the first three administrations of BI 905677 and for 3 hours following subsequent administrations if the previous administrations were well-tolerated. See Section 5.2.5.3 for details.

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[redacted]

[redacted]

ABBREVIATIONS

ADA	Anti-Drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine amino transferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of Covariance
APC	Adenomatous Polyposis Coli
AST	Aspartate amino transferase
AUC	Area under the Curve
BAP	Bone Alkaline Phosphatase
BI	Boehringer Ingelheim
BLQ	Below the limit of Quantification
BLRM	Bayesian Logistic Regression Model
BCVA	Best Corrected Visual Acuity
CA	Competent Authority
CL	Clearance
CML	Clinical Monitor Local
CR	Complete Response
CRA	Clinical Research Associate
CRC	Colorectal Cancer
CRF	Case Report Form
CRO	Contract Research Organisation
CRS	Cytokine Release Syndrome
CTCAE	Common Terminology Criteria for Adverse Events
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTX	Carboxy-terminal Telopeptide
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDTA	Ethylendiaminetetracetic Acid
EMA	European Medicines Agency
EOT	End of Treatment
ETDRS	Early Treatment Diabetic Retinopathy Score
EU	European Union
EudraCT	European Clinical Trials Database
EWOC	Escalation with Overdose Control
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GSK	Glycogen Synthase Kinase

HED	Human Equivalent Dose
HIV	Human Immunodeficiency Virus
HNSTD	Highest non-severely-toxic dose
HSA	Human Serum Albumin
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin
INR	International Normalised Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
i.v.	intravenous
LDH	Lactate Dehydrogenase
LPDD	Last Patient Drug Discontinuation
LRP	Low-density lipoprotein receptor-related protein
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMTV	Mouse Mammary Tumour Virus
mRNA	Messenger Ribonucleic Acid
MRSD	Maximum Recommended Starting Dose
MRT	Mean Residence Time
MTD	Maximum Tolerated Dose
N/A	Not Applicable
NC	Not Calculated
NCA	Non Compartmental Analysis
NOA	Not Analysed
NOAEL	No Observed Adverse Effect Level
NOP	No Peak Detectable
NOR	No Valid Result
NOS	No Sample
OPU	Operative Unit
OR	Objective Response
PD	Progressive Disease
PFS	Progression Free Survival
PK	Pharmacokinetics
P1NP	Procollagen type I N Propeptide
PR	Partial Response
PTF	Peak-Trough Fluctuation
PTT	Partial Thromboplastin Time
RA	Accumulation Ratio
RBC	Red Blood Cells
RDE	Recommended Dose for Expansion
RECIST	Response Evaluation Criteria in Solid Tumours
REP	Residual Effect Period
RNF	Ring Finger Protein
SAE	Serious Adverse Event
SD	Stable Disease
SD-OCT	Spectral Domain Optical Coherence Tomography
SMC	Safety Monitoring Committee

SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCF	T-Cell Factor
TDMAP	Trial Data Management and Analysis Plan
TK	Toxicokinetic
TNBC	Triple Negative Breast Cancer
TRACP	Tartrate-resistant Acid Phosphatase
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
V_{ss}	Volume of Distribution at steady state
WBC	White Blood Cells
WHO	World Health Organisation
WNT	Wingless Type MMTV Integration Site
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Despite the recent advancements in cancer treatment, cancer remains a leading cause of death globally. In 2012 there were approximately 14 million new cancer cases and 8.2 million cancer-related deaths worldwide (R15- 3504). In the majority of cases the disease is diagnosed in late, advanced stages and the vast majority of patients progress on available treatments and succumb to their disease. Therefore, there is a substantial need for novel therapeutic agents and treatment strategies to improve the treatment outcome for cancer patients.

Ligand- dependent Wnt signaling, mediated by LRP5 and LRP6, is highly activated in a subset of solid tumours (e.g. colorectal cancer (CRC), triple negative breast cancer (TNBC) and non-small cell lung cancer (NSCLC)). Activation leads to accumulation of intracellular β-catenin and expression of β-catenin dependent genes that promotes cancer cell proliferation and resistance to chemotherapy/immunotherapy. An antagonistic bi-paratopic antibody that binds LRP5 and LRP6 and blocks binding of Wnt ligands will block proliferation of malignant cells with activated Wnt signaling and increase sensitivity to immunotherapy. Therefore, the development of a LRP5/6 antagonist may constitute a valid therapeutic option against cancer.

1.2 DRUG PROFILE

1.2.1 Pharmacology

The LRP5/LRP6 antagonist BI 905677 is a new biological entity (potentially first in class) consisting of a tri-modular antagonistic antibody comprising two modules binding to distinct domains of LRP5 and LRP6 receptors and one module binding to human serum albumin (HSA). Modules are derived from single variable domains of camelidae heavy-chain antibodies (called nanobodies). BI 905677 binds to LRP5 and LRP6 and blocks binding of Wnt ligands to LRP5 or LRP6 receptors, leading to inhibition of Wnt/β-catenin signaling. BI 905677 has not been tested in humans.

The Wnt ligands, which bind to LRP5 and LRP6 and Frizzled receptor leading to activation of downstream signaling, can be divided into Wnt1 class and Wnt3a class, each requiring different domains of LRP5 and LRP6 for signaling [R17-1851]. In particular, BI 905677 binds to these different domains of LRP5 and LRP6 receptor (bi-paratopic binding), thereby blocking Wnt signaling mediated by both Wnt1 and Wnt3a class ligands, leading to:

1) Inhibition of LRP5 or LRP6 phosphorylation;

2) Activation of β-catenin degradation complex formed by APC/Axin/GSK3β;

3) Blockade of β-catenin nuclear translocation and binding to the TCF transcription factors;

4) Inhibition of transcription of Wnt/β-catenin target genes (e.g. Axin2 and Notum).

Blockade of LRP5 and LRP6 phosphorylation and inhibition of transcription of Wnt/β-catenin target genes (including, but not limited to, Axin2 and Notum), can be monitored *in vivo* as direct and indirect biomarkers for selective pathway engagement, respectively, in a Wnt driven tumour xenograft tissue [n00256247]. Inhibition of Wnt target gene expression in tumour cells is necessary but not sufficient for antitumour efficacy (*in vitro* and *in vivo*), indicating that it represents a pharmacodynamic biomarker, but not a biomarker of response to treatment with BI 905677. In mice pharmacodynamic biomarker modulation can be monitored *in vivo* in skin as surrogate tissue via detection of Axin2 gene expression [n00256248].

In a subset of cancer patients, activation of ligand dependent Wnt signaling is mediated by, amongst others, *RNF43* mutations or by R-spondin 3 fusion transcripts (R17-1850, R17-1849); hence, patients with tumours harbouring a loss of function *RNF43* mutation or R-spondin fusion could benefit from Wnt pathway inhibition by blocking the Wnt receptors LRP5 and LRP6. Nonclinical pharmacology and biomarker data support a patient enrichment biomarker strategy. Nonclinical proof of concept (efficacy and inhibition of Wnt/ β-catenin signalling) was demonstrated with BI 905677 in disease relevant models harboring either RNF43 mutation or R-spondin fusion. In contrast, BI 905677 did not show blockade of Wnt signaling nor impact on cell viability in RNF43 wild type tumour models (n00256243, n00256244).

1.2.2 Pharmacokinetics

The pharmacokinetics (PK) for BI 905677 were investigated in the cynomolgus monkey in a single dose PK and repeated dose toxicokinetic (TK) studies. Human *i.v.* PK prediction for BI 905677 was performed using single species scaling from cynomolgus monkey to human using a Dedrick plot. The PK curves were fitted using a 2-compartment model. BI 905677 demonstrated dose-proportional increases in C_{max} and Area under the Curve (AUC) with increasing dose levels in the PK and TK studies. A relatively high clearance (CL) and volume of distribution (V_{ss}) was observed. BI 905677 is cross-reactive with mouse LRP5 and LRP6 and a biodistribution study performed in the mouse demonstrated a rapid clearance of BI 905677 in the blood and rapid distribution predominantly to the liver.

Based on human PK parameter predictions and the minimal efficacious dose in the mouse MMTV-WNT1 breast cancer model, the predicted human therapeutic dose for BI 905677 is 1.1 mg/kg *i.v. q1w* (or 77 mg/patient *q1w* for a fixed-dose regimen in patients with an average body weight of 70 kg). Alternatively, a less frequent dosing schedule can be chosen while keeping the AUC/week constant, e.g. 3.3 mg/kg *i.v. q3w* (or 231 mg/patient *q3w* for a fixed-dose regimen in patients with an average body weight of 70 kg).

1.2.3 Toxicology

The toxicity profile for BI 905677 has been assessed in the repeat dose toxicity studies in monkeys and mice, in an *in vitro* cytokine release assay, and in an *in vitro* hemocompatibility study. The 6-week GLP repeat dose study in monkeys included safety pharmacology (cardiovascular,respiratory and neurological function) and immunotoxicology endpoints. Consistent with the mechanism of action, BI 905677-related key target organ of toxicity was the gastrointestinal (GI) tract and the adverse effects on the gastrointestinal tract (lymphoplasmacytic inflammation with epithelial loss, and/or erosive lymphoplasmacytic

inflammation with epithelial loss) were dose limiting toxicities that resulted in early euthanasia of some animals.

The results from the 6-week GLP monkey study indicated that animals given high dose level with less frequent dosing schedule showed better tolerability, lesser magnitude of the gastrointestinal tract injury, and better reversibility as compared to the administration of low dose level more frequently while the pharmacodynamic effects were still maintained with less frequent dosing schedule.

As anticipated with the role of Wnt signaling in skeletal development and homeostasis, there was a trend of marginal to slight decreases in bone formation markers (BAP and P1NP) due to Wnt signaling inhibition by BI 905677, but no changes in bone resorption markers (CTX and TRAcP) or any microscopic correlates. However, there may be adverse effects on the bone mass, especially osteoporosis, after long-term treatment in humans.

In an in vitro cytokine release assay, a potential for BI 905677 to induce cytokine release was identified in 2 of 11 whole blood samples from healthy human donors.

IL-2 and IL-10 levels were not elevated with BI 905677 treatment for any of the donors. Elevations of IL-6, IL-8, TNF-α and IFN-γ were observed in 2 of 11 donors at the two highest concentrations of BI 905677 (10 and 30 mg/mL). Among 4 cytokines, releases of TNF-α and IFN-γ (up to 619X vs Avastin negative control; up to 31X vs OKT3 or EX79969 positive control) were more pronounced than those of IL-6 and IL-8 (up to 6.6X vs Avastin negative control; up to 6X vs OKT3 or EX79969 positive control). Levels of these cytokines at the two lowest concentrations (0.3 and 3 μg/mL) were below the levels of the Avastin negative control. These two donor samples were confirmed to be negative for pre-existing anti-drug antibodies for BI 905677, indicating that cytokine release responses in two donors are not related to pre-existing anti-drug antibodies.

No abnormal findings were identified in the eye by ophthalmological and microscopic evaluations and no alopecia was observed in monkeys at any dose levels tested in the 6-week repeat dose study.

For a more detailed description of the BI 905677 profile please refer to the current Investigator's Brochure (IB).

1.3 RATIONALE FOR PERFORMING THE TRIAL

Based on the pre-clinical studies summarised in the previous section, the observed anti-tumour activity and safety profile warrant clinical testing of BI 905677. This study is the first-in-man study to determine the MTD and the safety profile of BI 905677 monotherapy in patients with advanced solid tumours. It is hoped that this trial will provide the foundation of a clinical development program which will ultimately benefit many cancer patients.

1.4 BENEFIT - RISK ASSESSMENT

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

As BI 905677 is a first-in-class compound, which has not been tested in humans before, the risks of treatment have been evaluated based on the expected effects of targeting the Wnt pathway (R17-1468) and on the nonclinical toxicology data.

In normal cells, Wnt signaling, mediated by both LRP5 and LRP6 co-receptors, is required for (1) homeostasis of intestinal epithelial stem cells, located in the crypts of the small and large intestines; (2) skeletal development and homeostasis (promotion of osteoblast differentiation from progenitors and osteocyte survival); (3) retinal angiogenesis and regulation of retinal endothelial cell differentiation (R17-1468, R18-0131, R18-1474, R18-1475) and (4) establishment of the hair follicle by activating bulge stem cells to progress toward hair formation. Thus, it is anticipated that potential on-target adverse events may occur in the gastrointestinal tract, bone, hair follicle, and eye (retina) when the Wnt signaling pathway is inhibited by BI 905677.

Several compounds targeting the Wnt pathway, but with a different mechanism of action compared to BI 905677 which selectively inhibits Wnt ligand dependent pathway activation, have been studied in clinical trials. These compounds include vantictumab (anti-frizzled receptor antibody), ipafricept (anti-frizzled 8 receptor antibody), rosmantuzumab (anti-RSPO3 antibody), Wnt-974 (cysteine palmitoyltransferase porcupine inhibitor) and ETC-159 (a selective small molecule porcupine inhibitor). Dysgeusia, fatigue, decreased appetite and gastrointestinal adverse reactions including nausea, vomiting and diarrhea were documented as frequent drug related adverse reactions (R17-4166, R17-4167, R17-4168, R18-1490). In clinical studies of vantictumab, rosmantuzumab, ipraficept and ETC-159, bone toxicity was observed, consisting of changes in bone markers (increase in β-Carboxy-terminal Telopeptide (β –CTX) and/or decrease in procollagen type 1 amino-terminal propeptide (P1NP)), decrease in bone density as determined by bone densitometry, and fragility fractures that occurred late in the course of therapy (R17-4166, R17-4167, R18-1420, R18-1421, R18-1490, R18-1494). To date, cytokine release syndrome and retinopathy have not been reported in any of these clinical studies.

Since the results of the 6-week GLP toxicology study in monkeys indicated that animals given high dose levels in a less frequent dosing schedule showed better tolerability, lesser magnitude of the gastrointestinal tract injury, and better reversibility as compared to the frequent schedules at low dose levels, in this study less frequent dosing schedules have been chosen to mitigate the gastrointestinal toxicity in the clinic. Gastrointestinal adverse events are common with many conventional anti-cancer therapies, and can be managed and indirectly monitored in the clinic (e.g., emesis, diarrhea/liquid stool, abdominal pain, and body weight loss). In this study, monitoring and supportive measures such as anti-emetics, anti-motility agents and stopping/dose modification criteria (see Section 4.1.4) will be implemented to reduce the frequency and guide the management of severe gastrointestinal AEs.

It is anticipated that there may be adverse effects on the bone mass; thus, in this study potential AEs and symptoms (e.g. bone pain, back pain, reduced height, pathologicand pathologic fractures) will be monitored using regular monitoring of serum bone biomarkers and bone densitometry. In patients with documented pre-existing osteoporosis, treatment with vitamin D and/or calcium carbonate is recommended. Management guidelines and stopping rules for bone toxicity are provided (see Sections 3.3.1 and 4.1.4.4).

Another safety aspect for BI 905677 administration is a potential to induce cytokine release as was observed in 2 of 11 whole blood samples from healthy human donors. Therefore, guidelines for monitoring and management of potential cytokine release syndrome are provided and must be followed thoroughly (see Section 4.1.4.3).

There were no BI 905677-related abnormal effects on the eyes (ophthalmological and microscopic examinations) observed in the 6-week repeat dose study in monkeys. Based on the published reports of a potential risk of retinal toxicity as a result of Wnt pathway inhibition, an ophthalmologic status assessment will be performed at baseline in all patients (section 5.2.5.4). In case of occurrence of visual symptoms (e.g. loss in visual acuity, blurred or distorted vision, floating specks or cobwebs, night vision changes or color vision changes) the same ophthalmologic assessment will be repeated. Guidelines for management of potential retinal toxicity are provided (see Section 4.1.4.5).

Throughout the study the safety of the participants will be monitored regularly by a Safety Monitoring Committee (SMC) (See Section 8.7). The assessments planned in this study are standard for oncology patients.

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients' safety, see also Section 5.2.6, adverse events of special interest.

In summary, the nonclinical safety package and data support the administration of BI 905677 to patients with advanced or metastatic cancer, although close monitoring of all adverse events with a focus on potential on-target adverse events is warranted. Given the unmet medical need of these patients, there is a case for potential benefit offered by this novel mode of action with acceptable risk.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The primary objective of this trial is to determine the maximum tolerated dose (MTD) of BI 905677 given as an intravenous infusion and to determine the recommended dose and dosing schedule for further trials in the development of BI 905677. The MTD will be defined based on the frequency of patients experiencing DLTs during the MTD evaluation period, which is defined as the first cycle of treatment. Separate MTDs will be determined for Schedule A and Schedule B.

The secondary objective of the trial is:

- To determine the pharmacokinetic profile of BI 905677

[redacted]

2.1.2 Primary endpoints

The primary endpoints of the trial are;

- The maximum tolerated dose (MTD) of BI 905677 which will be assessed based on the number of patients experiencing Dose Limiting Toxicities (DLTs), graded according to CTCAE Version 5.0, in the first cycle of treatment (3 weeks in Schedule A and 4 weeks in Schedule B). The MTD is defined as the highest dose with less than 25% risk of the true DLT rate being equal to or above 33%. Separate MTDs will be determined for Schedule A and Schedule B. For the definition of DLTs, refer to Section 5.2.7 and for more information on how the MTD will be determined, refer to Section 7.
- Number of patients experiencing adverse events (AEs) during the entire treatment period.

2.1.3 Secondary endpoints

The secondary endpoints of the trial are:

- The following PK parameters of BI 905677 will be evaluated after the first administration of BI 905677 (if feasible):
  - C_{max}: maximum measured concentration of BI 905677 in serum after first infusion
  - AUC_{0-tz}: area under the serum concentration-time curve over the time interval from 0 to the last measured time point (t_z)

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a Phase I, open-label, non-randomised study of BI 905677 administered intravenously as a single agent.

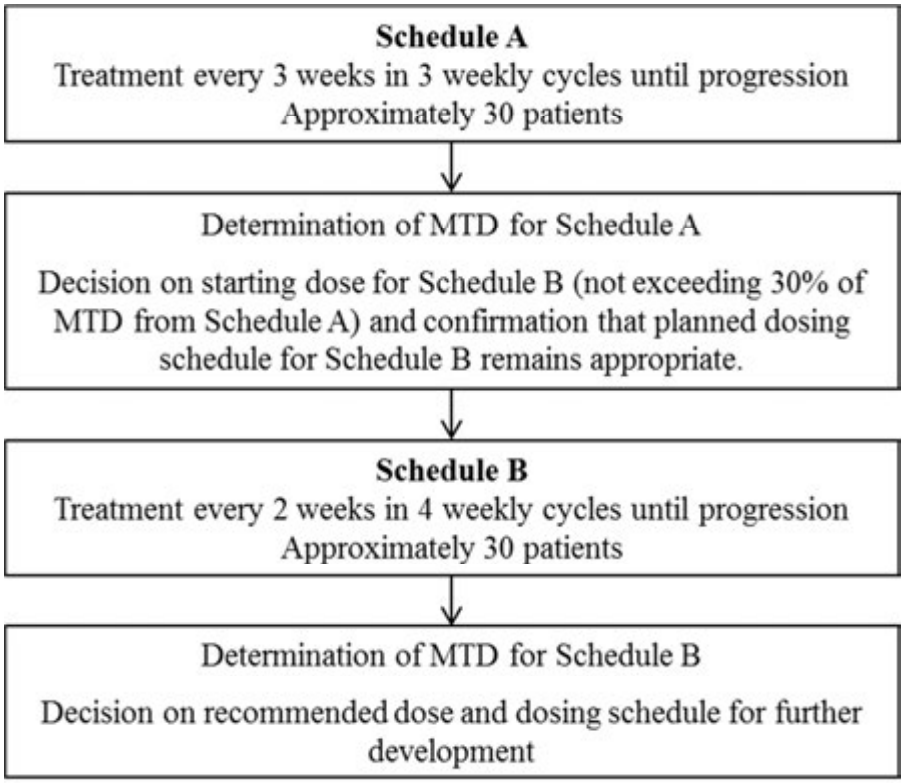

Figure 3.1: 1 Trial Design

The design of the trial allows an escalation of dose with intensive safety monitoring to ensure the safety of the patients.

A Bayesian logistic regression model (BLRM) with overdose control (R13-4803) will be used to determine the MTD estimate. The BLRM estimates the MTD by updating estimates of the probability of observing a DLT for each dose level. At any time in the trial, it will not be permitted to escalate to a dose which does not fulfil the escalation with overdose control (EWOC) principle (for further details refer to Section 7).

The trial will test two different dosing schedules for BI 905677 with two separate BLRM models; in Schedule A the cycles will be 3 weeks in duration and in Schedule B the cycles will be 4 weeks in duration. Recruitment into each dosing schedule will occur sequentially. Recruitment into Schedule B will start after the MTD of Schedule A is reached. Within each treatment cohort, patients will be treated at least 72 hours apart to allow adequate monitoring for CRS and implementation of preventive measures if required.

In each schedule, successive cohorts of patients will receive increasing doses of BI 905677 until the MTD is reached. Incremental dose increases in successive cohorts will be no more

than 100% of the previous dose level and all cohorts will include at least 3 patients. Three patients will be treated per dose cohort until a first AE of CTCAE Grade ≥ 2 occurs during the DLT evaluation period (the first cycle of treatment), excluding adverse events which are clearly related to disease progression or concurrent illness. Then, additional patients have to be entered at this dose and subsequent dose escalations will be restricted to a maximum of 50% from the previous dose until MTD is reached. A Safety Monitoring Committee (SMC, see Section 8.7) may also recommend the size for the next dose escalation cohort or recommend expanding the size of the recruiting cohort.

After all patients in a cohort have either experienced a DLT or have been observed for at least one cycle without experiencing a DLT, the Bayesian model will be updated with the newly accumulated data. The overdose risk will then be calculated for each potential dose and dose escalation will be permitted to all doses which fulfil the EWOC criterion. At the end of each dose level, based on the model and on additional information (PK, pharmacodynamics, patient profiles), the members of the SMC will reach a joint decision on the next dose level to be investigated.

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

The SMC may recommend stopping further dose escalation after the criterion for MTD (Section 7) is fulfilled. Further patients may be included to confirm this MTD estimate, i.e. to confirm that the EWOC criterion is still fulfilled. If no DLT is observed, the SMC may decide to declare the Recommended Dose for Expansion (RDE) based on PK/Pharmacodynamic endpoints and overall safety profile. Any DLTs occurring after the start of the second cycle will be considered for the evaluation of the RDE for BI 905677. The SMC can declare any dose fulfilling the EWOC criterion as the RDE, independent of the MTD estimate.

Patients will continue to receive treatment with BI 905677 until disease progression (PD) according to RECIST or until another reason requiring termination of treatment (see Section 3.3.4).

After completion of the dose escalation and determination of the MTD/RDE, a protocol amendment is planned to add expansion cohorts to the trial.

3.1.1 Trial Stopping Rules

All safety information will be carefully analysed by the sponsor. Enrollment will be temporarily stopped if one of the following conditions is met;

- > 20% of patients treated in the trial develop grade 3 osteoporosis or another bone-related DLT
- ≥ 2 patients treated in the trial develop a serious pathologic fracture
- > 20% of patients at a certain dose level experience a grade 3 Cytokine Release Syndrome and/or grade 3 hypersensitivity reaction and/or grade 3 infusion reaction

- One patient experiences a grade 4 Cytokine Release Syndrome and/or grade 4 hypersensitivity reaction and/or grade 4 infusion reaction

If this occurs, the SMC will conduct an in-depth analysis of the safety profile of BI 905677 and the benefit-risk profile of BI 905677 will be re-assessed. This assessment will be used to determine if the study should be continued as planned, permanently discontinued or whether the study should continue with modification to the protocol to adequately mitigate patient risk and to ensure that the benefit-risk assessment for continued investigation of BI 905677 remains positive. The SMC will also consider and provide guidance for the management of patients who are currently on treatment. The outcome of the analysis and the recommendations will be shared with all involved regulatory health authorities prior to a planned re-start of enrollment. In case the benefit-risk assessment is no longer considered to be positive, the trial will be discontinued.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

Dose escalation and cohort size will be determined based on the recommendation of the SMC, guided by a BLRM with overdose control. An EWOC design will increase the chance of treating patients at efficacious doses while reducing the risk of overdosing. This design is based on practical experience and is an efficient method due to its ability to identify the dose with a desired toxicity rate and its allocation of a greater proportion of patients to doses at, or close to, that desired dose (R13-4802, R13-4804, R13-4805). The use of Bayesian models for Phase I studies has also been advocated by the EMA guideline on small populations (R07-4856) and by the FDA (R13-4881).

3.3 SELECTION OF TRIAL POPULATION

Patients with advanced, unresectable and/or metastatic solid tumours who are either refractory after standard therapy for the disease or for whom standard therapy is not appropriate will be eligible. Patients must also have exhausted treatment options known to prolong survival for their disease. The trial will be conducted in approximately 5 sites and it is anticipated that approximately 60 patients (30 per dosing schedule) will be enrolled in the trial. The total number of patients will depend on the number of dose escalations necessary.

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

Assessments may be repeated within the screening period if patients do not initially meet the inclusion/exclusion criteria. Eligibility must always be assessed using the latest results available. In addition re-screening of patients who have previously failed screening will be permitted. In this situation patients will be handled as a new patient i.e. sign a new informed consent, allocated a new patient number, and undergo full screening assessments.

3.3.1 Main diagnosis for trial entry

Patients with histologically or cytologically confirmed advanced, unresectable and/or metastatic solid tumours who are either refractory after standard therapy for the disease or for

whom standard therapy is not appropriate. Patients must also have exhausted treatment options known to prolong survival for their disease.

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

3.3.2 Inclusion criteria

1. Histologically or cytologically confirmed diagnosis of an advanced, unresectable and/or metastatic non-haematologic malignancy. Patient must have measurable or evaluable lesions (according to RECIST 1.1).
2. Patient who has failed conventional treatment or for whom no therapy of proven efficacy exists or who is not eligible for established treatment options. Patient must have exhausted treatment options known to prolong survival for their disease.
3. Patient willing to undergo mandatory skin biopsy at the timepoints specified in the protocol.
4. Eastern Cooperative Oncology Group score of 0 or 1 (R01-0787).
5. Adequate organ function defined as all of the following:
    - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L; haemoglobin ≥ 9.0 g/dL; platelets ≥ 100 x 10^9/L without the use of hematopoietic growth factors within 4 weeks of start of study medication.
    - Total bilirubin ≤ 1.5 times the upper limit of normal (ULN), except for patients with Gilbert's syndrome: total bilirubin ≤ 3 x ULN or direct bilirubin ≤ 1.5 x ULN.
    - Creatinine ≤ 1.5 x ULN. If creatinine is > 1.5 x ULN, patient is eligible if concurrent creatinine clearance ≥ 50 ml/min (measured or calculated by CKD-EPI formula or Japanese version of CKD-EPI formula for Japanese patients).
    - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3 x ULN if no demonstrable liver metastases, or otherwise ≤ 5 x ULN
    - Alkaline Phosphatase < 5 x ULN
6. Recovered from any previous therapy-related toxicity to ≤ CTCAE Grade 1 at start of treatment (except for alopecia and stable sensory neuropathy which must be ≤ CTCAE Grade 2).
7. At least 18 years of age at the time of consent or over the legal age of consent in countries where that is greater than 18 years.
8. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.
9. Life expectancy ≥ 3 months at the start of treatment in the opinion of the investigator.
10. Male or female patients. Women of childbearing potential (WOCBP)[1] must only be included after a confirmed menstrual period within the past 4 weeks and a negative

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and

pregnancy test at screening. WOCBP with irregular menstruation may be included after two negative pregnancy tests during screening between 2 and 4 weeks apart. WOCBP and men who are able to father a child must be ready and able to use highly effective methods of birth control, per ICH M3 (R2), that result in a low failure rate of less than 1% per year when used consistently and correctly. These methods must be used during the study and for at least 6 months after the last dose of BI 905677. A list of contraception methods meeting these criteria is provided in the patient information and in Section 4.2.2.3.

3.3.3 Exclusion criteria

1. Major surgery (major according to the investigator's assessment) performed within 4 weeks prior to first trial treatment or planned within 6 months after screening.
2. Previous or concomitant malignancies other than the one treated in this trial within the last 2 years, except;
    a) effectively treated non-melanoma skin cancers
    b) effectively treated carcinoma in situ of the cervix
    c) effectively treated ductal carcinoma in situ
    d) other effectively treated malignancy that is considered cured by local treatment
3. Osteoporosis ≥ CTCAE Grade 2
4. Chronic corticosteroid use
5. Osteoporotic compression fracture within 12 months prior to informed consent which is clinically significant in the opinion of the investigator.
6. Patients who must or wish to continue the intake of restricted medications (see Section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial.
7. Previous treatment in this trial.
8. Treatment with a systemic anti-cancer therapy or investigational drug within 28 days or 5 half-lives (whichever is shorter) of the first treatment with the study medication.
9. Any history of or concomitant condition that, in the opinion of the investigator, would compromise the patient's ability to comply with the study or interfere with the evaluation of the safety and efficacy of the test drug.
10. Women who are pregnant, nursing, or who plan to become pregnant or nurse during the trial or within 6 months after the last dose of study treatment.
11. Active alcohol or drug abuse in the opinion of the investigator.
12. Patient unwilling or unable to comply with the protocol.
13. Presence or history of uncontrolled or symptomatic brain or subdural metastases, unless considered stable by the investigator and local therapy was completed. Use of corticosteroids is allowed if the dose was stable for at least 4 weeks. Inclusion of patients with newly identified brain metastasis/es at screening will be allowed if patients are asymptomatic.

bilateral oophorectomy. Tubal ligation is NOT a method of permanent sterilisation. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

14. Known history of human immunodeficiency virus (HIV) infection or an active hepatitis B or C infection which in the opinion of the investigator may interfere with participation in the trial.
15. History of severe hypersensitivity reactions to monoclonal antibodies.
16. History of allergy to kanamycin or similar class drugs (including streptomycin, gentamicin, amikacin, tobramycin and neomycin).

3.3.4 Withdrawal of patients from therapy or assessments

An excessive withdrawal rate can have a severe negative impact on the scientific value of the trial. Every effort should be made to keep patients in the trial as scheduled. This includes careful patient selection and appropriate explanation of the trial requirements and procedures prior to enrolment as well as an explanation of the consequences of premature withdrawal.

3.3.4.1 Withdrawal from trial treatment

An individual patient must discontinue trial treatment if the patient:
- Withdraws consent for study treatment or further study participation, without the need to justify the decision.
- Has radiological (or clinical) documentation of progressive disease on the current treatment (Section 5.1.1).
- Needs to take concomitant medication that is prohibited in this trial (Section 4.2.2)
- Is required to stop treatment due to adverse events as described in Section 4.1.4.
- Can no longer be treated with trial medication due to pregnancy or for other medical reasons (such as adverse events, concomitant diagnoses or concomitant therapies)
- Has a significant deviation from the protocol or eligibility criteria. The decision to continue or withdraw treatment will be made by the sponsor in agreement with the Investigator.

If a patient withdraws consent to all further trial procedures and follow-up activities, no additional study assessments will be completed. This will be documented in the electronic case report form (eCRF).

In all other cases, wherever possible, and given the patient's agreement, patients who withdraw from treatment prior to disease progression should be encouraged to return for full EOT and follow-up assessments as outlined in the Flowchart and Section 6.2.3. In particular, a follow-up visit should be performed wherever possible to ensure all adverse events are adequately followed up. For all patients the reason for withdrawal from treatment (e.g. adverse events) must be recorded in the eCRF. These data will be included in the trial database and reported.

Patients who withdraw for a reason other than DLT before completing the first treatment cycle, or who do not receive the full planned dose in the first treatment cycle without DLT, or who miss more than one visit during their first treatment cycle will be replaced. Patients who miss one visit during the first treatment cycle may be replaced after discussion between the sponsor and the investigator if the information that needs to be collected during this visit is not available and makes the patient non-evaluable for determining DLT.

All other patients who withdraw, including all patients who are withdrawn from the trial due to a DLT, and all patients who withdraw after the first treatment cycle, will not be replaced.

If a patient becomes pregnant during the trial, the treatment with BI 905677 must be stopped immediately. The patient will be followed up until delivery or termination of pregnancy. The data of the patient will be collected and reported in the eCRF.

3.3.4.2 Discontinuation of the trial by the sponsor

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

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

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

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Product

Table 4.1.1: 1 BI 905677

Substance:	BI 905677
Pharmaceutical formulation:	Solution for infusion Dilution in 5% Glucose is required
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	10 mg/mL (10 mL vial)
Posology:	Schedule A; Infusion on Day 1 of each cycle (1 cycle = 21 days) Schedule B; Infusion on Day 1 and 15 of each cycle (1 cycle = 28 days)
Route of administration:	i.v.

4.1.2 Selection of doses in the trial

4.1.2.1 Starting Dose for Schedule A

The nonclinical safety package and data support the administration of BI 905677 to patients with advanced cancers. The maximum recommended starting dose (MRSD) was made on the basis of the US FDA Guidance for Industry "S9 Nonclinical Evaluation for Anticancer Pharmaceuticals" [R11-5034]. Two approaches were taken to calculate the starting dose: (1) use of the lowest EC_{20} value determined in the *in vitro* cytokine release assay and (2) use of the highest non-severely-toxic dose (HNSTD) level determined in the 6-week repeat dose toxicology study in the monkey, the most relevant toxicology species. The lowest starting dose of 0.05 mg/kg BI 905677 was selected and is expected to be an adequate and safe starting dose.

Approach 1 (use of EC_{20} value): The MRSD is calculated to be 0.09 mg/kg/dose.

In an *in vitro* cytokine release assay [n00254050], whole blood samples from eleven healthy human donors were incubated for 24 hours with various concentrations of BI 905677 (0.3, 3, 10, and 30 mg/mL). Releases of interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), tumor necrosis factor-alpha (TNF-α) and interferon gamma (IFN-γ) were measured.

IL-2 and IL-10 levels were not elevated with BI 905677 treatment for any of the donors. Elevations of IL-6, IL-8, TNF-α and IFN-γ were observed in 2 of 11 donors at the two highest concentrations of BI 905677 (10 and 30 mg/mL). Levels of these cytokines at 0.3 and 3 µg/mL were below the levels of the Avastin negative control.

The EC_{20} values for the 4 responding cytokines (IL-6, IL-8, TNF-α, and IFN-γ) were calculated using the mean cytokine values obtained at 4 different concentrations of BI 905677 (0.3, 3, 10, and 30 mg/mL) from the two donors with cytokine release [n00259622]. A human dose that is estimated to result in a C_{max} equivalent to the EC_{20} was then calculated with the assumption of linear pharmacokinetics (Table 4.1.2.1: 1).

The calculated EC_{20} values are similar for 4 cytokines of two donors (see Table 4.1.2.1: 1). The lowest EC_{20} is 0.5 µg/mL for IL-8 and TNF-α in one donor (1465M). A human dose of 0.09 mg/kg is predicted to have a C_{max} of 0.5 µg/mL.

Table 4.1.2.1:1 Summary of Predicted Human Dose at EC_{20} values for Four Cytokines in Two Positive Human Donors

Cytokine	Positive Human Donor (1437F)		Positive Human Donor (1465M)	
	EC_{20} (µg/mL)	Predicted Human Dose (mg/kg)	EC_{20} (µg/mL)	Predicted Human Dose (mg/kg)
IL-6	1.1	0.20	0.8	0.14
IL-8	0.9	0.16	**0.5**	**0.09**
IFNγ	1.1	0.20	0.9	0.16
TNFα	1.1	0.20	**0.5**	**0.09**

The lowest EC_{20} and predicted human dose is in bold.

Approach 2 (use of HNSTD level): The MRSD is calculated to be 0.05 mg/kg/dose.

Step 1: Determination of HNSTD (Highest Non-Severely Toxic Dose) in the repeat dose toxicity study if non-rodent is the most appropriate species (6-week GLP study in the monkey)
Monkey: HNSTD = 1 mg/kg/dose *q1w*

Step 2: Conversion of $1/6^{th}$ animal HNSTD to Human Equivalent Dose (HED)
Monkey: $1/6^{th}$ HNSTD = 0.17 mg/kg/dose *q1w*
Conversion factor from monkey dose to HED: 0.324 (based on body surface area scaling factor for the drug molecular weight < 100 kDa)
HED = 0.17 mg/kg/dose x 0.324 = 0.055 mg/kg/dose *q1w*
HED = 3.3 mg/dose *q1w* (60 kg human body weight)

The selected starting dose of 0.05 mg/kg/dose is 22x or 66x below the predicted efficacious human dose of 1.1 mg/kg/dose *q1w* or 3.3 mg/kg/dose *q3w*, respectively. The estimated exposures in humans at 0.05 mg/kg are 0.28 µg/mL C_{max} and 14.82 µg•h/mL AUC_{0-168h} and these exposures are 42X (C_{max}) and 20X (AUC_{0-168h}) below the exposures achieved at the NOAEL/HNSTD determined in the 6-week monkey study (steady state mean males and females combined exposure of 11.8 µg/mL C_{max} and 299 µg•h/mL AUC_{0-168h} at 1 mg/kg/dose *q1w*).

Considering the key dose limiting toxicities are the gastrointestinal toxicity and potential cytokine releases which can be managed and closely monitored in the clinic, the starting dose of 0.05 mg/kg is considered to be adequately safe. For further details please refer to the Investigator's Brochure (c16307316).

At the end of each treatment cohort, BI will convene a meeting with the SMC members. At the dose escalation meeting, the clinical course (safety information including both DLTs and all CTCAE Grade >= 2 toxicity data during the DLT evaluation period, and all available PK data) for each patient in the current dose cohort will be described in detail. Updated safety data on other ongoing patients, including data beyond the DLT evaluation period, will be discussed as well. Based on that, a decision on the next dose level to be tested is made. Dose escalation will continue until identification of the MTD, safety concerns arise, or the trial is terminated for other reasons.

4.1.2.2 Starting Dose for Schedule B

After determination of the MTD in Schedule A, Schedule B will commence. The starting dose in Schedule B will be determined by the SMC, and will not exceed 30% of the MTD from Schedule A. The SMC will also review whether the planned dosing schedule, assessments and sample collection in Schedule B remain appropriate. Schedule B will utilise its own BLRM and prior distribution will be derived from data in Schedule A.

The dose levels and cohort sizes in Schedule B will be decided by the SMC, following the same process and rules as for Schedule A (described in Section 4.1.2.1).

Based on the observations of safety and tolerability in Schedule B (dosing every 2 weeks), the SMC may decide to reduce the dosing frequency in Schedule B to once every 4 weeks and the provisional dose levels and a new BLRM will be specified. If this occurs it will be documented in the CTMF, investigators will be informed in writing and the information for patients will be updated. The following activities/assessments on Day 15 of each cycle will not be performed; Physical Examination, weight, blood sample for anti-drug antibodies (ADAs), BI 905677 infusion.

4.1.3 Method of assigning patients to treatment groups

At any time during the trial, a single dose cohort will be open for recruitment and each patient will be allocated to the next available cohort. Medication will be assigned via Interactive Response Technology (IRT) for each treatment cycle. Each medication vial will have a unique medication number.

4.1.4 Drug assignment and administration of doses for each patient

The study drug will be prepared and handled according to the 'Clinical Supplies Handling Instruction' which will be filed in the ISF. Upon notification that a patient will be treated in the study, the pharmacy will prepare the study drug at the assigned dosage for administration to the patient.

The Cycle 1 Day 1 dose will be calculated using the Cycle 1 Day 1 weight as the reference weight. If the patient's weight changes by ≤ 5% compared to the reference weight, the dose (in mg) may remain the same for subsequent cycles. If the weight changes by > 5% the dose will be recalculated and the new weight will be used as the reference weight.

BI 905677 will be given as an intra-venous infusion by authorised site staff in a specialised unit where emergency care can be provided (e.g. intensive care unit available, medical personnel trained in advanced life support). The expected infusion time is approximately 60 minutes. Patients must remain under observation for potential signs and symptoms of cytokine release for at least 6 hours following the end of infusion of BI 905677. If no signs or symptoms are observed during the first three administrations the duration of observation may be reduced to 3 hours for subsequent administrations. For patients who require systemic steroids around the time of administration of BI 905677 or during the post-treatment monitoring period, hospitalisation and monitoring for at least 24 hours is mandatory. Appropriate drugs and medical equipment to treat anaphylactic reactions must be immediately available and study personnel must be trained to recognise and treat anaphylaxis.

No routine premedication will be required for BI 905677 i.v. infusion.

4.1.4.1 Re-treatment criteria

Before administering a treatment dose the investigator must review the assessments performed according to the Flowchart and assess eligibility to receive further treatment and check that the following criteria are met;

- Absence of disease progression
- Drug related AEs recovered to Grade ≤ 1 (or baseline if higher than Grade 1)
- For AEs that do not require a treatment interruption, a toxicity of CTCAE Grade 2 (e.g. hypophosphatemia, anorexia, neuropathy) may be acceptable, provided the investigator considers it safe for the patient to continue treatment

If the criteria for re-treatment are not met, the patient should be evaluated and the next dose of treatment may be delayed until the criteria are met. For patients on Schedule A the dose may be delayed for up to 14 days. For patients on Schedule B, the dose may be delayed for up to 7 days. Dose reduction may be appropriate (see Section 4.1.4.7).

4.1.4.2 Management of infusion-related reactions

Infusion-related reactions involve the immune system; however, they can have different mechanisms. Some are allergic in nature and are usually mediated by immunoglobulin E while others are not classical allergic reactions (so-called anaphylactoid reactions e.g. caused by cytokine release). Although infusional reactions can be allergic or nonallergic, clinical symptoms are difficult to distinguish and require rapid assessment and immediate management to avoid severe adverse events, including fatality.

If an infusion-related reaction of ≥ CTCAE Grade 3 occurs, study treatment must be permanently discontinued.

If symptoms of an infusion-related reaction of CTCAE Grade 2 occur, which do not qualify as DLT according to Section 5.2.7, the infusion should be temporarily stopped. Upon recovery, the following guidance must be followed;

- If more than 50% of the planned dose of BI 905677 was administered, no further BI 905677 will be administered until the next scheduled dose.
- If less than 50% of the planned dose of BI 905677 was administered due to CRS, a further dose of 50% of the intended total dose may be administered on the following day and after recovery to baseline for at least 24 hours.
- During the first re-exposure patients should be hospitalised for at least 24 hours and closely monitored during the first re-exposure.
- Premedication must be used for all subsequent treatment infusions. The recommended premedication is:
    - Acetaminophen/Paracetamol 650 mg - 1000 mg p.o., or equivalent
    - Antihistamine p.o. or i.v., equivalent to Diphenhydramine 50 mg i.v.
    - Glucocorticoid i.v., equivalent to prednisolone 50-100 mg
- The infusion rate for further treatment cycles may be adapted according to Investigator decision, but any adaption of the infusion rate must be agreed with the sponsor.

If infusion reactions and/or hypersensitivity reactions occur in a substantial proportion of treated patients without premedication, the SMC may decide that all future patients treated in the study must receive premedication (as described above) prior to BI 905677 infusion; the dosage and schedule of premedication will be aligned and will take into account any local clinical standards. Such a decision will be communicated to all investigators in writing.

4.1.4.3 Management of Cytokine Release Syndrome (CRS)

CRS is a disorder characterised by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines. As outlined above in section 4.1.4.2, clinical manifestations of CRS and other forms of infusion related reactions are difficult to distinguish (especially at first occurence) and require rapid diagnosis and immediate management to avoid severe adverse events, including fatality.

Patients will be closely monitored for potential signs and symptoms of CRS (e.g. hypotension, rash, tachypnea, hypoxia, tachycardia, fever, nausea, fatigue, headache, myalgias and malaise). Patients must remain under observation for potential signs and symptoms of cytokine release for at least 6 hours following the end of infusion of BI 905677. If no signs or symptoms are observed during the first three administrations patients the duration of observation may be reduced to 3 hours for subsequent administrations. For patients who require systemic steroids around the time of administration of BI 905677 or during the post-treatment monitoring period, hospitalisation and monitoring for at least 24 hours is mandatory.

Body temperature, pulse rate and blood pressure will be measured prior to the start of infusion, every 30 minutes (± 10 minutes) during the infusion, and then at the following regular intervals during the post-treatment observation period;

- every 30 minutes (± 10 minutes) during the first 3 hours after end of infusion
- every hour (± 10 minutes) between 3-6 hours after end of infusion (if relevant)

- every 4-8 hours from 6 hours after end of infusion until observation ends (if relevant)

In case of suspected or confirmed CRS, patients will be appropriately treated according to best medical judgement based on institutional standards and/or publications (e.g. R16-2323). Supportive therapy including antipyretics, intravenous fluids, and low dose vasopressors may be used. In patients who do not respond to this, corticosteroids and/or interleukin 6 receptor antagonists (R15-0031, R18-1685, R18-1686) may be required and patients should be monitored closely, preferably in an intensive care unit.

In the event of CTCAE ≥ Grade 3 CRS study treatment must be permanently discontinued.

In the event of CTCAE Grade 2 CRS the guidance for handling a CTCAE Grade 2 infusion-related reaction must be followed (section 4.1.4.2).

4.1.4.4 Management of bone toxicity

Patients will be monitored for bone toxicity using regular measurement of serum bone biomarkers (section 5.2.5.1) and bone densitometry (section 5.2.5.2). Treatment with vitamin D and/or calcium carbonate is recommended in patients with documented pre-existing osteoporosis.

In case of a β-CTX increase of ≥ 50% or a P1NP decrease of ≥ 50%, zoledronic acid or another bisphosphonate will be initiated according to the standards of the institution. In case of a pathological fracture of any grade, BI 905677 must be permanently discontinued.

4.1.4.5 Management of retinal toxicity

Visual symptoms (e.g.loss in visual acuity, blurred or distorted vision, floating specks or cobwebs, night vision changes or color vision changes) during study treatment will trigger the same ophthalmologic assessments as performed as baseline as well as a full retinal examination (see also section 5.2.5.4).

Treatment with BI 905677 must be discontinued if either of the following are observed:
- CTCAE grade ≥ 2 retinopathy
- Clinically meaningful changes in fundus photography and SD-OCT as determined by the examining ophthalmologist

4.1.4.6 General management of toxicities

Toxicities not covered within sections 4.1.4.2, 4.1.4.3, 4.1.4.4 and 4.1.4.5 will be handled according to the instructions in table 4.1.4.6:1 For the definition of a DLT, refer to Section 5.2.7.

Table 4.1.4.6: 1 Management of toxicity

Event	First occurrence	Second occurrence
Grade 4 non-haematological	• Permanently discontinue treatment	Not applicable

toxicity which is related to BI 905677	• Start supportive measures according to standards of the institution	
Haematological toxicity fulfilling criteria for DLT (see Section 5.2.7)	• Hold BI 905677 treatment until recovery to Grade ≤ 1 or baseline; start supportive measures according to standards of the institution (e.g. G-CSF, antibiotics, platelet transfusion) • Perform complete blood count at least twice per week until improvement to a lower grade • Patient may be eligible to continue BI 905677 treatment at a lower dose - see section 4.1.4.7	• Permanently discontinue BI 905677 • Start supportive measures according to standards of the institution (e.g. G-CSF, antibiotics, platelet transfusion) • Perform complete blood count at least twice per week until improvement to a lower grade
Non-haematological toxicity Grade <4 fulfilling the criteria for DLT (see Section 5.2.7)	• Hold BI 905677 treatment until recovery to Grade ≤ 1 or baseline; start supportive measures according to standards of the institution (e.g. anti-emetics, loperamide and/or other conventional anti-diarrheals) • Patient may be eligible to continue BI 905677 treatment at a lower dose - see section 4.1.4.7	• Permanently discontinue BI 905677 • Start supportive measures according to standards of the institution
Toxicity which does not meet DLT criteria e.g. nausea, vomiting, diarrhoea ≤ Grade 2	• Start supportive measures according to standards of the institution (e.g. anti-emetics, loperamide and/or other conventional anti-diarrheals) • If event is Grade ≥ 2, hold BI 905677 treatment until recovery to Grade ≤ 1. A toxicity of CTCAE Grade 2 (e.g. hypophosphatemia, anorexia, neuropathy) may be acceptable, provided the investigator considers it safe for the patient to continue treatment.	• As for first occurence

4.1.4.7 Dose Reduction

In the event of a DLT which meets certain criteria the patient may continue therapy at a reduced dose (see Table 4.1.4.6: 1 for criteria). Patients may continue therapy only after recovery from the DLT to grade ≤ 1 or baseline and when re-treatment criteria are met (Section 4.1.4.1). The patient will re-commence treatment at a reduced dose of BI 905677; the dose will be one dose level down (according to the BLRM for the relevant treatment schedule) from the previous dose administered to the patient.

A maximum of one dose reduction will be allowed for an individual patient during the whole trial and a subsequent dose increase will not be allowed. A dose reduction to a level below the trial starting dose is not allowed. In the event of a second occurrence of toxicity requiring dose reduction, the patient must permanently discontinue treatment.

4.1.5 Blinding and procedures for unblinding

Not applicable.

4.1.6 Packaging, labelling, and re-supply

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

4.1.7 Storage conditions

BI 905677 will be kept in its original packaging and in a secure limited access storage area according to the storage instructions as provided on the medication label. A temperature log must be maintained for documentation. If the storage conditions are found to be outside the specified range, the sponsor must be contacted immediately.

4.1.8 Drug accountability

The investigator and/or pharmacist and/or investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the Institutional Review Board (IRB) / ethics committee,
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated clinical trial protocol,
- Availability of the proof of a medical license for the Principal Investigator,
- Availability of FDA Form 1572 (if applicable).

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics.

The investigator and/or pharmacist and/or investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the administration to each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

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

At the time of return to the sponsor at the end of the trial, the investigator / pharmacist / investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed.

Rescue medications to reverse the actions of BI 905677 are not available. Potential adverse events should be treated symptomatically and must be recorded. Concomitant medications or therapy to provide adequate supportive care may be given as clinically necessary.

Radiotherapy for local symptom control of non-target lesions may be allowed if agreed between the investigator and sponsor.

All concomitant therapy, including pre-medication, anaesthetic agents, vitamins, homeopathic/herbal remedies and nutritional supplements must be recorded in the eCRF during the screening and treatment period, starting from the date of signature of informed consent, and ending at the EOT visit. Between the EOT visit and the individual patient's end of trial, only concomitant therapy indicated for treatment of an AE has to be reported. Concomitant therapies used as pre-medication prior to infusion of BI 905677 will be indicated in the eCRF.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The use of prophylactic haematopoietic growth factors (e.g. G-CSF) is prohibited in cycle 1.

No experimental anti-cancer treatment and/or standard chemo-, immunotherapy, hormone treatment, or radiotherapy (other than described in Section 4.2.1) is allowed concomitantly with the administration of study treatment.

4.2.2.2 Restrictions on diet and life style

There are no restrictions on diet and lifestyle.

4.2.2.3 Restrictions regarding women and men of childbearing potential

Women of childbearing potential (for the definition please refer to Section 3.3.2) and men able to father a child must use two medically approved methods of birth control throughout the trial, and for a period of at least 6 months after last trial drug intake. They must use one barrier method, i.e. condom or occlusive cap with spermicide, or vasectomized partner, and one highly effective non-barrier method including oral, injected or implanted hormonal contraceptives, intrauterine device or system.

Male patients:
Men whose partner is a woman of childbearing potential must use a condom during the study, and for a period of at least 6 months after the last dose of study drug.

Female patients:
Women of childbearing potential (WOCBP) must use a highly effective method of birth control per ICH M3 (R2) that results in a low failure rate of less than 1% per year when used consistently and correctly during the study, and for a period of at least 6 months after the last dose of study drug.
Acceptable methods of birth control for this trial are:

- Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral, intravaginal, transdermal).
- Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable).
- Intrauterine device (IUD) and intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion
- Vasectomised sexual partner with documented absence of sperm.

Or

Patients must abstain from male-female sex. This is defined as being in line with the preferred and usual lifestyle of the patient. Periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable.

4.3 TREATMENT COMPLIANCE

BI 905677 will be administered as an intravenous infusion at the clinical site under the supervision of trained site personnel. Therefore actual dosing is expected to follow the protocol. The dose administered will be recorded in the eCRF and any irregularities in dosing will also be documented in the eCRF by the investigator or designee.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 Tumour assessment

Tumour response will be evaluated according to RECIST Version 1.1 (R09-0262). The assessment by the Investigator and/or the local radiologist will be the basis for continuation or discontinuation of the trial in an individual patient (in addition to safety).

Baseline imaging should include imaging of all known or suspected sites of disease using an appropriate method. The investigator (or designee) will record the target and non-target lesions in the eCRF. Lesions in previously irradiated areas may not be considered measurable at baseline unless the lesions occurred after irradiation. The same method of assessment and the same imaging technique must be used at each subsequent timepoint to characterise each reported lesion throughout treatment and during follow-up.

Tumour assessment will be performed at the timepoints indicated in the Flowchart. Wherever possible the assessment schedule should not be changed, but if there is an interruption or delay to treatment, alteration of the tumour assessment schedule to align with clinical assessments is allowed. Additional unscheduled tumour assessments may be performed at the discretion of the Investigator.

Copies of images collected during this study may be sent to a central imaging facility of an independent CRO where they will be stored for up to 30 years. During this time, if needed, an independent assessment of tumour response using the stored images may be performed but individual results will not routinely be reported to investigators and will not influence treatment or medical decisions while the patient is participating in this study.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A physical examination will be performed at the timepoints specified in the Flowchart.

A full physical examination serves as a clinical tumour assessment and should include a cardiopulmonary examination, examination of the regional lymph nodes, 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. Wherever possible the same investigator should perform this examination.

Measurement of height (in cm), body weight (in kg) and the evaluation of the ECOG performance score (see Appendix 10.5) will be performed at the timepoints specified in the Flowchart.

5.2.2 Vital signs

Vital signs (body temperature, blood pressure and pulse rate after 2 minutes of supine rest) will be recorded at the time points specified in the Flowchart.

Body temperature, pulse rate and blood pressure will be measured prior to the start of infusion, every 30 minutes (± 10 minutes) during the infusion, and then at the following regular intervals during the post-treatment observation period (variable duration; see section 4.1.4.2 for details);

- every 30 minutes (± 10 minutes) during the first 3 hours after end of infusion
- every hour (± 10 minutes) between 3-6 hours after end of infusion (if relevant)
- every 4-8 hours from 6 hours after end of infusion until observation ends (if relevant)

In case of an infusion-related reaction the investigator should decide whether increased monitoring of vital signs is required.

5.2.3 Safety laboratory parameters

Safety laboratory parameters will be analysed at a local laboratory. Safety laboratory examinations will include tests as listed in Table 5.2.3:1, and should be obtained at the time points specified in the Flowchart.

Table 5.2.3:1 Safety Laboratory Tests

Category	Parameters
Haematology	Red blood cell count (RBC), haemoglobin, haematocrit, platelet count, reticulocytes, white blood cell count (WBC) with differential (neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils)
Coagulation	International Normalized Ratio (INR), activated Partial Thromboplastin Time (aPTT)
Biochemistry	Glucose, sodium, potassium, calcium, phosphate, magnesium, chloride, bicarbonate (HCO_3), urea, creatinine, AST, ALT, alkaline phosphatase, lactate dehydrogenase (LDH), bilirubin, total protein, albumin. Creatinine clearance, creatine phosphokinase, cholesterol and triglycerides if indicated.
Immunoglobulins	Serum immunoglobulin levels (IgG, IgM, IgA, IgE) and direct antiglobulin test to be measured at screening and repeated if an infusion related reaction occurs.
Urinalysis	pH, protein, glucose, blood, leucocytes, nitrite; in case of pathological finding further evaluation should be performed and results documented
Pregnancy test	β-HCG testing in urine or serum in women of

Category	Parameters
	childbearing potential (WOCBP)

In case of haematological toxicity of Grade 4, or other haematological AEs fulfilling the criteria for DLT, a complete blood count has to be performed at least twice per week until improvement to a lower grade. The investigator should complete additional evaluations of laboratory tests as clinically indicated. Any abnormal and clinically relevant findings from these investigations need to be reported as an Adverse Event.

In case the criteria for possible hepatic injury are fulfilled, a number of additional tests will be performed (please see Section 5.2.6.1 and the "DILI Checklist" provided in the study portal and the ISF).

In addition to the tests above, a blood test for Vitamin D will be performed at screening, every third cycle (Cycle 3 Day 1, Cycle 6 Day 1 etc) and at EOT. This will be analysed at a local laboratory.

5.2.4 Electrocardiogram

A 12-lead resting ECG will be performed at the timepoints indicated in the Flowchart and in section 10.2 and 10.3. The investigator or a designee will evaluate whether the ECG is normal or abnormal and whether it is clinically relevant, if abnormal. ECGs may be repeated for quality reasons and the repeated recording used for analysis.

On Day 15 of Cycle 1 (Schedule B only) and on Day 1 of each cycle from Cycle 2 onwards the ECG should be performed prior to treatment and reviewed as part of the assessment of eligibility for further treatment.

Additional ECGs may be performed for safety reasons. Dated and signed printouts of ECG with findings should be documented in patient's medical record. Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the Screening visit) or otherwise as adverse events and will be followed up and/or treated as medically appropriate.

5.2.5 Other safety parameters

5.2.5.1 Safety biomarkers for bone resorption

Biomarkers for bone resorption and formation (including, but not limited to, β-Carboxy-terminal Telopeptide (β-CTX), P1NP) will be assessed in a blood sample at baseline (Cycle 1 Day 1), at the start of cycle 2 and cycle 3 and then every 2 cycles (every odd-numbered cycle) and at EOT. Assessment will be performed in a central laboratory and results will be provided to investigators unless local regulations prohibit this. In the event that clinically significant changes are observed, these will be discussed within the SMC and appropriate action agreed.

When a blood sample for bone biomarkers is required, it will be obtained prior to administration of trial medication, before 9am, and in a fasting state (at least 8 hours since last food intake).

5.2.5.2 Bone densitometry

Bone densitometry will be performed at the times indicated in the Flowchart according to standard institution practice and bone mineral density will be recorded. In the event that bone mineral density changes by >5% from baseline, bone densitometry will be repeated at least two months after the change is first observed to determine whether the change has persisted and constitutes a DLT (see Section 5.2.7).

In addition to the above, the SMC will regularly review any reported bone mineral density changes of >5% from baseline which have not yet been confirmed after two months and if necessary, appropriate action will be agreed.

5.2.5.3 Testing for Cytokine Release

Patients must remain under observation for potential signs and symptoms of cytokine release for at least 6 hours following the end of infusion of BI 905677. If no signs or symptoms are observed during the first three administrations the duration of observation may be reduced to 3 hours for subsequent administrations. For patients who require systemic steroids around the time of administration of BI 905677 or during the post-treatment monitoring period, hospitalisation and monitoring for at least 24 hours is mandatory.

Clinical signs and symptoms of cytokine release will be recorded as AEs. In addition, a panel of cytokines (including, but not limited to IL-2, IL-6, IL-10, IFN-γ, TNF-α, MCP-1) will be measured in peripheral blood in order to monitor release of cytokines after BI 905677 administration. Cytokine measurements will be performed in conjunction with each infusion at the timepoints specified in Appendices 10.2 and 10.3.

In addition to the scheduled cytokine measurements, ferritin will be measured at baseline (Cycle 1 Day 1). If a clinically manifested cytokine release syndrome occurs at any timepoint, unscheduled blood sampling for cytokine and ferritin measurement will be performed, ideally at the start of symptoms (and before start of corticosteroid treatment) and 48-72 hours after the start of symptoms.

Cytokines and ferritin will be measured in a central lab authorised by Boehringer Ingelheim using immunoassay techniques, such as BD Cytometric Bead Array (CBA) and MSD assay. Details are specified in Appendices 10.2 and 10.3, and in the Laboratory Manual.

5.2.5.4 Ophthalmologic Assessment

Ophthalmologic assessment will be performed for all patients at the screening visit. The following assessments will be performed;

- Best corrected visual acuity (BCVA): BCVA will be determined using the early treatment diabetic retinopathy study (ETDRS) visual acuity chart starting at a test distance of 4 metres. The BCVA score is the number of letters read correctly by

the patient. The assessment will be performed by a trained person under standard conditions regarding examination room and equipment.

- Colour fundus photography: Seven-field or modified 4-field digital fundus photographs will be obtained from both eyes by a qualified person.

- Spectral domain optical coherence tomography (SD-OCT): The retinal layers and thickness can be visualized and measured by SD-OCT. The assessment will be performed by a qualified person, and only [redacted] equipment will be used.

The same ophthalmologic assessments will be repeated if the patient develops visual symptoms during the trial. If the ophthalmological assessments are repeated, they should be performed using the same devices/equipment as used at screening. Additionally, a full retinal examination must be performed.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

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

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

Serious adverse event
A serious adverse event (SAE) is defined as any AE which fulfils at least one of the following criteria:
- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.
- requires inpatient hospitalisation or
- requires prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly / birth defect,
  or
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

For Japan only: the following events will be handled as "deemed serious for any other reason". AEs which possibly lead to disability will be reported as SAEs.

AEs considered "Always Serious"
Every new occurrence of cancer of new histology must be classified as a serious event regardless of the duration between discontinuation of the trial medication and must be reported as described in 5.2.6.2, subsections "AE Collection" and **AE reporting to sponsor and timelines**".
In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as defined above.

The latest list of "Always Serious AEs" can be found in the eDC system. These events should always be reported as SAEs as described above.

Adverse events of special interest (AESIs)
The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see above. The sponsor will submit specific AESI reports to the regulatory authority in an expedited fashion where required by the authority.

The following are considered as AESIs:

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

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

- For patients with abnormal liver function at baseline (AST and/or ALT>ULN)
  - an elevation of AST and/or ALT ≥ 5 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, with the exclusion of the causes due to underlying diseases, and/or
  - Marked peak aminotransferase (ALT, and/or AST) elevations ≥ 10 fold ULN

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the study portal and in the ISF.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are

analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Dose Limiting Toxicity
Any medical event fulfilling the criteria of DLT (see Section 5.2.7) should be reported as an AESI.

Infusion-related Reactions (including Cytokine Release Syndrome)
The following terms describe those events that are to be considered infusion-related reactions. Regardless of grade, these events, when occurring within 72 hours of study drug administration, are considered AESIs and must be reported as such;

- Allergic reaction
- Anaphylaxis
- Cytokine-release syndrome
- Serum sickness
- Infusion reactions
- Infusion-like reactions
- Any other event which the investigator determines may be a potential infusion-related AE

Treatment of infusion-related reactions and the handling of subsequent trial dosing are described in Section 4.1.4.2.

The initial clinical sign of a CRS is fever that can rise to high temperatures and is often associated with flu-like symptoms (e.g. nausea, fatigue, headache, myalgias, malaise, chills, rigor, tremor, hypoxia, tachypnea, rash, vomiting, diarrhoea, abdominal pain, muscle and joint pain, and generalised weakness). CRS symptoms may occur quickly during or after administration, or after several hours or days. Patients will be assessed for signs and symptoms of CRS and CRS will be reported as an AESI.

Management guidelines and treatment of CRS are described in Section 4.1.4.3.

Retinal toxicity
Any retinal toxicity (Standardised MedDRA Query ‘Retinal Disorder’) will be reported as an AESI.

Other AESIs
Based on safety observations during the trial, the SMC may define additional AEs as AESIs. If this occurs, investigators will be informed in writing.

Severity of AEs
The severity of adverse events should be classified and recorded in the eCRF according to the CTCAE version 5.0 (R18-1357).

Causal relationship of AEs
Medical judgement should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

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

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

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

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

5.2.6.2 Adverse event collection and reporting

AE Collection
The investigator shall maintain and keep detailed records of all AEs in the patient files. The following must be collected and documented on the appropriate eCRF(s) by the investigator:

- From signing the informed consent onwards until the individual patient's end of trial: all AEs (serious and non-serious) and all AESIs.
- After the individual patient's end of trial: the investigator does not need to actively monitor the patient for AEs but should only report related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should however, not be reported in the eCRF.

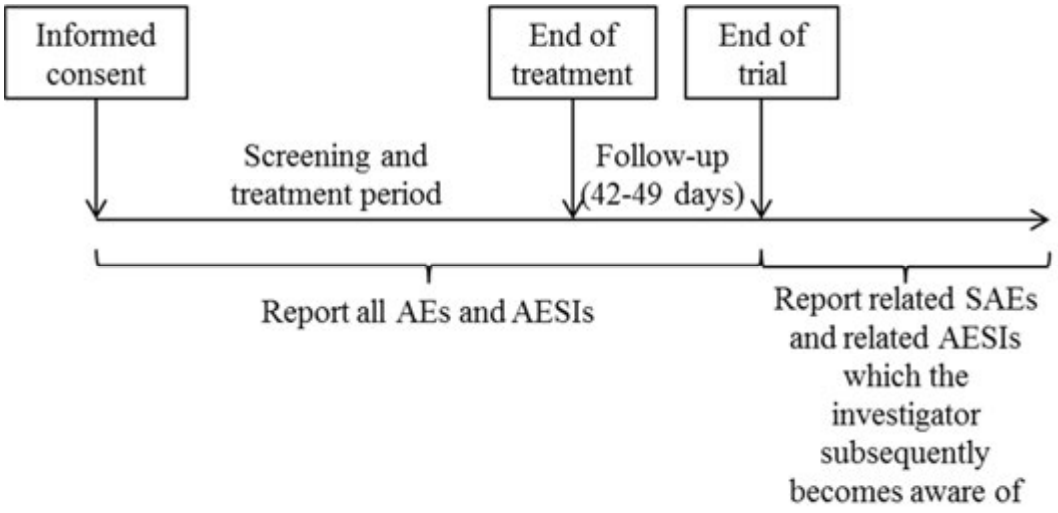

Figure 5.2.6.2: 1 Safety reporting

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

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

Information required
For each AE, the investigator should provide the information requested on the appropriate eCRF pages and the BI SAE form, if applicable. The investigator should determine the causal relationship to the trial medication.

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

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

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

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

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

Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires a written consent of the pregnant partner.

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

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

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

Exemptions to AE reporting

Disease Progression is recorded to enable analysis of efficacy endpoints. Progression of the patient's underlying malignancy will be recorded on the appropriate pages of the eCRF as part of efficacy data collection and will not be reported as an AE unless the criteria for seriousness are met (see 'Serious adverse event' definition), in which case SAE reporting procedures will be followed.

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

Clinical symptoms and/or signs of PD will be recorded as adverse events.

5.2.7 Definition of Dose Limiting Toxicity (DLT)

All DLTs occurring during the first or subsequent treatment cycles should be reported as AESIs according to the same timelines as serious AEs. Any of the following AEs will be classified as DLTs following review by the SMC and the Medical Monitor, unless unequivocally due to underlying malignancy or an extraneous cause;

- Schedule A; Any AE which prevents a patient starting Cycle 2 within 14 days of completion of Cycle 1
- Schedule B; Any AE which prevents a patient starting Cycle 2 within 7 days of completion of Cycle 1
- Bone mineral density change of >5% from baseline, confirmed at least 2 months after initial observation
- β-CTX increase of more than two-fold from baseline

- Grade 3 osteoporosis
- CTCAE grade ≥ 2 retinopathy and clinically meaningful changes in fundus photography and SD-OCT as determined by the examining ophthalmologist
- Any fracture without a history of trauma or as a result of a fall from standing height or less
- Haematologic toxicities:
  - Grade 4 anaemia
  - Grade 3 anaemia requiring blood transfusion
  - Neutropenia Grade 4 present for >7 days
  - Febrile neutropenia ≥ Grade 3
  - Neutropenia Grade 3 with documented infection
  - Any Grade 3 thrombocytopenia with bleeding or a requirement for platelet transfusions
  - Grade 4 thrombocytopenia (platelets <25,000/µL)
- Grade 4 vomiting or diarrhoea (irrespective of whether adequately treated)
- Any ≥ Grade 3 non-haematologic toxicity with the following exceptions:
  - Inadequately treated grade 3 vomiting or diarrhoea persisting for less than 48 hours after start of adequate treatment
  - Grade 3 vomiting or diarrhoea which persists for less than 48 hours after start of adequate treatment
  - Inadequately treated nausea
  - Grade 3 fatigue that persists <7 days
  - Any Grade 3 laboratory abnormality which is not considered clinically relevant by the investigator, resolves spontaneously or responds to conventional medical intervention

The frequency, time to onset, and severity of toxicities, as well as the success of standard medical management and dosing interruptions/delays, will be analysed to determine if a given toxicity should be considered a DLT for dose escalation purposes.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Pharmacokinetic profiles of BI 905677 in serum will be investigated after the first and after repeated doses. Standard PK parameters as listed in Appendix 10.1 will be calculated, if data allow and if scientifically reasonable.

Pharmacokinetic data may additionally be analysed using a population pharmacokinetic approach. Modelling and simulation activities will be planned and documented separately according to internal and external guidelines and SOPs.

Exploratory pharmacokinetic analyses can be performed as necessary for SMC decisions, but are not expected to be done more frequently than every second SMC meeting and do require sufficient lead time to collect samples, measure BI 905677 serum concentrations, analyse data and prepare meaningful outputs. The final exploratory analysis will be performed at the earliest after the cohort at MTD of treatment Schedule B completed the first treatment cycle.

For the purpose of these exploratory analyses, PK serum samples obtained up to at least 24 hours after drug administration will be used. A scientifically sound subset of the PK parameters listed in Appendix 10.1 will be calculated which may include C_{max}, AUC and $t_{1/2}$, if these parameters can be reliably determined from the available samples and serum concentration time profiles. In contrast to the final PK analysis, the exploratory analyses will be based on planned sampling times rather than on actual times; no supplementary subject information, e.g. on AEs or concomitant medication, will be used in these analyses, and the outputs will not be validated. Minor discrepancies between exploratory and final results may therefore occur.

5.3.2 Methods of sample collection

The timepoints for collection of PK samples are given in Appendices 10.2 and 10.3. Details of the sample collection, preparation, storage and shipment are described in the laboratory manual.

After completion of the trial, the samples may be used for further methodological investigations, e.g. for stability testing. However, only data related to the analyte will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years after the final study report has been signed.

[redacted]

5.3.4 Pharmacokinetic – pharmacodynamic relationship

No formal analysis of a pharmacokinetic/pharmacodynamic relationship is planned. Correlation between drug concentration and response may be made if adequate data are available. In addition, exploratory correlation may also be made between drug concentration and AEs.

Data may also be used to develop pharmacokinetic/pharmacodynamic models, if feasible. Modelling and simulation activities will be planned and documented separately according to internal and external guidelines and SOPs.

5.4 ASSESSMENT OF BIOMARKERS

This section refers to exploratory biomarkers. Established biomarkers of safety are described and discussed in Section 5.2. All biomarkers will be assessed in a central laboratory at BI or a by a designated CRO.

5.4.1 Biomarker analysis

[redacted]

detailed below. Baseline sampling must only be performed for patients who have undergone screening assessments and are expected to be eligible for treatment in the trial.

All samples are expected to be exhausted during the course of investigative analysis. Should this not be the case, samples might also be used for assay validation and concordance testing. Remaining samples will be disposed of at the latest 5 years after the end of the trial. Until then, samples will be stored at Boehringer Ingelheim or a designated CRO.

[redacted]

Pre-treatment and on-treatment skin biopsies will be obtained at the time points indicated in the Flowchart. Skin biopsy will be performed for all patients in the relevant schedule who start treatment after at least one of the following criteria has been met within the schedule;

- A Grade 2 AE has been observed (excluding toxicities which are clearly related to disease progression or concurrent illness)
- Dose escalation has reached a dose level ≥ 0.8 mg/kg

Data obtained from the analysis of skin biopsies will not be disclosed to patients because the analysis is exploratory. If consent is withdrawn, all samples and the data that had already been collected up to the time of withdrawal of consent will still be used.

5.4.1.1 Methods of sample collection for skin biopsies

Skin biopsies (6 mm punch) will be performed pre-treatment and on treatment 48-96 hours after infusion of Cycle 2. The exact timing of this sample may be modified based on the observations from the first patients in the trial. If this happens it will be documented in the CTMF, communicated to investigators in writing and the information given to new patients will be updated.

A 6 mm punch biopsy is to be obtained using the investigator's standard procedure. Upon attaining the skin biopsy the specimen should be immediately transferred to [redacted] tube and stored overnight in a refrigerator at approximately 2-8°C. The sample must be at the bottom of the tube. The next day samples are to be transferred to a freezer (approximately -20°C, non-self-defrost) and stored until ready to be shipped.

Detailed instructions for sampling, handling, and shipment of samples are provided in the ISF/laboratory manual.

5.4.2 Biobanking

No biobanking is planned.

5.5 OTHER ASSESSMENTS

5.5.1 Demographics and history

Demographic information including gender, year of birth and race/ethnicity, as well as general medical history and detailed oncological disease history will be collected. This will include date of first diagnosis of malignancy, staging and grading information, and details of previous treatment for malignancy.

5.5.2 Sampling for anti-drug antibodies (ADAs)

5.5.2.1 Methods of ADA sample collection

For the determination of anti-drug antibodies (ADA), approximately 3 mL of blood will be taken from a forearm vein in a blood drawing tube at those time points specified in the Flowchart and in Appendices 10.2 and 10.3.

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

[redacted]

5.6 APPROPRIATENESS OF MEASUREMENTS

Determination of MTD is based on toxicities graded according to CTCAE version 5.0 (R18-1357). The CTCAE criteria are commonly used in the assessment of AEs in cancer patients. RECIST 1.1 (R09-0262) is used for evaluation of response. These criteria are well-established and scientifically accepted.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients should adhere to the visit schedule as specified in the Flowchart. If treatment administration is delayed at any time, the schedule of all subsequent visits/cycles will be recalculated based on the actual date of treatment.

If a patient misses a visit during which there is no treatment administration planned, the visit should be rescheduled as soon as possible and the delayed visit documented with the actual date and the reason for the delay. The scheduling of subsequent visits must not be altered, so if it is not possible to reschedule prior to the next planned visit, the missed visit should be skipped.

If a patient is hospitalised for administrative reasons to allow treatment and PK sampling this will not be considered an SAE, unless any other criteria for an SAE are fulfilled.

In addition to the scheduled assessments, unscheduled assessments for safety reasons may be performed at any time according to clinical need.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

Following informed consent, the patient will undergo visit 1/screening assessments as indicated in the Flowchart. The assessments must fall within the acceptable Screening visit window but do not need to be performed on the same day. Screening assessments may be repeated as long as they fall within the Screening visit window. If more than one screening assessment is available, the latest assessment prior to the start of treatment must be used to assess eligibility.

Tumour assessments performed prior to informed consent as part of routine clinical practice will be accepted if they meet the requirements of the protocol and are performed within the Screening visit window.

There is no mandatory order of assessments, but the skin biopsy must only be performed on patients who are expected to be eligible. When applicable, the pre-treatment/baseline skin biopsy must be obtained prior to the first dose.

If the patient meets the eligibility criteria during screening, the first treatment visit should be scheduled. Any baseline conditions which are present at the Screening visit should be reported in the eCRF.

Re-screening of patients who have previously failed screening will be permitted. In this situation patients will be allocated a new patient number.

6.2.2 Treatment period

The investigator must perform a final assessment of eligibility when the results of all screening assessments are available. If the patient does not meet the eligibility criteria, the patient must be recorded as a screen failure.

If a patient is eligible for trial participation, treatment is allocated using IRT. The Cycle 1 Day 1 assessments as listed in the Flowchart are then performed. Some assessments do not need to be repeated if performed within 2 calendar days as part of the Screening visit; see Flowchart for details.

Subsequent visits during the treatment period are performed as described in the Flowchart. Patients may continue on treatment for unlimited cycles, until criteria for stopping treatment are met (see Section 3.3.4).

When a blood sample for bone biomarkers is required, it will be obtained prior to administration of trial medication, before 9am, and in a fasting state (at least 8 hours since last food intake).

6.2.3 Follow up period and trial completion

6.2.3.1 End of treatment visit

After a decision to permanently discontinue treatment within the trial is taken, no further administration of study medication should take place and the EOT visit should be performed within 7 days of the decision. If the decision to permanently discontinue trial treatment is taken during a scheduled visit, the EOT visit should be performed instead of the scheduled visit.

The assessments to be performed at the EOT visit are described in the Flowchart. The blood sample for bone biomarkers will be obtained before 9am and in a fasting state (at least 8 hours since last food intake).

6.2.3.2 Follow-up visit

A follow-up visit should be performed 42-49 days after the last administration of trial medication. The information collected at this visit should include all new AEs that occurred after EOT and a follow-up of AEs ongoing at EOT. Any subsequent anti-cancer therapy administered between EOT and follow-up should be reported.

Wherever possible the follow-up visit must be performed in person, but if the investigator judges appropriate (e.g. in the event the patient is undergoing end-of-life care), follow-up information may be collected by telephone.

The follow-up visit marks the completion of the study for the individual patient. After the completion of the study the patient will receive standard medical care.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

The trial will be performed as an open-label study. The objective of the design is to determine the MTD of BI 905677 defined as the highest dose with less than 25% risk of the true DLT rate being ≥ 33% (EWOC criterion). The dose-finding in Schedule A and B will be guided by Bayesian 2-parameter logistic regression models with overdose control (R13-4803). Separate MTDs will be determined for Schedule A and Schedule B.

The model is given as follows:
$\text{logit}(\pi_d) = \log(\alpha) + \beta * \log(d/d^*)$,
where $\text{logit}(\pi) = \log(\pi/(1-\pi))$.
π_d represents the probability of having a DLT in the MTD evaluation period at dose d, d* = 1.1 mg/kg/week is the reference dose, allowing for the interpretation of α as the odds of a DLT at dose d*, and $\theta = (\log(\alpha), \log(\beta))$ with $\alpha, \beta > 0$ is the parameter vector of the model.

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

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

The BLRM recommended dose for the next dose level is the level with the highest posterior probability of the DLT rate falling in the target interval [0.16, 0.33) among the doses fulfilling EWOC. Applying the EWOC criterion it should be unlikely (<25% posterior probability) that the DLT rate at that dose will exceed 0.33. However, the maximum allowable dose increment for the subsequent cohort will be no more than 50% from cohort to cohort, after a Grade ≥2AE is observed in Cycle 1 (excluding adverse events which are clearly related to disease progression or concurrent illness).

The MTD may be considered reached if all the following criteria are fulfilled:

1. Next recommended dose = current dose (stabilisation condition)
2. Number of DLTs in study is at least 1.
3. At least 9 patients have been treated in the trial.

and at least one of the following criteria is fulfilled:

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

The SMC may recommend stopping the trial after the criterion for MTD is fulfilled. Further patients may be included to confirm this MTD estimate. If no DLT is observed while information from the PK profile is considered sufficient, the SMC may recommended a dose for further testing. Any DLTs occurring after the start of the second cycle will be considered for the evaluation of the recommended dose for further testing for BI 905677.

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

This prior distribution will be specified as a mixture of three multivariate normal distributions, i.e.
$a(\theta) = a_1 f_1(\theta) + a_2 f_2(\theta) + a_3 f_3(\theta)$
with
a_i, i = 1, 2, 3 the prior mixture weights ($a_1 + a_2 + a_3 = 1$)
and
$f_i(\theta) = MVN(\mu_i, \Sigma_i)$
the multivariate normal distribution of the i-th component with mean vector μ_i and covariance matrix Σ_i, where

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

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

Prior derivation (Schedule A):

For the current trial, no relevant information in the form of human data was available, since no trial in a comparable population with comparable dosing schedule has been conducted. To support the interpretation of the prior distribution, the highest dose is assumed to be 8.5 mg/kg/q3w. Therefore, the three mixture components were established as follows:

- A weakly informative prior was derived reflecting the a priori assumption that the median DLT rate at the starting dose of 0.05 mg/kg/q3w would equal 0.001, and the median DLT rate at the highest dose of 8.5 mg/kg/q3w would equal 0.25. This yields μ_1 = (-2.169, 0.123). The standard deviations were set such that large uncertainty about the parameter means is reflected, and the correlation was set to 0, thus yielding $\sigma_{1,11}$ = 2, $\sigma_{1,22}$ = 1 and ρ_1 = 0, respectively. The prior weight a_1 for the first component was chosen as 0.9.
- A high-toxicity weakly informative prior was derived reflecting the case that the compound would be much more toxic than expected. For this prior component, it was assumed that the median DLT rate at the starting dose of 0.05 mg/kg/q3w would equal 0.005, and the median DLT at the highest dose of 8.5 mg/kg/q3w would equal 0.60. These assumptions yield μ_2 = (-0.644, 0.104). The standard deviations and correlations were set identical to the weakly informative prior, i.e. $\sigma_{2,11}$ = 2, $\sigma_{2,22}$ = 1 and ρ_2 = 0, respectively. The prior weight a_2 for the second component was chosen as 0.05.
- A low-toxicity weakly informative prior was derived reflecting the case that the compound would be much less toxic than expected. For this prior component, it was assumed that the median DLT rate at the starting dose of 0.05 mg/kg/q3w would equal 0.003, and the median DLT at the highest dose of 8.5 mg/kg/q3w would equal 0.03. These assumptions yield μ_3 = (-3.905, -0.790), i.e. basically a flat curve. The standard deviations and correlations were set to $\sigma_{3,11}$ = 5, $\sigma_{3,22}$ = 0.01, therefore almost fixing the slope parameter to its mean. The correlation was set to 0, i.e. ρ_3 = 0. The prior weight a_3 for the third component was chosen as 0.05.

A summary of the prior distribution is provided in Table 7.1.1. A detailed evaluation of the model using hypothetical data scenarios and operating characteristics is provided in the statistical appendix (see Table 10.4: 3).

Table 7.1.1 Summary of prior distribution

Prior Component	Mixture Weight	Mean Vector	SD Vector	Correlation
1: Weakly inf.	0.9	-2.169, 0.123	2.000, 1.000	0.000
2: High Tox	0.05	-0.644, 0.104	2.000, 1.000	0.000
3: Low Tox	0.05	-3.905, -0.790	5.000, 0.010	0.000

Prior derivation (Schedule B):

Schedule B will start after the MTD of Schedule A is reached and prior distribution of Schedule B will be derived based on the data observed from Schedule A. The starting dose of Schedule B will not exceed 30% of the MTD in Schedule A.
Statistical model assessment:

The model is assessed based on two different metrics:

Hypothetical data scenarios: for various potential data constellations as they could occur in the actual trial, the maximal next doses as allowed by the model and by certain escalation limit are investigated. Various data scenarios provide a way to assess the “on-study” behaviour of the model.

Simulated operating characteristics: these illustrate how often a correct dose would be declared as MTD by the model for different assumed true dose-toxicity relationships. They can be considered as an assessment of the “long-run” behaviour of the model.

7.2 NULL AND ALTERNATIVE HYPOTHESES

No formal hypothesis testing is planned in this trial. This is an exploratory study where the primary objective is the determination of MTD and RDE. All analyses in this trial are descriptive and exploratory in nature.

7.3 PLANNED ANALYSES

The primary analysis will be conducted once the MTD of both Schedules A and B or RDE are determined.

Only one analysis population will be considered for efficacy and safety analyses: the treated set. The treated set (TS) will consist of all patients who were treated with any dose of BI 905677. Patients will be analysed under the actual treatment received.

The PK set includes all subjects in the TS who provide at least one observation for at least one PK endpoint without important protocol violations relevant to the evaluation of PK. It is used for analysis of dose proportionality, exploratory food effect and time to steady state.

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

7.3.1 Primary endpoint analyses

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

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

The number of patients experiencing AEs during the entire treatment period will be summarised by dose level for each schedule.

7.3.2 Secondary endpoint analyses

All secondary endpoints will be analysed descriptively.

Details of the primary endpoint as well as the secondary endpoint analyses will be specified in the trial statistical analysis plan (TSAP).

[redacted]

7.3.4 Safety analyses

AEs will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All AEs with an onset between start of treatment and end of the residual effect period (REP), a period of 42 days after the last dose of trial medication, will be assigned to the on-treatment period for evaluation.

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned. Statistical analysis and reporting of AEs will concentrate on treatment-emergent adverse events, i.e. all AEs occurring between start of treatment and end of the residual effect period. AEs that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’.

Frequency, severity, and causal relationship of AEs will be tabulated by system organ class and preferred term after coding according to the current version of MedDRA at the database lock.

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

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

7.3.5 Pharmacokinetic and pharmacodynamic analyses

Refer to Appendix 10.1 for pharmacokinetic parameters to be calculated using non-compartmental analysis (NCA). The derivation of pharmacokinetic parameters is described in detail in the BI SOP [redacted]

All patients in the treated set who received at least one dose of BI 905677 and provided at least one valid serum concentration value will be included in the pharmacokinetic analysis. Patients who are considered as not evaluable will be listed with their individual serum concentrations and individual pharmacokinetic parameters, however, will not be included in descriptive statistics for serum concentrations, pharmacokinetic parameters or other statistical assessment.

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

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

Concentrations will be used for graphs and calculations in the format that is reported in the bioanalytical report. Noncompartmental pharmacokinetic analyses of the serum concentration-time data will be performed using a validated software program, e.g. Phoenix WinNonlin Version 5.2. Only concentrations within the validated concentration range will be used for the calculation of pharmacokinetic parameters. For pre-dose samples, the actual sampling time will be set to zero.

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

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

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

Dose proportionality of BI 905677 will be assessed if feasible based on $C_{max,ss}/AUC_{\tau,ss}$ and C_{max}, $AUC_{0-\infty}$. The attainment of steady state will be explored if feasible by plotting trough concentrations (C_{pre}, $C_{pre,N}$) against time.

Assessment of dose proportionality:
If necessary, dose proportionality will be explored using the power model that describes the functional relationship between the dose and PK endpoints, C_{max}, $AUC_{0-\infty}$, $C_{max,ss}$, $AUC_{\tau,ss}$. The basic model consists of a regression model applied to log-transformed data. The corresponding Analysis of Covariance (ANCOVA) model includes the logarithm of the dose as a covariate. Based on the estimate for the slope parameter β, a two sided 95% confidence interval for the slope will be computed. Perfect dose proportionality would correspond to a slope of 1. The assumption of a linear relationship between the log-transformed pharmacokinetic endpoint and the log-transformed dose will be checked.

If dose proportionality over the entire dose range investigated cannot be shown, an attempt will be made to identify dose range(s), where dose proportionality can be assumed. The model for dose proportionality analysis will be detailed in TSAP.

Attainment of steady state:
If applicable, the statistical model to explore the attainment of steady state using the trough concentrations described above for each dose level will be a repeated measures linear model on the logarithmic scale including 'subject' as a fixed effect and 'time' as a repeated effect. The corresponding model, if all dose levels are analysed simultaneously, will include the log-transformed 'dose' as a covariate. Both models allow modelling the covariance structure of the data. The structure of the covariance matrix generally is not known in advance and will therefore be determined on a data-driven basis. The strategy/criteria to determine the final structure will be described in the TSAP.

Subsequently, adjusted least square means and two sided 95% confidence intervals will be calculated and back transformed by exponentiation. Furthermore pairwise comparisons of the log-transformed differences between all subsequent time points ($\log(C_{pre,i}/C_{pre,j}) = \log(C_{pre,i}) - \log(C_{pre,j})$ where $j>i$) will be performed including the calculation of two sided 95% confidence intervals using t tests. Comparisons which reveal small p-values will be inspected to determine if the relevant differences between time points are resulting from not yet attaining steady state. In general, all dose levels will be analysed separately. If there is evidence that the patterns (or trend) of the trough concentration profiles are comparable across dose levels they will be analysed simultaneously if this is justified. Other analyses, such as regression over time may be considered as post-hoc analyses.

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

7.4 INTERIM ANALYSES

No formal interim analysis is planned.

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

7.5 HANDLING OF MISSING DATA

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

Pharmacokinetic parameters:
In the non-compartmental analysis, concentration data identified with NOS, NOR and NOA will not be considered. BLQ values of the profile will be ignored. Descriptive statistics of parameters will be calculated only when at least 2/3 of the individual parameter estimates of a certain parameter are available. Pharmacokinetic parameters which cannot be determined will be identified by "not calculated" (NC).

7.6 RANDOMISATION

Patients will be assigned, not randomised, into escalating dose cohorts by order of admission into the trial.

7.7 DETERMINATION OF SAMPLE SIZE

Simulation studies (refer to Table 10.4: 5) show a range of 3 to 51 patients are needed to assess 11 dose levels for Schedule A. Assuming Schedule A has an MTD of 3.3 mg/kg/q3w, and Schedule B starts at 0.4 mg/kg/q2w (which is less than 30% of the MTD for Schedule A), Schedule B requires a range of 3 to 45 patients. On average, it is around 30 patients for each Schedule. In total, the estimated sample size for the trial is around 60 patients.

The replacement of patients is described in Section 3.3.4.1.

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations.

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

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

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

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

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

The investigator or delegate must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible. The patient must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial

collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

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

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail). Data reported on the eCRF must be consistent with the source data or the discrepancies must be explained.

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

During the site visit the sponsor's Clinical Research Associate (CRA) or auditor must be granted access to the original patient file (please see Section 8.3.2). The investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents before sending them to the sponsor.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.

For the eCRF, data must be derived from source documents, for example:

- Patient identification: gender, year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)

- Dates of patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- AEs and outcome events (onset date (mandatory), and end date (if available))
- SAEs (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of patient's participation in the trial (end date; in case of premature discontinuation document the reason for it)
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria makes the patient ineligible for the clinical trial.
- Technical information collected on PK sampling days (e.g. PK sampling times, multiple vital signs measurements linked with PK sampling) may be collected on trial-specific PK logs, which will be considered as source data for related entries in the eCRF and are considered part of the ISF.

8.3.2 Direct access to source data and documents

The sponsor will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

Exemptions from expedited reporting are described in Section 5.2.6.2, if applicable.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

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

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.

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

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

Measures are in place to comply with the applicable rules for the collection, storage and future use of biological samples from clinical trial participants and the corresponding data, in particular

- A Quality Management System has been implemented to ensure the adherence with the Principles of Good Clinical Practice as outlined in 'Note For Guidance On Good Clinical Practice' (CPMP/ICH/13 5/95)
- The BI-internal facilities storing and analysing biological samples and data from clinical trial participants as well as the laboratories' activities for clinical trials sponsored by Boehringer Ingelheim are regularly audited. The analytical groups and the banking facility are therefore assessed to be qualified for the storage and use of biological samples and data collected in clinical trials.
- Samples and data are used only if an appropriate informed consent is available.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.

The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Out").

The "**Last Patient Drug Discontinuation"** (LPDD) date is defined as the date on which the last patient at an individual trial site ends trial medication (as scheduled per protocol or

prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPDD at their site.

Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.

The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

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

A Safety Monitoring Committee (SMC) composed of participating investigators and members of the BI trial team will be established to review individual and aggregated safety data at regular intervals to determine the safety profile and risk/benefit ratio and make decisions on next dose level/dose escalation/de-escalation/modification/next cohort size.

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

BI has appointed a Trial Clinical Monitor, responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of Local Clinical Monitors (CML), CRAs, and investigators of participating countries.

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

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

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

A central laboratory service, a central imaging service, and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual, Imaging Manual and Central Laboratory Manual, available in the ISF.

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10. APPENDICES

10.1 PHARMACOKINETIC ANALYSES

If data allow and if scientifically reasonable, the following pharmacokinetic parameters of BI 905677 will be evaluated using non compartmental analysis methods according to the internal BI SOP [redacted]

After the first doses (before steady state is achieved):

- C_{max} (maximum measured serum concentration of BI 905677 in serum).
- $AUC_{0-\infty}$ (area under the serum concentration-time curve of the analyte over the time interval from zero extrapolated to infinity).
- AUC_{0-tz} (area under the serum concentration-time curve of the analyte over the time interval from 0 up to the last quantifiable data point).
- AUC_{0-336} (q2w, area under the serum concentration-time curve over the time interval from 0 to 336 h).
- AUC_{0-504} (q3w, area under the serum concentration-time curve over the time interval from 0 to 504 h).
- $\%AUCt_{z-\infty}$ (the percentage of the $AUC_{0-\infty}$ that is obtained by extrapolation)
- AUC_{t1-t2} (area under the concentration time curve of the analyte in serum over the time interval t_1 to t_2)
- t_{max} (time from dosing to the maximum measured serum concentration).
- λ_z (terminal rate constant in serum)
- $t_{1/2}$ (terminal half-life).
- MRT_{inf} (mean residence time after intravenous infusion).
- CL (total clearance of the analyte in serum).
- V_z (apparent volume of distribution during the terminal phase).
- V_{ss} (volume of distribution after intravenous infusion).

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

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

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

If deemed necessary, further appropriate pharmacokinetic parameters might be calculated.

Blood sampling time points for PK, ADA,cytokines and ferritin are given in Appendices 10.2 and 10.3.

10.2 TIME SCHEDULE FOR PHARMACOKINETIC (PK), ADA AND CYTOKINE BLOOD SAMPLING AND ECG ASSESSMENT IN SCHEDULE A

Table 10.2: 1 Time schedule for PK, ADA and cytokine blood sampling and ECG assessment in Schedule A

Cycle	Day	Time Point (hh:min)	CRF Time / planned time	PK BI 905677	ADA	Cytokines	ECG
1 and 2	1	Before start of BI 905677 infusion	-0:05	X	X	X[a]	X[b]
		Start of BI 905677 infusion	0:00				
		End of infusion	1:00[c]				X[d,e]
		Immediately after end of infusion[e]	1:00[c]	X[f]		X[f]	
		0.5h after the end of infusion	1:30[c]	X			
		3h after the end of infusion	4:00[c]	X		X	
		7h after the end of infusion	8:00[c]	X		X	
	2	24h after start of infusion	24:00	X		X	
	4	48:00-96:00	72:00	X			
	8	144:00-192:00	168:00	X			X[d]
	15	288:00-384:00	336:00	X			
3 and 4	1	Before start of BI 905677 infusion	-0:05	X	X	X	X[b]
		Start of BI 905677 infusion	0:00				
		End of infusion	1:00[c]				X[e]
		Immediately after end of infusion[f]	1:00[c]	X[f]		X[f]	
		3h after the end of infusion	4:00[c]			X	
		7h after the end of infusion	8:00[c]			O	
	2	24h after start of infusion	24:00			X	
	8	144:00-192:00	168:00	X			
	15	288:00-384:00	336:00	X			
Cycle 5 onwards	1	Before start of BI 905677 infusion	-0:05	X	X	X	X[b]
		Start of BI 905677 infusion	0:00				
EOT	N/A	N/A	N/A	X	X		X
FU	N/A	N/A	N/A	X	X		

O = Optional. To be taken if the patient is already in the clinic.

a A sample for ferritin testing will collected before the start of infusion on cycle 1 day 1.
b Pre-dose ECG will be performed within 10 minutes prior to start of infusion.
c The planned times assume an infusion duration of 60 min. If the infusion duration is shorter or longer, the PK and cytokine sample times for the end of infusion sample and all subsequent Day 1 samples should be adjusted accordingly (timings calculated from the end of infusion, as indicated in the column 'Time Point') and the actual times recorded in the eCRF.
d Only required in Cycle 1
e End of infusion ECG will be performed within 10 minutes prior to the end of infusion
f PK sample must be taken within 5 min after the end of infusion. Cytokine sample must be taken within 30 min after the end of infusion.

10.3 TIME SCHEDULE FOR PHARMACOKINETIC (PK), ADA AND CYTOKINE BLOOD SAMPLING AND ECG ASSESSMENT IN SCHEDULE B

Table 10.3: 1 Time schedule for PK, ADA and cytokine blood sampling and ECG assessment in Schedule B

Cycle	Day	Time Point (hh:min)	CRF Time / planned time	PK BI 905677	ADA	Cytokines	ECG
1 and 2	1	Before start of BI 905677 infusion	-0:05	X	X	X[a]	X[b]
		Start of BI 905677 infusion	0:00				
		End of infusion	1:00[c]				X[d, e]
		Immediately after end of infusion[e]	1:00[c]	X[f]		X[f]	
		0.5h after the end of infusion	1:30[c]	X			
		3h after the end of infusion	4:00[c]	X		X	
		7h after the end of infusion	8:00[c]	X		X	
	2	24h after start of infusion	24:00	X		X	
	4	48:00-96:00	72:00	X			
	8	144:00-192:00	168:00	X			X[d]
	15	Before start of BI 905677 infusion	335:55	X	X	X	X[b,d]
		Start of BI 905677 infusion	336:00				
		End of infusion	337:00[c]				
		Immediately after end of infusion[e]	337:00[c]	X[f]		X[f]	
		3h after the end of infusion	340:00[c]			X	
		7h after the end of infusion	344:00[c]			X	
	16	24h after start of infusion	360:00	X		X	
	22	480:00-528:00	504:00	X			
3 and 4	1	Before start of BI 905677 infusion	-0:05	X	X	X	X[b]
		Start of BI 905677 infusion	0:00				
		End of infusion	1:00[c]				X[e]
		Immediately after end of infusion[e]	1:00[c]	X[f]		X[f]	
		3h after the end of infusion	4:00[c]			X	
		7h after the end of infusion	8:00[c]			O	
	2	24h after start of infusion	24:00			O	
	8	144:00-192:00	168:00	X			
	15	Before start of BI 905677 infusion	335:55	X		X	
		Start of BI 905677 infusion	336:00				
		End of infusion	337:00[c]				
		Immediately after end of infusion[e]	337:00[c]			X[f]	
		3h after the end of infusion	340:00[c]			X	

Table 10.3:1 – Continued Time Schedule for PK, ADA and cytokine blood sampling and ECG assessment in Schedule B

Cycle	Day	Time Point (hh:min)	CRF Time / planned time	PK BI 905677	ADA	Cytokines	ECG
		7h after the end of infusion	344:00[c]			O	
Cycle 3 and 4 (cont.)	16	24h after start of infusion	360:00			O	
	22	480:00-528:00	504:00	X			
Cycle 5 onwards	1	Before start of BI 905677 infusion	-0:05	X	X	X	X[b]
		Start of BI 905677 infusion	0:00				
	15	Before start of BI 905677 infusion	335:55	X[g]		X	
		Start of BI 905677 infusion	336:00				
EOT	N/A	N/A	N/A	X	X		X
FU	N/A	N/A	N/A	X	X		

O = Optional. To be taken if the patient is already in the clinic.

a A sample for ferritin testing will collected before the start of infusion on cycle 1 day 1.
b Pre-dose ECG will be performed within 10 minutes prior to start of infusion.
c The planned times assume an infusion duration of 60 min. If the infusion duration is shorter or longer, the PK sample times for the end of infusion sample and all subsequent Day 1 samples should be adjusted accordingly (timings calculated from the end of infusion, as indicated in the column 'Time Point') and the actual times recorded in the eCRF.
d Only required in Cycle 1
e End of infusion ECG will be performed within 10 minutes prior to the end of infusion
f PK sample must be taken within 5 min after the end of infusion. Cytokine sample must be taken within 30 min after the end of infusion.
g Only required in Cycles 5 and 6

10.4 STATISTICAL APPENDIX INCLUDING MODEL PERFORMANCE AND DATA SCENARIOS

Table 10.4: 1 Provisional dose levels for escalation in Schedule A

Dose level	Proposed dose	Increment from previous dose
1	0.05 mg/kg/q3w	
2	0.1 mg/kg/q3w	100%
3	0.2 mg/kg/q3w	100%
4	0.4 mg/kg/q3w	100%
5	0.8 mg/kg/q3w	100%
6	1.6 mg/kg/q3w	100%
7	2.4 mg/kg/q3w	50%
8	3.3 mg/kg/q3w (predicted efficacious human dose)	38%
9	4.5 mg/kg/q3w	36%
10	6.2 mg/kg/q3w	38%
11	8.5 mg/kg/q3w	37%

A table of provisional dose levels for escalation in Schedule A is provided (Table 10.4:1) to support the simulations of the dose escalation plan. Additionally, the prior probabilities of DLTs at different doses, as well as the corresponding probability of under-, targeted and overdosing, are shown in Table 10.4: 2. Graphically, the prior medians with accompanying 95% credible intervals are shown in Figure 10.4: 1. As can be seen from both the table and the figure, the prior medians of the DLT probabilities are in line with the prior medians derived from the weakly informative prior, and the uncertainty around the medians is large, showing the low amount of information this prior provides. This is also supported by the prior sample size, i.e., the information contained in the prior. This is approximately equal to 1.6 patients.

Table 10.4: 2: Prior probabilities of DLT at selected doses

Dose	Probability of true DLT rate in					Quantiles		
	[0-0.16)	[0.16-0.33)	[0.33-1]	Mean	SD	2.50%	50%	97.50%
0.05	0.936	0.032	0.032	0.037	0.116	<0.001	0.001	0.400
0.1	0.922	0.039	0.039	0.044	0.127	<0.001	0.002	0.466
0.2	0.903	0.047	0.050	0.055	0.140	<0.001	0.003	0.538
0.4	0.876	0.058	0.065	0.069	0.156	<0.001	0.007	0.617
0.8	0.832	0.078	0.089	0.092	0.177	<0.001	0.015	0.693
1.6	0.76	0.106	0.134	0.129	0.204	<0.001	0.036	0.782
2.4	0.685	0.134	0.182	0.167	0.226	<0.001	0.063	0.836
3.3	0.592	0.162	0.246	0.215	0.250	0.001	0.105	0.882
4.5	0.490	0.172	0.337	0.282	0.288	0.001	0.167	0.948
6.2	0.410	0.161	0.430	0.352	0.321	0.002	0.244	0.987
8.5	0.351	0.147	0.502	0.414	0.344	0.002	0.334	0.998

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

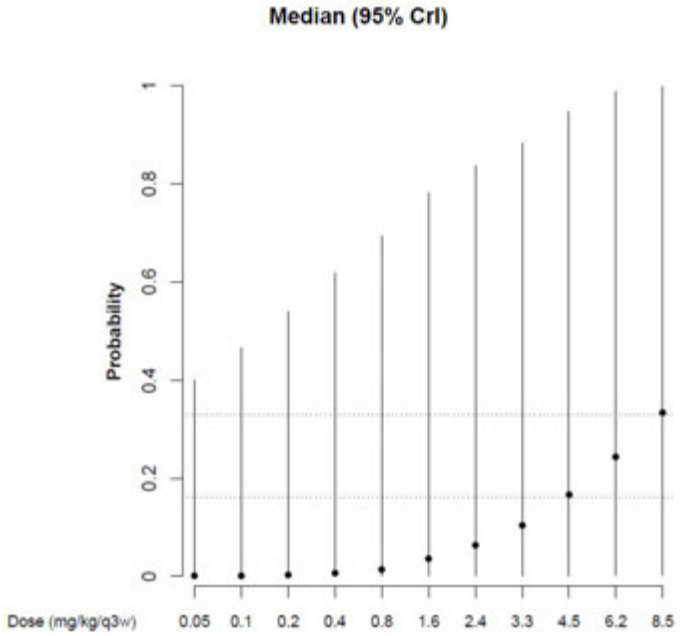

Figure 10.4: 1: Prior medians and 95% credible intervals. Note that the following intervals are marked by the two dashed lines at 0.16 and 0.33: Under dosing: [0.00, 0.16], Targeted toxicity: [0.16, 0.33] and Over toxicity: [0.33, 1.00]

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

Hypothetical data scenarios

Hypothetical data scenarios for dosing Schedule A are shown in Table: 10.4: 3. These scenarios reflect potential on-study data constellations and related escalation as allowed by the model. For each scenario, the probability of overdose for the current dose, as well as the next potential dose and related probabilities of under-dosing, target dose and over-dosing are shown. The actual dose chosen for the next cohort will be determined by the SMC after taking into consideration the recommended dose from the model as well as other relevant data from this study.

In scenarios 2 to 10, it is assumed that no DLT is observed until the dose level of 2.4 mg/kg/q3w, which is one level below the predicted efficacious human dose of 3.3 mg/kg/q3w. To be more specific, in scenario 7, when 1 DLT is observed at 2.4 mg/kg/q3w, the next dose permitted by the model is the same dose level and 3 more patients are enrolled at 2.4 mg/kg/q3w in scenario 8 and observed no DLT. In this case, the model advises to escalate to the next dose level of 3.3 mg/kg/q3w. Assuming 1 DLT is then observed at 3.3 mg/kg/q3w, which is demonstrated in scenario 9, the model proposed to stay at dose level of 3.3 mg/kg/q3w and enroll 3 more patients. Finally in scenario 10, assuming no additional DLT is observed, the criteria for MTD are met and MTD is reached at 3.3 mg/kg/q3w.

In extreme cases when DLT is not observed until the reference dose, the adaptive feature of the model is fully illustrated in scenarios 11, 12 and 13. Despite the fact that no DLTs were observed in the first seven cohorts with 21 patients in total, the model reacts immediately to

the data observed at 3.3 mg/kg/q3w and advises to stay at current dose in scenario with 1 observed DLT in scenario 12 and de-escalate with 2 observed DLTs in scenario 13.

Table 10.4:3 Hypothetical data scenarios for dosing Schedule A

Scenario	Dose (mg/kg/q3w)	# DLT	# Pat	Current Dose: P(OD)	Next Dose (mg/kg/q3w)	Next Dose		
						P(UD)	P(TD)	P(OD)
1	0.05	0	3	0.003	0.1	0.975	0.019	0.006
2	0.05 0.1	0 0	3 3	0.001	0.2	0.978	0.018	0.004
3	0.05 0.1 0.2	0 0 0	3 3 3	0.001	0.4	0.974	0.022	0.004
4	0.05 0.1 0.2 0.4	0 0 0 0	3 3 3 3	<0.001	0.8	0.965	0.029	0.006
5	0.05 0.1 0.2 0.4 0.8	0 0 0 0 0	3 3 3 3 3	0.001	1.6	0.924	0.060	0.016
6	0.05 0.1 0.2 0.4 0.8 1.6	0 0 0 0 0 0	3 3 3 3 3 3	0.003	2.4	0.899	0.075	0.026
7	0.05 0.1 0.2 0.4 0.8 1.6 2.4	0 0 0 0 0 0 1	3 3 3 3 3 3 3	0.082	2.4	0.663	0.255	0.082
8	0.05 0.1 0.2 0.4 0.8 1.6 2.4	0 0 0 0 0 0 1	3 3 3 3 3 3 6	0.027	3.3	0.586	0.267	0.147

Table 10.4:3 – Continued Hypothetical data scenarios for dosing Schedule A

Scenario	Dose (mg/kg/q3w)	# DLT	# Pat	Current Dose: P(OD)	Next Dose (mg/kg/q3w)	Next Dose		
						P(UD)	P(TD)	P(OD)
9	0.05 0.1 0.2 0.4 0.8 1.6 2.4 3.3	0 0 0 0 0 0 1 1	3 3 3 3 3 3 6 3	0.202	3.3	0.403	0.395	0.202
10	0.05 0.1 0.2 0.4 0.8 1.6 2.4 3.3	0 0 0 0 0 0 1 1	3 3 3 3 3 3 6 6	0.070	3.3	0.586	0.344	0.070
11	0.05 0.1 0.2 0.4 0.8 1.6 2.4	0 0 0 0 0 0 0	3 3 3 3 3 3 3	0.006	3.3	0.855	0.098	0.048
12	0.05 0.1 0.2 0.4 0.8 1.6 2.4 3.3	0 0 0 0 0 0 0 1	3 3 3 3 3 3 3 3	0.017	3.3	0.592	0.291	0.117
13	0.05 0.1 0.2 0.4 0.8 1.6 2.4 3.3	0 0 0 0 0 0 0 2	3 3 3 3 3 3 3 3	0.433	2.4	0.641	0.297	0.062

Operating characteristics

Operating characteristics are a way to assess the long-run behaviour of a model. Under an assumed true dose-toxicity curve, metrics such as the probability of recommending a dose with true DLT rate in the target interval can be approximated via simulation. In order to assess the operating scharacteristics of the model, we assume 5 true dose-toxicity scenarios. As is shown in Table 10.4: 4, these scenarios reflect a wide range of possible cases as follows:

- Scenario 1: The true dose-toxicity relationship is aligned with prior means
- Scenario 2: Very high toxicity values are assumed corresponding to the respective dose levels
- Scenario 3: Very low toxicity values are assumed corresponding to the respective dose levels
- Scenario 4: A non-logistic dose-toxicity relationship is assumed
- Scenario 5: Low toxicity values followed by high toxicity values are assumed, i.e. a very steep dose-toxicity curve is adopted.

Table 10.4: 4 Assumed true dose-toxicity scenarios (Schedule A)

P(DLT)	Dose (mg/kg/q3w)										
Scenario	0.05	0.1	0.2	0.4	0.8	1.6	2.4	3.3	4.5	6.2	8.5
1 (Prior)	0.037	0.045	0.055	0.074	0.092	0.129	**0.167**	**0.215**	**0.282**	0.352	0.414
2 (High Tox)	0.110	0.130	0.150	**0.170**	**0.190**	**0.260**	**0.320**	0.400	0.480	0.550	0.610
3 (Low Tox)	0.020	0.035	0.050	0.070	0.090	0.110	0.150	**0.180**	**0.220**	**0.250**	**0.270**
4 (Non-Logistic)	0.040	0.070	0.090	0.140	**0.190**	**0.220**	**0.250**	**0.280**	**0.310**	0.350	0.380
5 (Low-High)	0.030	0.050	0.080	0.105	0.130	**0.160**	**0.280**	0.350	0.390	0.430	0.470

Bold numbers indicate true DLT rates in the target interval [0.16, 0.33].

For each of these scenarios, 1000 trials were simulated based on dosing Schedule A. It was then assessed how often a dose was declared as MTD with true DLT rate in the under-, targeted or over-dose range. Furthermore, the average, minimum and maximum number of patients per trial and the average number of DLTs per trial are reported. Results are shown in Table 10.4: 5.

Table 10.4: 5 Simulated operating characteristics (Schedule A)

Scenario	% of trials declaring an MTD with true DLT rate in				# Patients	# DLT
	underdose	Target dose	overdose	STOPPED	Mean (Min – Max)	Mean (Min – Max)
1	24.4	60.5	14.5	0.6	23.13 (3 – 48)	3.61 (1 – 12)
2	15.6	70.9	8.2	5.3	19.13 (3 – 45)	4.08 (1 – 12)
3	35.0	64.6	0	0.4	23.78 (3 – 45)	3.24 (1 – 9)
4	15.7	75.6	7.6	1.1	20.51 (3 – 48)	3.66 (1 – 11)
5	30.1	46.4	22.9	0.6	21.80 (3 – 51)	3.95 (1 – 14)

Scenario 1 reflects the case that the true dose-toxicity is aligned with prior means, 60.5% of the simulated trials declared a dose as MTD with true DLT rate in the targeted dose range.

In scenario 2 (high-toxicity scenario), the starting dose has a probability of 0.11 to observe DLTs in the first cohort. This contributes to the high percentage (5.3%) of all simulated trials for which the trial is stopped since none of the doses is considered tolerable anymore. This is an expected situation for a high-toxicity scenario.

Scenario 3 (low-toxicity scenario) shows, that even with small toxicity rates the model declares MTDs with true DLT rate in the targeted interval in a high percentage of trials (64.6%). Since none of the pre-defined dose levels has a true DLT rate in the overdose range, only very few trials (0.4%) are stopped prematurely.

In scenarios 4 and 5, 75.6% and 46.4% of the simulated trials declared a dose as MTD with true DLT rate in the targeted dose range, respectively.

The mean patient numbers range from 19.13 patients (high-toxicity scenario) to 23.78 patients (low-toxicity scenario) and the maximum number of patients was 51. Therefore, the patient numbers are as expected and increase when moving away from the high-toxicity scenario.

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

Hypothetic scenarios and operating characteristics for dosing Schedule B will be derived once the MTD of Schedule A is determined and updated for each dose cohort. Similarly in Schedule B, the actual dose chosen for the next cohort will be determined by the SMC after taking into consideration the recommended dose from the model as well as other relevant data from this study.

10.5 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

R01-0787

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		23 May 2018
EudraCT number		2017-002945-31
BI Trial number		1401-0001
BI Investigational Product(s)		BI 905677
Title of protocol		An open-label, Phase I trial to determine the maximum-tolerated dose and investigate safety, pharmacokinetics and efficacy of BI 905677 administered intravenously in patients with advanced solid tumours
To be implemented only after approval of the IRB / IEC / Competent Authorities		X
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		All sections
Description of change		Phase Ib (dose expansion) part of study removed throughout the protocol.
Rationale for change		Details of planned dose expansion cannot be provided yet and therefore will be added later when available.
Section to be changed		All sections
Description of change		Optional tumour biopsy and corresponding blood sample for DNA analysis removed throughout the protocol.
Rationale for change		A re-evaluation of the benefits and risks of obtaining tumour samples led to the conclusion that tumour biopsies were no longer required during the dose escalation phase.
Section to be changed		Synopsis and 2.1.2
Description of change		Primary endpoint changed from ‘Number of patients experiencing drug-related AEs during the

		entire treatment period' to 'Number of patients experiencing AEs during the entire treatment period'
Rationale for change		To reflect that all AEs will be taken into consideration.
Section to be changed		Synopsis and sections 3.3, 3.3.1 and 3.3.2
Description of change		Added inclusion requirement that patients must have exhausted treatment options known to prolong survival for their disease.
Rationale for change		To ensure that an appropriate patient population is considered for the trial.
Section to be changed		Synopsis and section 4.1.2
Description of change		Starting dose in Schedule B will not be pre-specified but will be determined using the MTD from Schedule A. Separate MTDs will be determined for Schedule A and Schedule B.
Rationale for change		Schedule A and B will now be performed sequentially so information from Schedule A can be used to determine the most appropriate starting dose in Schedule B.
Section to be changed		All sections
Description of change		CTCAE updated from version 4.03 to version 5.0 throughout
Rationale for change		Administrative change to ensure latest version is used
Section to be changed		Flowchart and sections 4.1.4.3 and 5.2.2
Description of change		Additional guidance provided on frequency of monitoring of vital signs during and after infusion.
Rationale for change		To ensure consistent monitoring of patients in the trial.
Section to be changed		Flowchart and section 5.2.3
Description of change		Vitamin D testing added
Rationale for change		Additional safety monitoring
Section to be changed		Flowchart and section 5.2.5.4
Description of change		Ophthalmologic assessments added
Rationale for change		To ensure consistent and adequate monitoring of patients for ophthalmologic toxicity.
Section to be changed		Footnote to flowcharts, section 1.2.1, and section 8.7
Description of change		Correction of spelling and grammatical errors
Rationale for change		Correction

Section to be changed		Footnote to flowchart and section 5.2.5.1
Description of change		Addition of bone biomarker sample at Cycle 2 Day 1 in both schedules
Rationale for change		To ensure that early changes to bone biomarkers are detected.
Section to be changed		Footnote to flowcharts, section 5.2.5.3, 10.2 and 10.3
Description of change		Additional of further cytokine sample timepoints and modification of PK and ADA sampling for consistency. Addition of ferritin sampling at baseline and when CRS occurs.
Rationale for change		To ensure that adequate data is collected regarding the potential of BI 905677 to induce Cytokine Release Syndrome.
Section to be changed		Footnote to flowcharts, section 4.1.4 and section 5.2.5.3
Description of change		Modification to requirements for post-infusion monitoring
Rationale for change		To ensure that patients are adequately monitored for Cytokine Release Syndrome.
Section to be changed		Abbreviations
Description of change		Addition of various new abbreviations. Removal of redundant abbreviations.
Rationale for change		Administrative
Section to be changed		1.2.3
Description of change		Further information added regarding the potential of BI 905677 to cause cytokine release syndrome and to be consistent with updated Investigator Brochure.
Rationale for change		To ensure information is available to investigators.
Section to be changed		1.4
Description of change		Further information and references provided regarding the expected safety profile of BI 905677 based on published data from compounds with a similar mechanism of action.
Rationale for change		To provide investigators with further information regarding the risk:benefit of the trial, the potential side effects of treatment and the considerations for management of side effects.
Section to be changed		2.1.1, 3.1 and 4.1.2
Description of change		Trial design updated to perform Schedule A and B

		sequentially.
Rationale for change		Schedule A and B will be performed sequentially in order to eliminate bias in the selection of patients for each Schedule, to allow the MTD of each Schedule to be determined independently and to allow the information from Schedule A to influence the starting dose in Schedule B.
Section to be changed		2.1.1
Description of change		Trial objectives and endpoints updated to reflect deletion of phase Ib dose expansion and separate MTDs for Schedule A and Schedule B
Rationale for change		Administrative
Section to be changed		3.1
Description of change		Trial design changed to allow a maximum dose increase of 100% between dose cohorts and to require at least three patients per dose cohort.
Rationale for change		The dose escalation steps have been made more conservative in order to protect patient safety.
Section to be changed		3.1
Description of change		Rationale for gap of 72 hours between patients added
Rationale for change		Additional explanation
Section to be changed		3.1.1
Description of change		New section added to describe circumstances under which trial would be temporarily stopped to re-evaluate risk/benefit ratio.
Rationale for change		To ensure that clear guidance is available to investigators and SMC regarding events which would necessitate a temporary stop to the trial.
Section to be changed		3.3.2
Description of change		Inclusion criteria 10 changed to add additional requirement to include WOCBP only after a confirmed menstrual period and a negative pregnancy test at screening. WOCBP with irregular menstruation may be included after two negative pregnancy tests during screening between 2 and 4 weeks apart.
Rationale for change		Modified to ensure consistency with ‘Recommendations related to contraception and pregnancy testing in clinical trials’ by the Clinical trial Facilitation Group

Section to be changed		3.3.3
Description of change		Exclusion criteria added to exclude patients with ≥ Grade 2 Osteoporosis and patients with chronic corticosteroid use.
Rationale for change		To ensure that patients at potentially higher risk of toxicity are not included in the trial.
Section to be changed		4.1.2.1
Description of change		Section describing selection of starting dose re-written.
Rationale for change		To be consistent with the IB.
Section to be changed		4.1.3
Description of change		Section updated to reflect that there is no longer a possibility that two dose cohorts in different schedules will be open at the same time.
Rationale for change		Updated to be consistent with new trial design
Section to be changed		4.1.2.2
Description of change		Addition of new section to describe how starting dose for Schedule B will be determined.
Rationale for change		Method of determining starting dose has changed because Schedule A and Schedule B will now be performed sequentially.
Section to be changed		4.1.4.1
Description of change		Minor modifications and further guidance added to re-treatment criteria and guidelines
Rationale for change		To ensure patients are only re-treated when appropriate.
Section to be changed		4.1.4.2
Description of change		Clarification added on identification and handling of different grades of infusion-related reaction.
Rationale for change		Clarification and update to be consistent with new guidance on handling of CRS.
Section to be changed		Addition of new section 4.1.4.3
Description of change		Addition of new section 4.1.4.3 to give guidance on management of Cytokine Release Syndrome
Rationale for change		To ensure that patients are adequately monitored for CRS and that CRS events are adequately managed and treated.
Section to be changed		Addition of new section 4.1.4.4
Description of change		Addition of new section 4.1.4.4 to give guidance on management of bone toxicity
Rationale for change		To ensure consistent and adequate management of

		bone toxicity throughout the trial.
Section to be changed		Addition of new section 4.1.4.5
Description of change		Addition of new section 4.1.4.5 to give guidance on management of retinal toxicity
Rationale for change		To ensure consistent and adequate management of retinal toxicity throughout the trial.
Section to be changed		4.1.4.6
Description of change		Further guidance added for management of Grade 4 non-haematological toxicity and for situations where dose reduction may be considered.
Rationale for change		Further guidance required to ensure consistent management of toxicities.
Section to be changed		4.1.4.7
Description of change		Dose reduction will not be decided by the investigator but will be restricted to the previous dose level tested. Clarification that patients who experience a second occurrence of toxicity requiring dose reduction must permanently discontinue treatment.
Rationale for change		To provide clearer guidance on dose reduction.
Section to be changed		4.2.1
Description of change		Clarification added to indicate that concomitant therapies used as pre-medication prior to BI 905677 infusion will be recorded in the eCRF.
Rationale for change		Clarification
Section to be changed		5.2.4, 10.2 and 10.3
Description of change		Clarification that ECG performed on Day 1 of Cycle should be performed within 10 minutes prior to start of infusion and end of infusion ECG should be performed within 10 minutes prior to end of infusion. Addition of three further ECGs.
Rationale for change		Requirement to add further guidance and for additional ECGs at anticipated maximal plasma concentration.
Section to be changed		5.2.5.2
Description of change		Added requirement to record bone mineral density measurements and to repeat bone densitometry after at least two months if a change in bone mineral density of >5% is observed. Added explanation that SMC will regularly review any reported changes.
Rationale for change		To ensure that changes in bone density are

		followed up so that accurate assessment of DLTs can be made.
Section to be changed		5.2.5.4
Description of change		Addition of new section on ophthalmologic assessment.
Rationale for change		To ensure patients are adequately monitored for retinal toxicity.
Section to be changed		5.2.6.1
Description of change		Addition of further details regarding Cytokine Release Syndrome and addition of Retinal toxicity to the list of Adverse Events of Special Interest
Rationale for change		To ensure that adequate information is captured regarding these events and reported to authorities where required.
Section to be changed		5.2.6.2
Description of change		Clarification that disease progression is not a study endpoint but instead is recorded to enable analysis of efficacy endpoints
Rationale for change		Administrative correction
Section to be changed		5.2.7
Description of change		Additional events have been added to the list of DLTs and existing DLTs have been clarified.
Rationale for change		To ensure that all potential toxicities of BI 905677 are accounted for when assessing the tolerability of the compound.
Section to be changed		7.1, 7.7 and 10.4
Description of change		Statistical models, derivations and simulations updated.
Rationale for change		Updates required due to changes to design of trial.
Section to be changed		8.1
Description of change		Change of formatting to clarify that text is applicable for all countries.
Rationale for change		Administrative correction.
Section to be changed		9
Description of change		Addition of new references used in protocol. Removal of redundant references. Removal of personnel names for unpublished references. Updates to references where status has changed.
Rationale for change		Administrative change

Number of global amendment		2
Date of CTP revision		05 July 2018
EudraCT number		2017-002945-31
BI Trial number		1401-0001
BI Investigational Product(s)		BI 905677
Title of protocol		An open-label, Phase I trial to determine the maximum-tolerated dose and investigate safety, pharmacokinetics and efficacy of BI 905677 administered intravenously in patients with advanced solid tumours
To be implemented only after approval of the IRB / IEC / Competent Authorities		
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		Amendment is neither logistical nor administrative but has been classified as non-substantial in accordance with relevant legislation
Section to be changed		3.3.3 Exclusion criteria
Description of change		New exclusion criterion added 'History of allergy to kanamycin or similar class drugs (including streptomycin, gentamicin, amikacin, tobramycin and neomycin).'
Rationale for change		Trace amounts of kanamycin may be present in the IMP therefore patients who are known to be at risk of allergic reaction will be excluded.
Section to be changed		4.1.4, 4.1.4.3, 5.2.5.3
Description of change		Deletion of '6-hour' from '6-hour post-treatment monitoring period'
Rationale for change		Administrative correction. The post-treatment monitoring period is of variable length.
Section to be changed		4.1.4.6 General management of toxicities
Description of change		Deletion of examples of supportive measures
Rationale for change		Correction of administrative error – examples are not relevant and not required
Section to be changed		10.3
Description of change		Reference to footnote changed from 'c' to 'f'
Rationale for change		Correction of administrative error

Number of global amendment		3
Date of CTP revision		02 August 2018
EudraCT number		2017-002945-31
BI Trial number		1401-0001
BI Investigational Product(s)		BI 905677
Title of protocol		An open-label, Phase I trial to determine the maximum-tolerated dose and investigate safety, pharmacokinetics and efficacy of BI 905677 administered intravenously in patients with advanced solid tumours
To be implemented only after approval of the IRB / IEC / Competent Authorities		X
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		3.3.3 Exclusion criteria
Description of change		Women who are pregnant, nursing, or who plan to become pregnant during the trial. Changed to; Women who are pregnant, nursing, or who plan to become pregnant or nurse during the trial or within 6 months after the last dose of study treatment.
Rationale for change		For consistency with other sections, the exclusion criteria is updated to exclude patients who plan to become pregnant or nurse within 6 months after end of treatment.
Section to be changed		3.3.4.1 Withdrawal from trial treatment
Description of change		Patients who withdraw for a reason other than DLT before completing the first treatment cycle or who miss more than one visit during their first treatment cycle will be replaced. Changed to;

		Patients who withdraw for a reason other than DLT before completing the first treatment cycle, or who do not receive the full planned dose in the first treatment cycle without DLT, or who miss more than one visit during their first treatment cycle will be replaced.
Rationale for change		Patients who do not receive the full planned dose in the first treatment cycle without DLT will be replaced to ensure adequate evaluation of the dose level and accurate determination of the MTD.
Section to be changed		Table 4.1.4.6: 1 Management of toxicity 4.1.4.7 Dose Reduction
Description of change		Clarification of requirements for management of toxicity and dose reduction.
Rationale for change		To ensure consistency between table and text.
Section to be changed		4.2.2.1
Description of change		Addition of the following text 'The use of prophylactic haemotopoietic growth factors (e.g. G-CSF) prior to treatment is prohibited in cycle 1.'
Rationale for change		To ensure adequate assessment of the toxicity/MTD of the study treatment.
Section to be changed		5.2.7
Description of change		Addition of Grade 3 anaemia requiring blood transfusion as a DLT
Rationale for change		To ensure adequate assessment of the toxicity/MTD of the study treatment.
Section to be changed		5.4.1 Biomarker analysis
Description of change		The following text has been added; Data obtained from the analysis of skin biopsies will not be disclosed to patients because the analysis is exploratory. If consent is withdrawn, all samples and the data that had already been collected up to the time of withdrawal of consent will still be used.
Rationale for change		Provision of additional information about skin biopsies.

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Therapeutic Area [redacted]	[redacted]	03 Aug 2018 10:00 CEST
Approval-Clinical Program [redacted]		03 Aug 2018 10:32 CEST
Author-Trial Clinical Monitor		03 Aug 2018 11:22 CEST
Author-Trial Clinical Pharmacokineticist		03 Aug 2018 12:11 CEST
Author-Trial Statistician		03 Aug 2018 15:59 CEST
Verification-Paper Signature Completion		07 Aug 2018 12:26 CEST

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Meaning of Signature	Signed by	Date Signed