Clinical Trial Protocol

	Document Number:	**c29037963-02**
EudraCT No.: **EU Trial No:**	2019-003490-25	
BI Trial No.:	1424-0001	
BI Investigational Product(s):	BI 905681	
Title:	An open-label, Phase I trial to determine the maximum-tolerated dose and investigate safety, pharmacokinetics and efficacy of BI 905681 administered intravenously in patients with advanced solid tumours	
Lay Title:	A trial to find the safe dose for BI 905681 in patients with incurable tumours or tumours that have spread	
Clinical Phase:	Phase I	
Clinical Trial Leader	[redacted] Phone: [redacted] / Fax: [redacted]	
Team Member Medicine	[redacted] Phone.: [redacted] / Fax: [redacted]	
Coordinating Investigator:	[redacted]	
Status:	Final Protocol (revised protocol [based on global amendment 1])	
Version and Date:	**Version: 2.0**	**Date: 15 November 2019**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Finished product name	Not applicable
Active ingredient name:	BI 905681
Protocol date	28 August 2019
Revision date	15 November 2019
Trial number	1424-0001
Title of trial:	An open-label, Phase I trial to determine the maximum-tolerated dose and investigate safety, pharmacokinetics and efficacy of BI 905681 administered intravenously in patients with advanced solid tumours
Coordinating Investigator	[redacted]
Trial site(s):	5 sites
Clinical phase:	Phase I
Objective(s):	The primary objective of this trial is to determine the maximum tolerated dose (MTD)/optimal biological dose (OBD) of BI 905681 given as an intravenous infusion and to determine the recommended dose and dosing schedule for further trials in the development of BI 905681. The MTD will be defined based on the frequency of patients experiencing dose-limiting toxicities (DLTs) during the MTD/DLT 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 (PK) profile of BI 905681. [redacted]
Methodology:	This is a Phase I, open-label, non-randomised study of BI 905681 administered intravenously as a single agent. The trial aims to test two different dosing schedules for BI 905681 (Schedule A: q3w in a 3-week cycle and Schedule B:q2w in a 4-week cycle) 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.

Number of patients entered:	It is anticipated that approximately 60 patients (30 per dosing schedule) will be enrolled in the trial.
Diagnosis :	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.

in- and exclusion criteria	Inclusion 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.
	• Patients (only those who harbour a historically confirmed RNF43 mutation or R-spondin fusion) willing to undergo mandatory tumour biopsy at the time points specified in the protocol.
	• Eastern Cooperative Oncology Group Score of 0 or 1 (R01-0787).
	• 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
	• 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 • 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 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 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 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 4 months after the last dose of BI 905681. A list of contraception methods meeting these criteria is provided in the patient information. Exclusion criteria • 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 • 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 • Osteoporosis ≥ CTCAE Grade 2 • Chronic corticosteroid use, except as permitted for the maintenance therapy of brain metastases (see Exclusion Criterion 13) • Osteoporotic compression fracture within 12 months prior to informed consent which is clinically significant in the opinion of the investigator. • Patient who must or wishes to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial. • Previous treatment in this trial. • 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. • 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

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

	efficacy of the test drug. • 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. • Active alcohol or drug abuse in the opinion of the investigator. • Patient unwilling or unable to comply with the protocol. • 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. • 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. • History of Grade 3 hypersensitivity reactions (including cytokine release syndrome) to monoclonal antibodies. • History of allergy to kanamycin or similar class drugs (including streptomycin, gentamicin, amikacin, tobramycin and neomycin).
Test product(s):	BI 905681
Dose :	Increasing doses of BI 905681 starting at 1.0 mg/kg/q3w. Dose escalation will be guided by a Bayesian logistic regression model (BLRM) with overdose control until the MTD/OBD is reached.
Mode of administration:	Intravenous infusion
Duration of treatment:	Administration will continue until progression of disease (PD), unacceptable toxicity
Endpoints	The primary endpoints of the trial are: • The MTD/OBD of BI 905681. The MTD will be assessed based on the number of patients experiencing DLTs, graded according to Common Terminology Criteria for Adverse Events (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 • Number of patients experiencing adverse events (AEs) during the entire treatment period The secondary endpoints of the trial are: • The following PK parameters of BI 905681 will be evaluated after the first administration of BI 905681 (if feasible): o C_{max}: maximum measured concentration of BI 905681 in serum after first infusion o AUC_{0-tz}: area under the serum concentration-time curve over the time interval from 0 to the last measured time point (t_z)

	[redacted]
Safety criteria:	Adverse events (AEs) according to CTCAE Version 5, incidence of DLTs for determination of the MTD/OBD, results of physical examinations, laboratory evaluations, vital signs, and electrocardiograms (ECGs).
Statistical methods:	The trial will be performed as an open-label study. The objective of the design is to determine the MTD of BI 905681 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. Separate MTDs will be determined for Schedule A and Schedule B.

FLOW CHART: BI 905681 (REFMAL 638) SCHEDULE A TRIAL ASSESSMENTS

Schedule A Flow Chart **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***** ±72 hrs	**Day 2†** ±1 day	**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) [b]	X	X			X[b]		X	
Safety laboratory blood tests and urinalysis[c]	X	X			X	X	X	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 assessment[h]	X	Repeated if clinically indicated						
Height	X							
Weight	X	X					X	
Tumour Assessment[i]	X	Every 6 weeks (± 7 days) from start of treatment until documented progression						
Tumour Biopsy	X[j]		X[j]					
Blood sample for bone biomarkers[k]		X[k]					X	
Blood samples for cytokine release testing		X[l]	X[l]					
Blood samples for pharmacokinetics[m]		X[m]	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 905681 Infusion[o]		X						

Schedule A Flow Chart **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***** ±72 hrs	**Day 2†** ±1 day	**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**
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.

** 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, Eastern Cooperative Oncology Group (ECOG) performance status, vital signs, ECG, safety laboratory blood tests, urinalysis, pregnancy test, weight) do not need to be performed if done within 3 calendar days (during the Screening visit) and in the opinion of the investigator a repeat assessment 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.

†Cycle 2 only

a Vital signs measurement on day of infusion as specified in Section 5.2.2

b ECG required on Day 8 of Cycle 1,but not on Day 8 of Cycle 2 and subsequent cycles.

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 at Screening, on Day 1 of every third cycle (i.e. Cycle 3 Day 1, Cycle 6 Day 1) and at the EOT.

f Pregnancy test is only required for women of childbearing potential.

g Bone densitometry at the EOT visit is not required if bone densitometry has been performed within the previous 4 weeks.

h Ophthalmologic assessment will be performed for all patients at Screening visit and if the patient develops visual symptoms during the trial. The following assessments should be performed: BCVA, colour fundus photography, and spectral domain optical coherence tomography (SD-OCT) (see Section 5.2.5.4).

i 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. 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.

j Pre- and on-treatment tumour biopsy collections for biomarker analyses are mandatory from all patients who have a historically confirmed RNF43 mutation or R-spondin fusion entering the trial from Cohort 2 A total of 2 tumour biopsies are required. The first tumour biopsy may be obtained any time prior to the first dose. For a fresh baseline sample a minimum of 2 core needle biopsies or 1 punch biopsy must be taken between Screening and the day before first treatment with BI 905681. An archival sample, from the most recent relapse, will be acceptable as the pre-treatment biopsy, if taken within 6 months of trial start. A second tumour biopsy sample (two core-needle biopsies or 1 punch biopsy, preferably from the same

lesion) will be obtained 24 hours after Cycle 2 infusion (the on-treatment biopsy time point may be adapted based on PK analysis).See Section 5.4.1.

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 and the EOT visit.

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 905681 and for 3 hours following subsequent administrations if the previous administrations were well-tolerated.

FLOW CHART: BI 905681 (REFMAL 638) SCHEDULE B TRIAL ASSESSMENTS

Schedule B Flow Chart **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*** ±72 hrs**	**Day 2† ±1 day**	**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) [b]	X	X			X[b]	X[b]		X	
Safety laboratory blood tests and urinalysis[c]	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[h]	X	Repeated if clinically indicated							
Height	X								
Weight	X	X				X		X	
Tumour Assessment[i]	X	Every 8 weeks (± 7 days) from start of treatment until documented progression							
Tumour Biopsy	X[j]		X[j]						
Blood sample for bone biomarkers[k]		X[k]						X	
Blood samples for cytokine release testing		X[l]	X[l]			X[l]			
Blood samples for pharmacokinetics[m]		X[m]	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

Schedule B Flow Chart **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*** ±72 hrs**	**Day 2† ±1 day**	**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**
Assess eligibility for further treatment		X[o]				X[o]			
BI 905681 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.

** 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.

† Cycle 2 only

a Vital signs measurement on day of infusion and as specified in Section 5.2.2.

b ECG required on Day 8 and 15 of Cycle 1, but not on Day 8 and 15 of Cycle 2 and subsequent cycles.

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 at Screening, on Day 1 of every third cycle (i.e. Cycle 3 Day 1, Cycle 6 Day 1) and at the EOT.

f Pregnancy test is only required for women of childbearing potential.

g Bone densitometry at the EOT visit is not required if bone densitometry has been performed within the previous 4 weeks.

h Ophthalmologic assessment will be performed for all patients at Screening visit and if the patient develops visual symptoms during the trial. The following assessments should be performed: BCVA, colour fundus photography, SD-OCT (see Section 5.2.5.4).

i 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.

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.

j Pre- and on-treatment tumour biopsy collections for biomarker analyses are mandatory from all patients who have a historically confirmed RNF43 mutation or R-spondin fusion entering the trial from Cohort 2 A total of 2 tumour biopsies are required. The first tumour biopsy may be obtained any time prior to the first dose. For a fresh baseline sample a minimum of 2 core needle biopsies or 1 punch biopsy must be taken

between Screening and the day before first treatment with BI 905681. An archival sample, from the most recent relapse, will be acceptable as the pre-treatment biopsy, if taken within 6 months of trial start. A second tumour biopsy sample (two core-needle biopsies or 1 punch biopsy, preferably from the same lesion) will be obtained 24 hours after Cycle 2 infusion (the on-treatment biopsy time point may be adapted based on PK analysis). See Section 5.4.1.

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 and the EOT visit.

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 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 10.2.

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 905681 and for 3 hours following subsequent administrations if the previous administrations were well-tolerated.

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ABBREVIATIONS

ADA	Anti-drug antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine transaminase
ANC	Absolute neutrophil count
AST	Aspartate transaminase
AUC	Area under the Curve
BAP	Bone Alkaline Phosphatase
ß-CTX	Beta- Carboxy-terminal Telopeptide
BI	Boehringer Ingelheim
BLQ	Below the limit of quantification
BCVA	Best Corrected Visual Acuity
BLRM	Bayesian logistic regression model
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	Clearance
CR	Complete Response
CRA	Clinical Research Associate
CRC	Colorectal Cancer
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract research organization
CRS	Cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
DCR	Disease control rate
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EDTA	Ethylendiaminetetracetic Acid
EMA	European Medicines Agency
EOT	End of Treatment
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
GLP	Good Laboratory Practice
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
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
i.v.	Intravenous
LDH	Lactate Dehydrogenase
LPDD	Last Patient Drug Discontinuation
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMTV	Mouse Mammary Tumour Virus
MRSD	Maximum recommended starting dose
MST	Medical Sub Team
MTD	Maximum tolerated dose
NCA	Non-compartmental analysis
NOAEL	No-observed-adverse-effect level
NSCLC	Non-small cell lung cancer
OBD	Optimal biological dose
ORR	Objective response rate
P1NP	N-terminal Propeptide of Type 1 Procollagen
PD	Progressive disease
PDc	Pharmacodynamics
PFS	Progression Free Survival
PK	Pharmacokinetics
p.o.	per os (oral)
PR	Partial Response
q2w/q3w	Every 2 weeks/ every 3 weeks
RDE	Recommended Dose for Expansion
RECIST	Response Evaluation Criteria in Solid Tumours
REP	Residual Effect Period
RNF	Ring Finger Protein
RP2D	Recommended Phase 2 dose
RSD	Recommended Starting Dose
SAE	Serious Adverse Event
SD	Stable Disease
SD-OCT	Spectral domain optical coherence tomography
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
TK	Toxicokinetic
TNBC	Triple Negative Breast Cancer
TRACP	Tartrate-resistant Acid Phosphatase
TSAP	Trial Statistical Analysis Plan
ULN	Upper limit of normal
WHO	World Health Organization
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Despite the recent advancements in 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 promote cancer cell proliferation and resistance to chemotherapy/immunotherapy. An antagonistic paratopic antibody that binds LRP5 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 an LRP5 antagonist may constitute a valid therapeutic option against cancer and supports testing of BI 905681 in humans with the objective to improve patients' outcome. The first step in clinical development is this first in human trial to define the safety profile of BI 905681 and the Maximum tolerated dose (MTD)/ Optimal Biological Dose (OBD)for further development.

The most recent and more detailed information is available in the current Investigator's Brochure (IB) (c27125909-01).

1.2 DRUG PROFILE

1.2.1 Pharmacology

BI 905681 is a new biological entity consisting of three modules: two modules (bi-paratopic) binding to distinct epitopes of LRP5 and one module binding to human serum albumin (HSA) for half-life extension. The three modules are [redacted] connected by two peptide linkers. BI 905681 binds to LRP5 and blocks binding of Wnt ligands to the co-receptor complex, leading to inhibition of Wnt/β-catenin signaling.

The Wnt ligands, which bind to LRP5 and Frizzled receptor leading to activation of downstream signaling, can be divided into Wnt1class and Wnt3a class, each requiring different domains of LRP5 for signaling (R17-1851). In particular, BI 905681 antagonistically binds to these different domains of LRP5 receptor (bi-paratopic binding), thereby blocking Wnt signaling mediated by both Wnt1 and Wnt3a class ligands, leading to:

- Inhibition of LRP5 phosphorylation,
- Activation of β-catenin degradation complex formed by APC/Axin/GSK3β,

- Blockade of β-catenin nuclear translocation and binding to the TCF transcription factors, and
- Inhibition of transcription of Wnt/β-catenin target genes.

Blockade of LRP5 phosphorylation and inhibition of transcription of Wnt/β-catenin target genes (Axin2 and Notum), can be monitored in vivo as direct and indirect biomarkers for selective pathway engagement, respectively, in a Wnt driven tumor xenograft tissue (n00267727). Inhibition of Wnt target gene expression in tumor cells is necessary but not sufficient for antitumor efficacy (in vitro and in vivo), indicating that it represents a pharmacodynamic (PDc) biomarker, but not a biomarker of response to treatment with BI 905681. In mice PDc biomarker modulation can be monitored in vivo using skin as surrogate tissue via detection of Axin2 and Notum gene expression (n00267728).

LRP5 and LRP6 mediated Wnt pathway activation is regulated by the E3 ligase RNF43 and the secreted R-spondin proteins. RNF43 inhibits Wnt pathway activation by inducing the degradation of the Frizzled/LRP5 or LRP6 receptor complex via endocytosis. The RNF43 gene has been found to be frequently mutated/ inactivated in a subset of colorectal cancer (CRC) and pancreatic ductal adenocarcinoma samples (R17-1850). Furthermore, in a separate study, activating R-spondin fusion transcripts, leading to aberrantly inactivating RNF43 mutations have been shown to enhance ligand dependent Wnt signaling in vitro by increasing the abundance of Frizzled receptors on the cell surface.
Nonclinical proof of concept (inhibition of Wnt/β-catenin signaling and efficacy) was demonstrated with BI 905681 in mechanistic Wnt-driven and disease-relevant models harbouring RNF43 mutations. In particular, BI 905681 demonstrated effective blockade of ligand-dependent Wnt signaling in in vitro (RNF43 mutant pancreatic cancer cell lines and RNF43 mutant CRC patient-derived organoids) and *in vivo* models (Wnt driven breast cancer xenograft), as detected by reduction of Axin2 expression (and Notum gene expression in the *in vivo* model). Furthermore, BI 905681 demonstrated in vitro inhibition of cell viability and potent *in vivo* anti-tumor activity in the cancer models mentioned above. In contrast, BI 905681 did not block Wnt signaling (i.e. lack of inhibition of Axin2 expression) nor affect cell viability in RNF43 wild type pancreatic cancer cell and RNF43 wild type CRC patient derived organoid models, supporting the proposed patient enrichment biomarker strategy (n00267725, n00267729).

1.2.2 Pharmacokinetics

The pharmacokinetics (PK) for BI 905681 were investigated in the cynomolgus monkey in a single dose PK and immunogenicity study and a repeat dose toxicokinetic (TK) and immunogenicity study. BI 905681 demonstrated dose-proportional increases in C_{max} and AUC with increasing dose levels in these studies. Human i.v. PK for BI 905681 was predicted using single species scaling from cynomolgus monkey to human using a Dedrick plot. The PK curves were fitted using a 2-compartment model.

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 905681 is 1.4 mg/kg i.v. q1w. Alternatively, a less frequent dosing schedule can be chosen while keeping the C_{plasma} trough level constant, e.g. 3.5 mg/kg i.v. q2w or 6.6 mg/kg i.v. q3w.

1.2.3 Toxicology

The toxicity profile for BI 905681 has been assessed in repeat dose toxicity studies in monkeys and mice, an in vitro cytokine release assay, and an in vitro hemocompatibility study. The 4-week Good Laboratory Practice (GLP) repeat dose study in monkeys included safety pharmacology (cardiovascular, respiratory, and neurological function) and immunotoxicology endpoints.

A traditional tissue cross reactivity (TCR) study on cryosections of normal human tissues using immunohistochemistry was not conducted with BI 905681 due to the high nonspecific background staining of non-target-expressing cell types or non-cellular elements (e.g. interstitial matrix). However, a target tissue distribution study was conducted to determine the distribution of LRP5 in formalin-fixed, paraffin embedded human tissues. LRP5 staining was present in the stomach, small intestine, large intestine, salivary gland, endocrine pancreas, thyroid, kidney, ureter, urinary bladder, uterus, fallopian tube, placenta, testis, breast tissue, and brain. LRP5 staining was generally comparable between humans and cynomolgus monkeys.

The ready-to-use solution of BI 905681 (10 mg/mL in 25 mM acetate, 230 mM trehalose dihydrate, 0.05% (w/v) polysorbate 20, pH 5.5) demonstrated no hemolytic potential in human whole blood.

In repeat dose toxicity studies in monkeys, no mortality was observed. Once weekly intravenous administration of BI 905681 for up to 4 weeks (total 5 doses) and up to 150 mg/kg/dose in the cynomolgus monkey was well tolerated and resulted in no adverse findings in any of the parameters examined. In the 4-week repeat dose toxicity study, there were non-adverse trends for or slight decreases in bone formation markers (bone specific alkaline phosphatase (BAP) and/or procollagen type 1 amino-terminal propeptide (P1NP)) as a result of Wnt signaling inhibition by BI 905681, but no changes in bone resorption markers (β-Carboxy-terminal Telopeptide (β- CTx) and TRACP-5b) or microscopic correlates. The potential effect on bone mass can be monitored by serum bone biomarkers and bone densitometry assessment during the clinical development.

In addition, the implementation of an ophthalmologic monitoring plan is recommended if the patient displays visual symptoms during BI 905681 treatment.

The no-observed-adverse-effect level (NOAEL) was determined to be 150 mg/kg/dose q1w, and this dose is also considered as the highest non-severely toxic dose (HNSTD) in the 4-week monkey study. At 150 mg/kg/dose q1w, the steady state mean exposures were 5,290 µg/mL (C_{max}) and 498,000 µg•h/mL (AUC_{0-168h}). These exposures are 88X, 50X, and 31X (C_{max}), or 73X, 46X, and 29X (AUC_{0-168h}) to the estimated exposure at a 1.4 mg/kg q1w, 3.5 mg/kg q2w, and 6.6 mg/kg q3w therapeutic dose, respectively.

Collectively, the nonclinical package of pharmacology, pharmacokinetics, safety studies and data support the administration of BI 905681 to patients with advanced cancers. To date, no clinical trials have been conducted with BI 905681.

For a more detailed description of the BI 905681 profile please refer to the current IB.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Based on the pre-clinical studies summarized in the previous section, the observed anti-tumour activity and safety profile warrant clinical testing of BI 905681 monotherapy in patients with advanced solid tumours. The therapeutic benefit or specific adverse events in patients cannot always be anticipated during the trial setup. As the trial progresses there may be new scientific knowledge about biomarkers and other factors contributing to diseases or the action of a drug.

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 905681 is a first-in-class compound with no prior testing in humans, the risks of treatment have been evaluated based on the expected effects of targeting the Wnt pathway (R17-4168) and on the nonclinical toxicology data.

Under normal conditions, 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. In preclinical mouse models (1) specific ablation of LRP5 in intestinal cells had no effect on intestinal epithelial cell homeostasis which is attributed to the compensatory role of LRP6-mediated Wnt signaling in the mouse intestinal development (R17-1470); and (2) specific ablation of LRP5 in mature osteoblasts showed reduced bone density, but the phenotype was more pronounced in the absence of both LRP5 and LRP6 with the development of severe osteopenia (R18-0131).

Several compounds targeting the Wnt pathway, but with a different mechanism of action compared to BI 905681 which selectively inhibits Wnt ligand dependent pathway activation, have been and continue to be studied in clinical trials. These compounds include vantictumab (anti-frizzled receptor antibody), ipafricept (frizzled 8 IgG fusion protein), 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 events including nausea, vomiting and diarrhoea were documented as frequent drug related adverse reactions (R17-4166, R17-4167, R17-4168, R18-1490). In clinical studies of vantictumab, rosmantuzumab, ipafricept 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.

A 4-week GLP monkey toxicology study revealed that BI 905681 at dose levels up to 150 mg/kg/dose q1w was very well tolerated with no adverse effects. Slight decreases of bone formation biomarkers (BAP and P1NP) were observed and were considered on target related effects. These changes were considered non-adverse based on minimal severity and lack of histopathology findings in bones. Bone resorption markers were not affected. No other on- or off-target effects of BI 905681 have been observed; thus, the no-observed-adverse-effect level (NOAEL) or the highest non-severely toxic dose (HNSTD) was determined to be 150 mg/kg/dose q1w in the monkey, the most relevant toxicology species.

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, and 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 3.1.1 and 4.1.6.4).

Although the nonclinical GLP toxicology study of BI 905681 did not reveal a risk to induce cytokine release syndrome (CRS), patients will be monitored and guidelines for management of potential cytokine release syndrome are provided and must be followed thoroughly (see Section 4.1.6.3).

There were no BI 905681-related abnormal effects on the eyes (ophthalmological and microscopic examinations) observed in the 4-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. 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 colour vision changes) the same ophthalmologic assessment will be repeated. Guidelines for management of potential retinal toxicity are provided (see Section 4.1.6.5). Monitoring of asymptomatic patients with spectral domain optical coherence tomography (SD-OCT) and full ophthalmologic exams is not needed based on published literature. The published literature of related competitors do not include retinopathy or any other retinal toxicity as drug-related adverse event.

Throughout the study the safety of the participants will be monitored regularly by a Safety Monitoring Committee (SMC). 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 905681 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 Objectives

The primary objective of this trial is to determine the maximum tolerated dose (MTD)/optimal biological dose (OBD) of BI 905681 given as an intravenous infusion and to determine the recommended dose and dosing schedule for further trials in the development of BI 905681. The MTD will be defined based on the frequency of patients experiencing dose-limiting toxicities (DLTs) during the MTD/DLT 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 (PK) profile of BI 905681.

2.1.2 Primary endpoint(s)

The primary endpoints of the trial are:
- The MTD/OBD of BI 905681. The MTD will be assessed based on the number of patients experiencing DLTs, graded according to Common Terminology Criteria for Adverse Events (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
- Number of patients experiencing adverse events (AEs) during the entire treatment period

2.1.3 Secondary endpoint(s)

The secondary endpoints of the trial are:
- The following PK parameters of BI 905681 will be evaluated after the first administration of BI 905681 (if feasible):
    - C_{max}: maximum measured concentration of BI 905681 in serum after first infusion
    - $AUC_{0\text{-}tz}$: 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 905681 administered intravenously as a single agent.

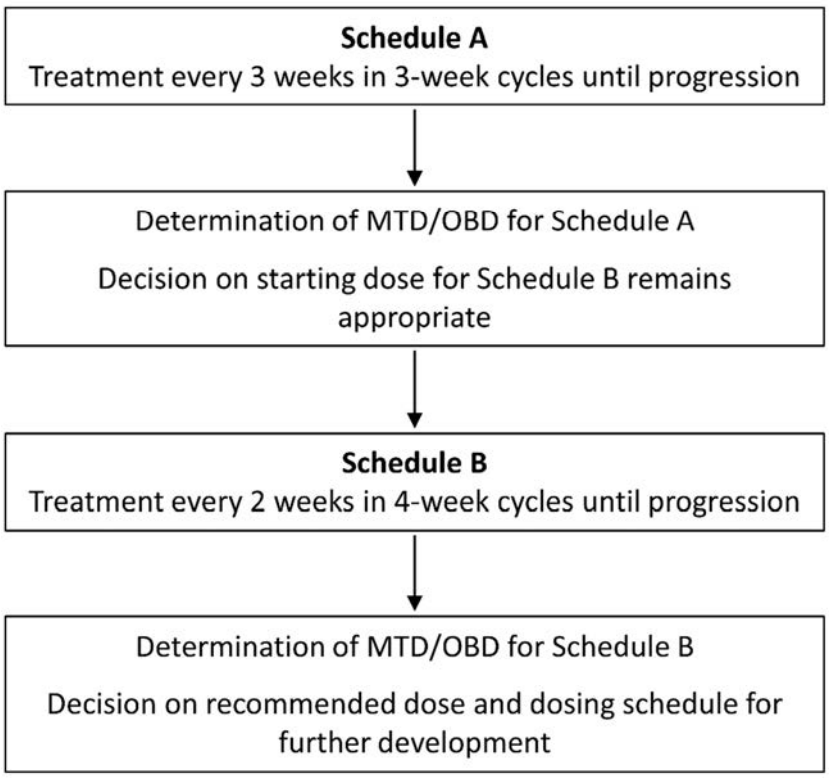


Figure 3.1: 1 Trial Design

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 aims to test two different dosing schedules for BI 905681 (every 3 weeks (q3w) in a 3-week cycle and every 2 weeks (q2w) in a 4-week cycle) 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/OBD of Schedule A is reached. The

starting dose in Schedule B will be determined by the SMC. The SMC will also review whether the planned dosing schedule, assessments and sample collection in Schedule B remain appropriate, and may decide not to pursue testing of another Schedule. 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 905681 until the MTD/OBD is reached. Dose escalation steps will depend on the observed AEs and occurrence of DLTs during the first treatment cycle. However, relevant safety information from all treatment cycles will be considered for the determination of the MTD/OBD and recommended dose for further development. In each dose cohort a minimum of 2 patients will be treated until a first AE of CTCAE Grade ≥2 occurs during the DLT evaluation period (the first cycle of treatment), excluding AEs which are clearly related to disease progression or concurrent illness. In that case a minimum of 3 patients will be treated at the recruiting cohort and subsequent dose cohorts. The SMC may also recommend the size for the next dose escalation cohort or recommend expanding the size of the recruiting cohort.

Starting at dose Cohort 2 the aim is to recruit a minimum of 2 patients with solid tumours harbouring the RNF43 mutation or R-spondin fusion. In case fewer than 2 patients harbouring the RNF43 mutation or R-spondin fusion can be recruited to the current dose cohort, additional patients harbouring the RNF43 mutation or R-spondin fusion will be recruited as “back-filled” cohorts. Patients included in the “back-filled” cohorts will be treated at a dose level below the current dose level being investigated. These patients will be used to permit correlation between exposure and PDc effects. The safety data from the “back-filled” patients will be evaluated additionally in a descriptive manner and provided to the SMC.

As soon as all patients enrolled for safety evaluation on a dose level have completed the MTD evaluation period, a BLRM with overdose control will be applied using all available data (from both the main cohorts and the “back-filled” cohorts) to determine the next permitted dose level and evaluate MTD. The overdose risk will then be calculated for each preliminary dose level from Table 4.1.3: 1 and dose escalation will be permitted to all doses which fulfil the EWOC criterion. Specifications and details of the BLRM are depicted in Section 7.1 and Appendix 10.3. 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.

In case an MTD cannot be determined, and pharmacometric modelling and simulation has demonstrated that the dose levels reached provide the required exposure over the dosing interval, the SMC can decide to stop dose escalation and recommend a dose for further clinical development.

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. After the criterion for MTD is fulfilled, there will be no further dose escalation regardless of the SMC recommendation.

If no DLT is observed, the SMC may decide to declare the Recommended Dose for Expansion (RDE) based on PK/pharmacodynamics 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 905681. 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 905681 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/OBD, 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 (CRS) and/or Grade 3 hypersensitivity reaction and/or Grade 3 infusion reaction
- One patient experiences a Grade 4 CRS 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 905681 and the benefit-risk profile of BI 905681 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 905681 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 GROUP(S)

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 European Medicines Agency (EMA) guideline on small populations (R07-4856) and by the US Food and Drug Administration (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. 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.

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 v 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.
3. Patients (only those who harbour a historically confirmed RNF43 mutation or R-spondin fusion) willing to undergo mandatory tumour biopsy at the time points specified in the protocol.
4. Eastern Cooperative Oncology Group (ECOG) 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 haematopoietic growth factors within 4 weeks of start of study medication.
- Total bilirubin ≤1.5 x 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 the Chronic Kidney Disease Epidemiology Collaboration (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 (ALP) <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)[2] must only be included after a confirmed menstrual period within the past 4 weeks 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. WOCBP and men able to father a child must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a 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 4 months after the last dose of BI 905681. A list of contraception methods meeting these criteria is provided in the patient information.

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

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

d) other effectively treated malignancy that is considered cured by local treatment

3. Osteoporosis ≥ CTCAE Grade 2
4. Chronic corticosteroid use, except as permitted for the maintenance therapy of brain metastases (see Exclusion Criterion 13)
5. Osteoporotic compression fracture within 12 months prior to informed consent which is clinically significant in the opinion of the investigator.
6. Patient who must or wishes to continue the intake of restricted medications 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.
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 Grade 3 hypersensitivity reactions (including cytokine release syndrome) 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

Patients may potentially be withdrawn from trial treatment or from the trial as a whole ("withdrawal of consent") with very different implications, please see Sections 3.3.4.1 and 3.3.4.2 below.

Every effort should be made to keep the patients in the trial: if possible on treatment, or at least to collect important trial data.

Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to enrolment, as well as the explanation of the consequences of withdrawal.
The decision to withdraw from trial treatment or from the whole trial as well as the reason must be documented in the patient files and electronic case report form (eCRF).

3.3.4.1 Withdrawal from trial treatment

An individual patient is to be withdrawn from trial treatment if:

- The patient wants to withdraw from trial treatment, without the need to justify the decision.
- Has radiological (or clinical) documentation of progressive disease on the current treatment.
- The patient needs to take concomitant drugs that interfere with the investigational product or other trial medication.
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, AEs, other diseases, or pregnancy).
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart (FC) and Section 6.2.3.

For all patients the reason for withdrawal from trial treatment (e.g. AEs) must be recorded in the CRF. These data will be included in the trial database and reported. 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 Flow Chart. In particular, a follow-up visit should be performed wherever possible to ensure all adverse events are adequately followed up.

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

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

If a patient should become pregnant during the trial, the treatment with BI 905681 must immediately be stopped. The patient will be followed up until delivery or termination of pregnancy (see Section 5.2.6.2 for information on pregnancy forms). The data of the patient will be collected and reported in the eCRF until the last patient's last visit and any events occurring thereafter will be reported in the BI drug safety database as described in Section 5.2.6.

3.3.4.2 Withdrawal of consent for trial participation

Patients may withdraw their consent for trial participation at any time without the need to justify the decision.

This will however mean that no further information may be collected for the purpose of the trial and negative implications for the scientific value may be the consequence. Furthermore it may mean that further patient follow up on safety cannot occur.

If a patient wants to withdraw consent, the investigator should explain the difference between treatment withdrawal and withdrawal of consent for trial participation and explain the options for continued follow up after withdrawal from trial treatment, please see Section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

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

- Failure to meet expected enrolment goals overall or at a particular trial site
- Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial
- Violation of GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial
- Completion of treatment by all patients and the sponsor determines that sufficient data have been collected.

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

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Description of test product BI 905681 solution for infusion:

Substance:	BI 905681
Pharmaceutical formulation:	Solution for infusion Dilution in 0.9% sodium chloride 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 Days 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 estimation of the recommended starting dose (RSD) was made on the basis of the ICH Guidance for Industry "S9 Nonclinical Evaluation for Anticancer Pharmaceuticals" (R11-5034).

Two approaches were taken to calculate the starting dose: (1) use of the HNSTD level determined in the 4-week repeat dose toxicity study in the monkey, the most relevant toxicology species and (2) use of the minimal efficacious dose level determined using an EC_{50} value from the *in vivo* pharmacology study (Wnt driven breast cancer xenograft model). An approach using the STD_{10} (a severely toxic dose that causes death or irreversible severe toxicity in 10% of rodents) from the 2-week non-GLP mouse study was not feasible due to morbidity and mortality that was likely a result of anti-drug antibody (ADA) immune complex-related hypersensitivity reactions. The lowest starting dose of 1.0 mg/kg BI 905681 was selected and is expected to be an adequate and safe starting dose.

Approach 1 (use of HNSTD level in the 4-week repeat dose toxicity study in the monkey): The RSD is calculated to be 8.1 mg/kg.

In the 4-week GLP repeat dose toxicity study, the NOAEL was determined to be 150 mg/kg/dose q1w (highest dose tested) and this dose is also considered as the HNSTD based on lack of overt toxicities.

Step 1: Determination of the HNSTD in the repeat dose toxicity study if non-rodent is the most appropriate species (4-week GLP study in the monkey)
Monkey: HNSTD = 150 mg/kg

Step 2: Conversion of $1/6^{th}$ animal HNSTD to Human Equivalent Dose (HED)
Monkey: $1/6^{th}$ HNSTD = 25 mg/kg

Conversion factor from monkey dose to HED: 0.324 (based on body surface area scaling factor for the drug molecular weight (43.2 kDa <100 kDa)
HED = 25 mg/kg x 0.324 = 8.1 mg/kg

Approach 2 (use of minimal efficacious dose level determined using an EC_{50} value from the *in vivo* pharmacology model): The RSD is calculated to be 1.0 mg/kg.

A Wnt driven breast cancer xenograft model has been used as a mechanistic *in vivo* model to test the anti-tumor activity of BI 905681. BI 905681 was administered at doses of 50, 15 or 5 mg/kg by i.v. injection twice per week. The significant tumor regression was achieved at 15 or 50 mg/kg (regression in 7/7 animals) and treatments at these dose levels were well tolerated with no overt clinical signs or significant change in body weight. A dose-dependent pharmacodynamics modulation (inhibition of Axin2 and Notum gene expression) was detected at the end of the efficacy study in tumor tissues. In addition, a PK-PDc time-course experiment performed in the same xenograft model revealed that full pathway modulation (measured by Axin2 down regulation) was achieved up to 48 hours after single dose administration of 15 mg/kg, which corresponded to plasma concentrations higher than 715 nM. Since continuous inhibition of the Wnt pathway is desired, this threshold is considered as the EC_{90} value of the concentration-effect relationship (in terms of human equivalent C_{trough}). According to the formula [$EC_F = (F \div (100 - F)) \times EC_{50}$], and the EC_{50} of 79.4 nM was calculated which is considered appropriate to determine a starting dose in humans. By simulation of the human PK profile using predicted PK parameters, a human dose of 1.0 mg/kg was estimated to provide a C_{trough} concentration of 77.3 nM at steady state (assuming steady state is reached after 9 weeks), based on a once every three week (*q3w*) dosing schedule.

The RSD of BI 905681 is 1.0 mg/kg administered via i.v. infusion, which is the lowest starting dose determined by using the EC_{50} value from the *in vivo* pharmacology model (Approach 2). This dose is expected to be a safe staring dose that has minimal pharmacologic effects and is 8-fold below the RSD determined using the HNSTD from the 4-week repeat dose toxicity study in monkeys.

At the 1.0 mg/kg starting dose, the human exposure is predicted to be C_{max} of 21.8 µg/mL and $AUC_{0\text{-}168h}$ of 1,900 µg•h/mL. The steady state combined males and females C_{max} and $AUC_{0\text{-}168h}$ at the NOAEL, 150 mg/kg/dose from the 4-week toxicity study in monkeys are 5,290 µg/mL and 498,000 µg•h/mL, respectively. The safety margins are 243X and 262X for

C_{max} and $AUC_{0\text{-}168h}$, respectively. Thus, it is considered that the starting dose of 1.0 mg/kg is a conservative starting dose that should assure the safety of patients in the initial clinical trial, while allowing the potential for benefit. The estimated exposure multiples versus the exposures at the monkey NOAEL are shown in Table 4.1.2.1:1. For further details please refer to the IB.

Table 4.1.2.1:1 Recommended starting dose (1.0 mg/kg) and estimated exposure multiples versus exposures at the monkey NOAEL

C_{max} at the monkey NOAEL (µg/mL)	Estimated C_{max} at 1.0 mg/kg (µg/mL)	Exposure Multiple vs Monkey NOAEL C_{max} †	$AUC_{0\text{-}168h}$ at the monkey NOAEL (µg•h/mL)	Estimated $AUC_{0\text{-}168h}$ at 1.0 mg/kg (µg•h/mL)	Exposure Multiple vs Monkey NOAEL $AUC_{0\text{-}168h}$ †
5,290	21.8	243X	498,000	1,900	262X

† Exposure multiple = C_{max} or $AUC_{0\text{-}168h}$ at the NOAEL in monkeys ÷ estimated C_{max} or $AUC_{0\text{-}168h}$ at 1.0mg/kg in humans; To calculate the exposure multiples, $AUC_{0\text{-}168h}$ at 1.0 mg/kg was estimated from q3w dosing schedule

4.1.3 Dose-escalation scheme

Table 4.1.3: 1 Provisional (Example Only) dose levels for escalation in Schedule A

Dose Level	Proposed dose	Increment from previous dose
1	1.0 mg/kg/q3w	Starting dose
2	2.5 mg/kg/q3w	150%
3	4.5 mg/kg/q3w	80%
4	6.5 mg/kg/q3w	44.4%
5	8.5 mg/kg/q3w	30.8%

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 to be made. Dose escalation will continue until identification of the MTD/OBD, safety concerns arise, or the trial is terminated for other reasons. The absolute maximum clinical dose must not exceed 1120 mg/dose.

4.1.4 Starting Dose for Schedule B

After determination of the MTD/OBD 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, and may decide not to

pursue testing of this schedule. 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 3.1). The absolute maximum clinical dose must not exceed 1120 mg/dose.

4.1.5 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 slot. Medication will be assigned via Interactive Response Technology (IRT) for each treatment cycle. Each medication vial will have a unique medication number.

4.1.6 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 905681 will be given as an i.v. 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 or infusional reactions for at least 6 hours following the end of infusion of BI 905681. 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 905681 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 905681 i.v. infusion.

4.1.6.1 Re-treatment criteria

Before administering a treatment dose the investigator must review the assessments performed according to the respective Flow Charts (Schedule A, Table 10.2:1 and Schedule B, Table 10.2:2) 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 and will be discussed in the SMC (see Section 4.1.6.7).

4.1.6.2 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 AEs, 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 a DLT, the infusion should be temporarily stopped. Upon recovery, the following guidance must be followed:

- If more than 50% of the planned dose of BI 905681 was administered, no further BI 905681 will be administered until the next scheduled dose.
- If less than 50% of the planned dose of BI 905681 was administered due to IRR/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.
- 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 905681 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.

4.1.6.3 Management of Cytokine Release Syndrome (CRS)

Cytokine release syndrome 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 4.1.6.2, clinical manifestations of CRS and other forms of infusion-related reactions are difficult to distinguish (especially at first occurrence) and require rapid diagnosis and immediate management to avoid severe AEs, 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 905681. 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 administered due to CRS around the time of administration of BI 905681 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 4.1.6.2).

4.1.6.4 Management of bone toxicity

Patients will be monitored for bone toxicity using regular measurement of serum bone biomarkers and bone densitometry. Treatment with vitamin D and/or calcium carbonate is recommended in patients with documented pre-existing osteoporosis, per standard of care and/or investigator's discretion.

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 905681 must be permanently discontinued.

4.1.6.5 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 at baseline, as well as a full retinal examination. These assessments have to be performed within 48-72 hours after occurrence. Treatment with BI 905681 will be withheld until this ophthalmologic assessment confirms it is safe to restart BI 905681.

Treatment with BI 905681 must be discontinued if either of the following are observed:

- CTCAE Grade ≥2 retinopathy
- Clinically meaningful changes in fundus photography and spectral domain optical coherence tomography (SD-OCT) as determined by the examining ophthalmologist

4.1.6.6 General management of toxicities

Toxicities not covered within Sections 4.1.6.2, 4.1.6.3, 4.1.6.4 and 4.1.6.5 will be handled according to the instructions in Table 4.1.6.6: 1

Table 4.1.6.6: 1 Management of toxicity

Event	First occurrence	Second occurrence
Grade 4 non-haematological toxicity which is related to BI 905681	Permanently discontinue treatment Start supportive measures according to standards of the institution	Not applicable
Haematological toxicity fulfilling criteria for DLT	Hold BI 905681 treatment until recovery to Grade ≤1 or baseline; start supportive measures according to standards of the institution (e.g., granulocyte-colony stimulating factor [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 905681 treatment at a lower dose - see Section 4.1.6.7	Permanently discontinue BI 905681 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	Hold BI 905681 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 905681 treatment at a lower dose - see Section 4.1.6.7	Permanently discontinue BI 905681 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 905681 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.	Same as for first occurrence

4.1.6.7 Dose Reduction

In the event of a DLT which meets certain criteria the patient may continue therapy at a reduced dose (see Table 4.1.6.6: 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 4.1.6.1). The patient will re-commence treatment at a reduced dose of BI 905681; 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.

4.1.7 Definition of dose-limiting toxicity

Dose-limiting toxicities (DLTs) will be recorded throughout the trial. Any DLT must be reported to the [redacted] Medical Monitor by the Investigator or designee within 24 hours of first knowledge, and to the [redacted] as an AESI (as described in Section 5.2.6.1). All DLTs will be agreed upon between the Sponsor, the Study Chair, the [redacted] Medical Monitor, and the Investigators after review of the data from each cohort. Only DLTs starting in the first cycle of BI 905681 are necessary for dose-escalation decisions made by the SMC. DLT information from later cycles will be taken into consideration if available.

All relevant safety information (including DLTs) together with data on target engagement will be considered when selecting the recommended doses for the expansion cohorts.

Severity of AEs will be graded according to CTCAE Version 5.0. Any of the following AEs will be classified as DLTs following review by the Investigators and the [redacted] 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.

4.1.8 Blinding and procedures for unblinding

Not applicable.

4.1.9 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.

4.1.10 Storage conditions

BI 905681 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 local clinical monitor (as provided in the list of contacts) must be contacted immediately.

4.1.11 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)/Independent Ethics Committee (IEC),
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site,
- Approval/notification of the regulatory authority, e.g., competent authority,
- 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 use by each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational 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 clinical trial protocol (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 and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

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

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Concomitant therapy, with reasons for the treatment, must be recorded in the eCRF during the Screening and treatment periods, starting at the date of signature of informed consent and ending after the residual effect period (REP) a period of 42 days after the last dose of trial medication. After REP, only concomitant therapy indicated for treatment of a related AE has to be reported. If a new anti-cancer treatment is started, it will be documented in the CRF, on a separate page of follow-up therapy, different from the concomitant therapies pages.

4.2.2.2 Restrictions on diet and life style

The usual restrictions on diet and life style that were already applicable for a given patient before entry into the trial, according to his/her medical condition, have to be continued.

4.2.2.3 Restrictions regarding women of childbearing potential

Due to the advanced stage of disease of Phase I trial patient populations and the high medical need, females of childbearing potential can be included in this trial provided that they agree to use a highly-effective contraception method. These are methods of birth control per the International Council for Harmonisation (ICH) M3 (R2) that result in a failure rate of less than 1% per year when used consistently and correctly.

Highly-effective methods of contraception include:
- Oral, injected, or implanted hormonal methods of contraception, or
- Intrauterine device or intrauterine system, or
- 'Double-barrier' methods of contraception: Male condom in combination with female diaphragm/cervical cap plus spermicidal foam/gel/film/cream.

Details of these contraception methods are described in the patient information in the ICF.

Women of childbearing potential must follow these methods during the trial and for at least 6 months after the end of the trial treatment. Although use of a contraceptive pill is considered a highly-effective method of birth control, women of childbearing potential taking a contraceptive pill must use an additional barrier method for the entire duration of the trial treatment intake and for 6 months after the end of the trial treatment intake.

Male patients with partners of childbearing potential must agree to use condoms and ensure their partner is using an additional highly-effective method of birth control, during the trial and until at least 6 months after the end of the trial treatment.

4.3 TREATMENT COMPLIANCE

BI 905681 will be administered by i.v. infusion at the sites by the Investigator and/or trained site personnel, and dosing will be recorded in the eCRF. Therefore, actual dosing is expected to precisely follow the prescribed drug regimen. Missed or interrupted doses will be recorded in the eCRF with the associated reasons. The method of collecting dosing information assures that total exposure can be calculated programmatically taking into account any missing doses.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

The 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).

The baseline imaging must have been performed within 4 weeks prior to treatment with the trial medication and the Investigator will record the target and non-target lesions in the eCRF. The same method of assessment and the same technique must be used to characterise each reported lesion at baseline and during treatment. Lesions in previously irradiated areas may not be considered measurable at baseline unless the lesions occurred after irradiation.

Tumour assessment will be performed at the time points indicated in the respective Flow Charts (Schedule A, Table 10.2:1 and Schedule B, Table 10.2:2) Wherever possible the assessment schedule should not be changed, but if there is an interruption or delay of 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 will 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

The safety of BI 905681 will be assessed by a descriptive analysis of incidence and severity of AEs graded according to CTCAE (Version 5.0), the incidence of DLTs, laboratory data, and results of physical examination. Safety will be assessed in a descriptive way without confirmatory analysis.

Dose-limiting toxicities observed during the MTD evaluation period (first 3 weeks of Schedule A or first 4 weeks of Schedule B) will be considered for MTD determination. However, DLTs observed in all treatment cycles will be considered for determining a recommended Phase 2 dose (RP2D). The BLRM model will be re-run including the DLT information from all cycles. Based on both estimates, the recommended dose for further development will be selected. At regular intervals, all available safety data including AEs qualifying as DLTs will be submitted to the SMC. The SMC will independently assess this information and provide recommendations for trial conduct and dose escalation. If there are too few or no DLTs for BLRM guided dose selection, PK and/or biomarker data will be taken into consideration for RP2D determination.

5.2.1 Physical examination

A physical examination will be performed at the time points specified in the Flow Charts.

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, body weight and the evaluation of the ECOG performance score (see Appendix 10.4) will be performed at the time points specified in the Flow Charts.

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 Flow Charts.

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 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 Flow Chart.

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 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 AE.

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 (25-hydroxy 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 time points indicated in the Flow Charts and in Appendix 10.2. 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 AEs 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-CTX and 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 upon.

When a blood sample for bone biomarkers is required, it will be obtained prior to administration of trial medication, before 9:00 am, 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 Flow Chart according to standard institutional 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.

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 upon.

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 905681. 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 905681 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 905681 administration. Cytokine measurements will be performed in conjunction with each infusion

at the time points specified in Appendix 10.2.

In addition to the scheduled cytokine measurements, ferritin will be measured at baseline (Cycle 1 Day 1). If a clinically manifested CRS occurs at any time point, 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 Appendix 10.2, and in the Laboratory Manual.

5.2.5.4 Ophthalmologic Assessment

Ophthalmologic assessment will be performed for all patients at Screening. This will require a visit to the opthamologist. 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 meters. 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 Heidelberg, Zeiss or Topcon equipment will be used.

The same ophthalmologic assessments will be repeated within 48-72 hours 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. Treatment with BI 905681 will be withheld until this ophthalmologic assessment confirms it is safe to restart BI 905681.

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.

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

- Worsening of pre-existing conditions (for the underlying disease adhere to chapter "Exemptions to SAE reporting" in Section 5.2.6.2)
- Changes in vital signs, ECG, physical examination, laboratory test results and other safety parameters included in Section 5.2.5, if they are judged clinically relevant by the investigator.

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

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,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

AEs considered "Always Serious"

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as defined above. A copy of the latest list of "Always Serious AEs" will be provided upon request. These events should always be reported as SAEs as described in Section 5.2.6.2.

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 Section 5.2.6.2, subsections "AE Collection" and "AE reporting to sponsor and timelines".

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 [redacted] within the same timeframe that applies to SAEs, please see 'AE reporting to sponsor and timelines.'

For this trial, the following events will be 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 times ULN combined with an elevation of total bilirubin ≥2 times ULN measured in the same blood draw sample, and/or
- aminotransferase (ALT, and/or AST) elevations ≥10 times ULN

For patients with abnormal liver function at baseline (AST and/or ALT > ULN)

- an elevation of AST and/or ALT ≥5 times ULN combined with an elevation of total bilirubin ≥2 times ULN measured in the same blood draw sample, and/or
- Marked peak aminotransferase (ALT, and/or AST) elevations ≥10 times ULN

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "Potential DILI checklist" provided 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 (i.e., 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 Potential DILI checklist should be followed.

Dose Limiting Toxicity
Any medical event fulfilling the criteria of DLT (see Section 4.1.7) 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 4.1.6.2.

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 4.1.6.3.

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 AEs should be classified and recorded in the CRF according to the CTCAE v5.0.

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 any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see Section 5.2.6.2), but not on the eCRF.

Vital Status Data Collection

For patients who discontinue trial medication prematurely and agree to be contacted further but do not agree to physical visits: should be followed up, and from withdrawal from trial treatment until the individual patient's end of the trial the investigator must report all deaths/fatal AEs regardless of relationship, and trial treatment related SAEs and trial treatment related AESIs the investigator becomes aware of.

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 secure e-mail connection or via fax

immediately (within 24 hours) to the [redacted]:

- Secure email ([redacted] SAE mailbox: [redacted] or
- Fax ([redacted] fax number): [redacted]

The same timeline applies if follow-up information becomes available. In specific occasions the Investigator could inform the [redacted] upfront via telephone by calling the [redacted] phone number ([redacted]). This does not replace the requirement to complete and fax the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained.

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. Reporting and consenting must be in line with local regulations. The ISF will contain the trial specific information and consent for 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 SAE reporting
The outcome "disease progression" is used to assess trial endpoints for the analysis of efficacy. It will be recorded on the appropriate page of the eCRF. Only if it meets standard seriousness criteria (see 'Serious adverse event' definition) it will also be recorded on the AE page in the eCRF and on the BI SAE form and SAE reporting process will be followed.
Clinical symptoms and/or signs of PD will be recorded on the AE page in the eCRF. If signs and symptoms of disease progression of the patient's underlying malignancy meet standard

seriousness criteria, they will additionally be reported on the BI SAE form and SAE reporting procedures will be followed.

Exempted events are monitored at appropriate intervals throughout the study at SMC meetings.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

If data allow, the PK parameters of BI 905681 mentioned as secondary endpoints will be evaluated using non-compartmental analysis (NCA) methods according to the current BI internal and [redacted] Standard Operation Procedures (SOPs).

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.

5.3.2 Methods of sample collection

For quantification of analyte serum concentrations, samples will be drawn at the time points listed in the respective Flow Charts (Schedule A, Table 10.2:1 and Schedule B, Table 10.2:2).

If collected from an arm, it is essential to collect blood from the arm that is opposite to the arm used for infusion in order to avoid artificially high or low drug concentration determinations. Further details on sample characteristics, processing, handling, and shipment are provided in the Laboratory Manual. After completion of the trial, serum samples may be used for further methodological investigations, e.g. stability testing. However, only data related to the analyte or bioanalytical assay will be generated by these additional investigations. The trial samples will be discarded after completion of the additional investigations but not later than 5 years after the final trial report has been signed.

[redacted]

5.3.4 Pharmacokinetic – pharmacodynamic relationship

No formal analysis of a PK/PDc 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 PK-PDc 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 BIOMARKER(S)

The evaluation of several biomarkers will be performed in an exploratory manner as a means of identifying whether, for example, pharmacodynamics modulation is achieved during the dose escalation part of the trial. Where consent is given, tumour samples will be obtained as detailed below. Tumor sampling must only be performed for patients who have undergone screening assessments, have a historically confirmed RNF43 mutation or R-spondin fusion, and are expected to be eligible for treatment in the trial. The following exploratory biomarkers are planned to be examined in tumor biopsies attained during the trial:

- Pharmacodynamics modulation of genes associated with Wnt signaling including but not limited to *AXIN2* mRNA expression.
- Tumour microenvironment changes induced by BI 905681 intervention, as determined by an analysis of an immune-oncology-related panel of genes.
- β-catenin staining pattern using immunohistochemistry.
- Genomic profiling of tumour samples implementing next generation sequencing.
- Immune oncology related targets including but not limited to CD8 and PDL1.

The aforementioned analysis will be undertaken should enough formalin-fixed and paraffin-embedded (FFPE) material be available. 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. Until then, samples will be stored at Boehringer Ingelheim or [redacted].

5.4.1 Methods of sample collection

Biopsies should be taken according to the Flow Chart. Pre- and on-treatment tumour biopsy (where feasible, from the same lesion) collections for biomarker analyses will be mandatory from all patients who have a historically confirmed RNF43 mutation or R-spondin fusion entering the trial starting from Cohort 2. Where mandatory, an archival sample (25 x 4-5µm-sections), from the most recent relapse, will be acceptable as the pre-treatment biopsy, if taken within 6 months of trial start. Otherwise a pre-treatment fresh tumour biopsy must be taken and formalin fixed paraffin embedded (FFPE) and stored at room temperature. On-treatment samples must also be FFPE and stored at room temperature until shipped. Detailed instructions for sampling, handling, and shipment of samples are provided in the laboratory manual, but in short:

- For a fresh baseline sample a minimum of 2 core needle biopsies or 1 punch biopsy must be taken between screening and the day before first treatment with BI 905681. An archival sample, from the most recent relapse, will be acceptable as the pre-treatment biopsy (25 x 4-5µm-sections), if taken within 6 months of trial start.
- Two core-needle biopsies (preferably from the same lesion) 24 hours after Cycle 2 infusion (the on-treatment biopsy time point may be adapted based on PK analysis).

All samples must be adequately labelled by the trial site personnel. Details about tumour tissue, labelling of tubes, storage, and shipment (frequency and addresses) will be provided in the laboratory manual.

As medical knowledge in this field is constantly evolving, other tissue/blood biomarkers that may become relevant as predictive markers of treatment response may also be explored via available tissues/blood or acquisition of additional tumour tissues/blood. The list of biomarkers planned to be studied during the trial may change based on new information in the literature or early analyses.

5.5 OTHER ASSESSMENTS

5.5.1 ADA assessments

For ADA assessment, samples will be drawn at the time points listed in the respective Flow Charts (Schedule A, Table 10.2:1 and Schedule B, Table 10.2:2).

Details on sample collection, characteristics, processing, handling, and shipment are provided in the Laboratory Manual. The trial samples will be discarded after completion of the additional investigations but not later than 5 years after the final trial report has been signed.

Note that for some disease indications, it may be necessary to use serum samples collected prior to administration of test article in order to assess the performance of the ADA assay. Such use of pre-dose samples will not compromise the collection of valid ADA data for those pre-dose samples.

[redacted]

5.6 APPROPRIATENESS OF MEASUREMENTS

All assessments have been planned in accordance with traditional oncology Phase I trial methodology.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Patients meeting the inclusion and exclusion criteria for the part they are participating in and who have signed a written ICF, are eligible for participation in the trial. Patients will visit the clinical site at the time points specified in Schedule A Flow Chart and Schedule B Flow Chart specific to each part. If a patient misses a scheduled visit, and reports to the Investigator between the missed visit and the next scheduled visit, the assessments for the missed visit must be done with the actual date and the reason must be given for the delayed visit. The next visit must then take place at the scheduled time after the first administration of the trial drug in the respective treatment cycle.

Once the decision is made for any reason for a patient to stop the treatment with BI 905681, an EOT visit must occur as soon as possible (no later than 7 days after stopping treatment). After the EOT visit, the patient must undergo a follow-up safety evaluation 42 (+7) days after the last administration of trial therapy.

The trial will be conducted according to the principles of GCP.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

The procedures required at each trial visit in both portions of the trial are presented in Schedule A Flow Chart and Schedule B Flow Chart of this protocol. The key procedures required include:

- PK samples throughout the trial
- Reporting of all AEs occurring after the ICF has been signed
- Baseline and on-treatment blood biomarker and immunogenicity assessments
- Tumour biopsy biomarker assessments
- Tumour assessments (based on computed tomography [CT] / positron emission tomography [PET] and/or magnetic resonance imaging [MRI] scan) according to RECIST Version 1.1 must be performed once every 2 cycles (meaning every 6 weeks for Schedule A and every 8 weeks for Schedule B if there are no delays in cycles but as close as possible to the end of the second of the 2 cycles of treatment if there was a delay) after the start of BI 905681.

6.2.1 Screening and run-in period(s)

6.2.1.1 Screening Period

The Screening period may run over a period of 28 days (period within the trial and before the first intake of BI 905681). For the detailed description of the tests to be performed during this period and their timing, please refer to Schedule A Flow Chart and Schedule B Flow Chart.

6.2.1.2 Baseline Conditions

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

6.2.1.3 Medical History

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

Previously administered chemotherapy, vaccine therapy, antibodies therapy, kanamycin or similar class drugs (including streptomycin, gentamicin, amikacin, tobramycin and neomycin), immune therapy, and hormone therapy will be reported, including start and end dates (month and year may be sufficient), as well as whether therapy was given as neoadjuvant, adjuvant, or palliative therapy. The date of tumour progression after previous line of treatment will be recorded, if known.

6.2.1.4 Concomitant therapies

Relevant concomitant diagnoses and/or therapies present at trial entry and/or during Screening and relevant to the patient's safety during the trial as judged by the Investigator will be recorded in the eCRF (see Section 4.2.2 for details on concomitant medications). Post-trial therapy for advanced or metastatic disease will also be documented.

6.2.2 Treatment period(s)

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

6.2.3 Follow up period and trial completion

6.2.3.1 End-of-treatment visit

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

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.

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 905681 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* = 4.5 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 posterior probability of the DLT rate falling in the target interval [0.16, 0.33] without skipping any dose level. Applying the EWOC criterion it should be unlikely (<25% posterior probability) that the DLT rate at that dose will exceed 0.33.

The MTD may be considered reached if 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 recommend 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 905681.

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 1.0 mg/kg/q3w would equal 0.02, and the median DLT rate at the highest dose of 8.5 mg/kg/q3w would equal 0.1. This yields μ_1 = (-2.701,-0.233). The standard deviations were set such that large uncertainty about the parameter means is reflected, and the correlation was set to 0, thus yielding $\sigma_{1,11} = 2$, $\sigma_{1,22} = 1$ and $\rho_1 = 0$, respectively. The prior weight 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 1.0 mg/kg/q3w would equal 0.09, and the median DLT at the highest dose of 8.5 mg/kg/q3w would equal 0.40. These assumptions yield μ_2 = (-0.973,-0.115). The standard deviations and correlations were set identical to the weakly informative prior, i.e. $\sigma_{2,11} = 2$, $\sigma_{2,22} = 1$ and $\rho_2 = 0$, respectively. The prior weight 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 1.0 mg/kg/q3w would equal 0.01, and the median DLT at the highest dose of 8.5 mg/kg/q3w would equal 0.02. These assumptions yield μ_3 = (-4.101,-1.113), i.e. basically a flat curve. The standard deviations and correlations were set to $\sigma_{3,11} = 5$, $\sigma_{3,22} = 0.01$, therefore almost fixing

the slope parameter to its mean. The correlation was set to 0, i.e. $\rho_3 = 0$. The prior weight a_3 for the third component was chosen as 0.05.

A summary of the prior distribution is provided in Table 7.1.1. Additionally, the prior probabilities of DLTs at different doses, as well as the corresponding probability of under-, targeted and overdosing, are shown in Table 7.1: 2. Graphically, the prior medians with accompanying 95% credible intervals are shown in Figure 7.1: 1. As can be seen from both, the table and the figure, the prior medians of the DLT probabilities are in-line with the prior medians derived from the weakly informative prior, and the uncertainty around the medians is large, showing the low amount of information this prior provides. This is also supported by the prior sample size, i.e., the information contained in the prior. This is approximately equal to 1.8 patients. A detailed evaluation of the model using hypothetical data scenarios and operating characteristics is provided in the statistical appendix (see Appendix 10.3).

Table 7.1: 1 Summary of prior distribution

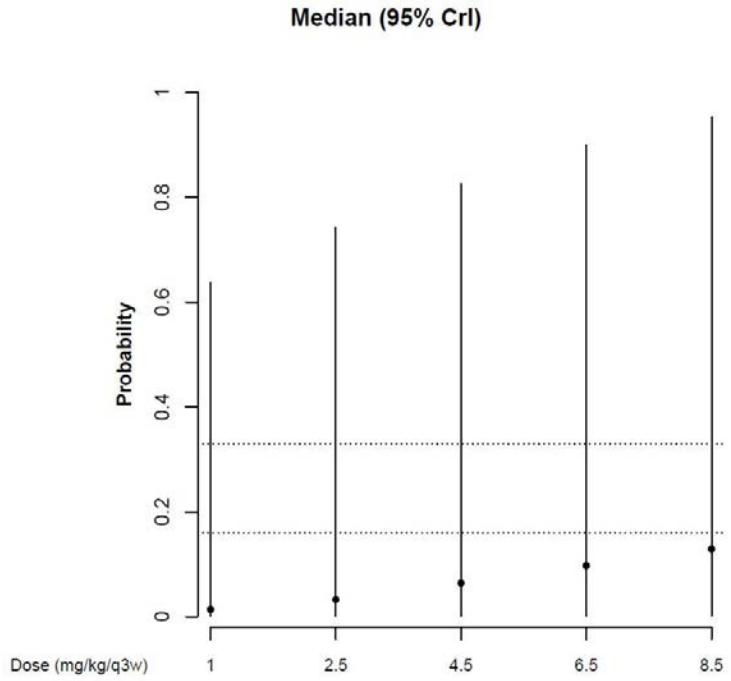
Prior Component	Mixture Weight	Mean Vector	SD Vector	Correlation
1: Weakly inf.	0.9	-2.701,-0.233	2.000, 1.000	0.000
2: High Tox	0.05	-0.973,-0.115	2.000, 1.000	0.000
3: Low Tox	0.05	-4.101,-1.113	5.000, 0.010	0.000

Table 7.1: 2 Prior probabilities of DLT at selected doses

Dose	Probability of true DLT rate in					Quantiles		
	[0-0.16)	[0.16-0.33)	[0.33-1]	Mean	SD	2.50%	50%	97.50%
1	0.853	0.075	0.072	0.081	0.162	<0.001	0.014	0.637
2.5	0.780	0.106	0.114	0.118	0.191	<0.001	0.034	0.742
4.5	0.685	0.138	0.177	0.165	0.221	0.001	0.065	0.826
6.5	0.601	0.155	0.244	0.214	0.256	0.001	0.099	0.900
8.5	0.544	0.161	0.295	0.254	0.283	0.001	0.130	0.953

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

Figure 7.1: 1: Prior medians and 95% credible intervals



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.

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 for this trial.

7.3 PLANNED ANALYSES

For the determination of the MTD, only MTD-evaluable patients will be considered. For other analyses of efficacy and safety endpoints, all patients in the treated set (i.e., patients

treated with at least one dose of trial medication) will be included in the analysis. Any other analysis sets will be defined in the Trial Statistical Analysis Plan (TSAP).

No per protocol set will be used in the analysis. However, important protocol violations will be summarised with details specified in the TSAP.

7.3.1 Primary endpoint analyses

In order to identify the MTD of the trial, the number of patients with DLTs at each dose level during the MTD evaluation period (first three weeks for Schedule A and the first 4 weeks for Schedule B) must be presented. Patients who discontinue during the first treatment course for reasons other than a DLT will be excluded from the determination of the MTD.

In addition, the number of patients with DLTs that occurred during the entire treatment period will be summarised at each dose level. The BLRM will be rerun to re-evaluate the MTD and RP2D together with all relevant data collected during the study.

7.3.2 Secondary endpoint analyses

All secondary endpoints will be analysed descriptively.

Details on statistical inference for PK parameters, e.g., dose proportionality using C_{max} and AUC etc., and all other secondary endpoints analysis will be specified in the TSAP.

[redacted]

7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the 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 adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the residual effect period. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent.’

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of 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 current BI and [redacted] SOPs.

All patients in the treated set who received at least one dose of BI 905681 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, they 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: N, arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. For the PK parameters in addition to the previous descriptive statistics P10, Q1, Q3, and P90 will be also calculated. The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of pharmacokinetic parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the clinical trial report.

7.4 INTERIM ANALYSES

No formal interim analysis is planned.

The sponsor will continuously monitor safety. The dose-escalation design dictates that the sponsor and the SMC perform regular safety evaluations. These evaluations will be unblinded to dose.

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

7.5 HANDLING OF MISSING DATA

No imputation will be performed on missing efficacy data. Missing baseline laboratory values will be imputed by the respective values from the Screening visit. No other imputations will be performed on missing data although every effort will be made to obtain complete information on all AEs, with particular emphasis on potential DLTs.

7.6 RANDOMISATION

No randomisation will be performed.

7.7 DETERMINATION OF SAMPLE SIZE

The actual number of patients will depend on the number of dose cohorts and the cohort sizes actually tested. Given the pre-specified possible dose levels and the number of patients per dose level, simulation studies show a range (refer to Table 10.3:3) of 3 to 51 patients is needed to assess five dose levels for Schedule A. Assuming Schedule B has a starting dose of 1.0 mg/kg/q2w, a similar range of patients is required to assess the dose levels. Taken into account the number of patients recruited into the “back-filled” cohorts, around 30 patients are needed for each schedule. In total, the estimated sample size for the dose escalation phase 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 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 finalization of the Clinical Trial Report.

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

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 Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

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

The patient must be given sufficient time to consider participation in the trial. The investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

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

Case report forms for individual patients will be provided by the sponsor. For drug accountability, refer to Section 4.1.11.

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 CRF must be consistent with the source data or the discrepancies must be explained.

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

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

8.3.2 Direct access to source data and documents

[redacted] 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 CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g., FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

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

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

[redacted]: [redacted] will retain trial documents according to contractual agreements with the Sponsor.

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 Suspected Unexpected Serious Adverse Reactions (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.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

A contract research organisation, [redacted], is responsible for project management, medical management, site management, data management, site regulatory document management, management of the Trial Master File, some aspects of safety management and reporting, medical writing, and medical monitoring.

A Safety Monitoring Committee (SMC) will be established. Members of the SMC will include:

- [redacted] Medical Monitor for the trial, or delegate
- Principal Investigators, or delegates, from each investigational site
- BI Safety Physician, or delegate
- BI Clinical Program Leader, or delegate, responsible for the project.
- BI TSTAT
- BI TCPK, according to agenda

The BI Safety Physician (or delegate), BI Clinical Program Leader (or delegate) should always attend the SMC to discuss safety issues.

The [redacted] Medical Monitor, or delegate, should always be present at the SMC. Other BI and non-BI subject matter experts may also be invited, as appropriate. The SMC documentation for this trial will define the exact membership and who should be present for decisions to be made.

The SMC will be responsible for assessing the progress of the clinical trial, including making safety and efficacy assessments at specified intervals, making dose-escalation decisions for BI 905681, making decisions on the next cohort size, and recommending to the Sponsor whether to continue, modify, or stop the trial. Minutes from these meetings will be prepared and circulated to the trial team and each investigator for comment prior to finalisation.

The tasks and responsibilities of the SMC will be documented. The SMC will maintain written records of all its meetings.

Relevant documentation on the participating investigators and other important participants, including their curricula vitae, will be filed in an ISF.

The statistical analysis 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 and [redacted] SOPs as agreed upon and documented. A list of responsible persons and relevant local information can be found in the ISF.

A central laboratory service and an Interactive Response Technology (IRT) vendor will be used in this trial for development of shipment orders and assignment of trial medication. Details will be provided in the IRT Manual and Central Laboratory Manual, available in the ISF.

The [redacted] Study Chair is responsible for coordinating investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

The organisation of the trial in the participating countries will be performed by [redacted] with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

A central laboratory service will be used in this trial. Details will be provided in the Central Laboratory Manual, available in the ISF.

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 an 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, and
- 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.

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.

9. REFERENCES

9.1 PUBLISHED REFERENCES

R01-0787 Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5:649-655.

R07-4856 European Medicines Agency (EMEA). Committee for Medicinal Products for Human Use (CHMP): guideline on clinical trials in small populations. London, 27 July 2006: doc. ref. CHMP/EWP/83561/2005.

R09-0262 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (Version 1.1). Eur J Cancer 2009 Jan;45(2):228-47.

R11-5034 Guidance for industry: S9 nonclinical evaluation for anticancer pharmaceuticals (ICH, March 2010). Website.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guida nces/ucm085389.pdf (access date: 5 December 2011); Rockville: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER); 2010.

R13-4802 Jaki T, Clive S, Weir CJ. Principles of dose finding studies in cancer: a comparison of trial designs. Cancer Chemother Pharmacol. 2013; 71:1107-1114.

R13-4803 Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Stat Med. 2008; 27:2420-2439.

R13-4804 Rogatko A, Schoeneck D, Jonas W, Tighiouart M, Khuri FR, Porter A. Translation of innovative designs into phase I trials. J Clin Oncol. 2007; 25(31):4982-4986.

R13-4805 Tourneau C le, Gan HK, Razak ARA, Paoletti X. Efficiency of new dose escalation designs in dose-finding phase I trials of molecularly targeted agents. Plos One. 2012; 7(12):e51039.

R13-4881 FDA's critical path initiative. U.S. Food and Drug Administration: 2012 webpage updated 28 December 2012: accessed 8 November 2013. http://www.fda.gov/ScienceResearch/Special/Topics/CritialPathInitiative/cm076689.htm.

R15-0031 Maude SL, Barrett D, Teachey DT, Grupp SA. Managing cytokine release syndrome associated with novel T cell-engaging therapies. Cancer J (Sudbury) 2014. 20(2):119-122.

R15-3504 GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012 (homepage). World Health Organization International Agency on Cancer; 2012. http://globocan.iarc.fr/Default.aspx.

R16-2323 Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014. 124(2):188-195.

R17-1468 Clevers H. Wnt/beta-catenin signaling in development and disease. Cell 2006;127(3):469-480.

R17-1470 Zhong Z, Baker JJ, Zylstra-Diegel CR, Williams BO. Lrp5 and Lrp6 play compensatory roles in mouse intestinal development J. Cell. Biochem. 2011; 113: 31–38.

R17-1850 Giannakis M, Hodis E, Mu XJ, et al. RNF43 is frequently mutated in colorectal and endometrial cancers. Nature Genet 2014;46(12):1264-1266.

R17-1851 Ettenberg SA, Charlat O, Daley MP, Liu S, Vincent KJ, Stuart DD, et al. Inhibition of tumorigenesis driven by different Wnt proteins requires blockade of distinct ligand-binding regions by LRP6 antibodies. Proc Natl Acad Sci U S A 107(35), 15473-8 (2010).

R17-4166 Jimeno A, Gordon M, Chugh R, Messersmith W, Mendelson D, Dupont J, et al. A first-in-human phase 1 study of the anti-cancer stem cell agent ipafricept (OMP-54F28), a decoy receptor for Wnt ligands, in patients with advanced solid tumors. Clinical Cancer Research, Author Manuscript Published Online First on September 27, 2017, doi: 10.1158/1078-0432.CCR-17-2157 Clin Cancer Res 2017

R17-4167 Papadopoulos K, Rosen L, Chugh R, Goldman J, Yen YC, Yeung P, et al. A phase la study in patients with advanced solid tumors for the human monoclonal antibody vantictumab (OMP-18R5; anti-Frizzled) targeting the WNT pathway. ECC 2013, Eur Cancer Cong of the European Cancer Organization, the European Society for Medical Oncology, and the European Society for Radiation and Oncology (ECCO-ESMO-ESTRO), Amsterdam, 27 Sep - 1 Oct 2013 (Poster) 2013

R17-4168 Janku F, Connolly R, LoRusso P, Jonge M de, Vaishampayan U, Rodon J, et al. Phase I study of WNT974, a first-in-class porcupine inhibitor, in advanced solid tumors. AACR-NCI-EORTC Int Conf on Molecular Targets and Cancer Therapeutics, Boston, 5-9 Nov 2015 (Poster) 2015

R18-0131 Regard JB, Zhong Z, Williams BO, Yang Y. Wnt signaling in bone development and disease: making stronger bone with Wnts. Cold Spring Harbor Perspectives in Biology 2012; 4:1-17.

R18-1420 Messersmith W, Cohen SJ, Shahda S, Lenz HJ, Weekes C, Dotan E, et al. Phase 1b study of WNT inhibitor vantictumab (VAN, human monoclonal antibody) with nab-paclitaxel (Nab-P) and gemcitabine (G) in patients (pts) with previously untreated stage IV pancreatic cancer (PC). 41st Ann Cong of the European Society for Medical Oncology (ESMO), Copenhagen, 7 - 11 Oct 2016 (Poster) 2016

R18-1421 Mita M, Becerra C, Richards D, Mita A, Shagisultanova E, Osborne C, et al. Phase 1b study of WNT inhibitor vantictumab (VAN, human monoclonal antibody) with paclitaxel (P) in patients (pts) with 1st- to 3rd-line metastatic HER2-negative breast cancer (BC). 52nd Ann Mtg of the American Society of Clinical Oncology (ASCO), Chicago, 3 - 7 Jun 2016 (Poster) 2016

R18-1474 Ye X, Wang Y, Cahill H, Yu M, Badea TC, Smallwood PM, Peachey NS, and Nathans J. Norrin, Frizzled-4, and Lrp5 Signaling in Endothelial Cells Controls a Genetic Program for Retinal Vascularization. Cell 2009; 139:285-298.

R18-1475 Hackam AS. Critical Review: The Wnt Signaling Pathway in Retinal Degenerations. Life 2005; 57:381-388.

R18-1490 Ng M, Tan DSP, Subbiah V, Weekes CD, Teneggi V, Diermayr V, et al. First-in-human phase 1 study of ETC-159 an oral PORCN inhbitor in patients with advanced solid tumours. 53rd Ann Mtg of the American Society of Clinical Oncology (ASCO), Chicago, 2 - 6 Jun 2017 J Clin Oncol 2017. 35(15)(Suppl) Abstr 2584

R18-1494 Bendell J, Eckhardt SG, Hochster HS, Morris VK, Strickler J, Kapoun AM, et al. Initial results from a phase 1a/b study of OMP-131R10, a first-in-class anti-RSPO3 antibody, in advanced solid tumors and previously treated metastatic colorectal cancer (CRC). 28th EORTC-NCI-AACR Symp on Molecular Targets and Cancer Therapeutics, Munich, 29 Nov - 2 Dec 2016 (Poster) 2016

R18-1685 Frey N. Cytokine release syndrome: who is at risk and how to treat. Baillieres Best Pract Res Clin Haematol 2017. 30:336-340.

R18-1686 Frey NV, Porter DL. Cytokine release syndrome with novel therapeutics for acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program 2016. 2016(1):567-572.

9.2 UNPUBLISHED REFERENCES

c27125909-01 BI 905681 Investigator's Brochure.

n00267725 Effects of the LRP5 specific antagonist BI 905681 on viability of RNF43 mutant pancreatic cancer cell lines

n00267727 Assessment of efficacy, tolerability and PD biomarker modulation by BI 905681 in MMTV-Wnt1 tumor-bearing BomTac:NMRI-Foxn1nu mice

n00267728 Assessment of pharmacodynamics biomarker in skin tissue in tumor bearing BomTac:NMRI-Foxn1nu mice treated with BI 905681

n00267729 Effects of the LRP5 specific antagonist BI 905681 on viability of RNF43 mutant CRC patient derived organoids

10. APPENDICES

10.1 PHARMACOKINETIC ANALYSES

If data allow and if scientifically reasonable, the following pharmacokinetic parameters of BI 905681 will be evaluated using non compartmental analysis methods according to the current internal BI and [redacted] SOPs.

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

- C_{max} (maximum measured serum concentration of BI 905681 in serum).
- [redacted]
- 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).

[redacted]

[redacted]

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

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

[redacted]

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

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 905681	ADA	Cytokines	ECG	Tumour Biopsy
		Any time before 1st infusion						X
1 and 2	1	Before start of BI 905681 infusion	-0:05	X	X	X[a]	X[b]	
		Start of BI 905681 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 (±5 min)	1:30[c]	X				
		3h after the end of infusion (±10 min)	4:00[c]	X		X		
		7h after the end of infusion (±15 min)	8:00[c]	X		X		
	2	24h after start of infusion (±1 hr)	24:00	X		X		X[g]
	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 905681 infusion	-0:05	X	X	X	X[b]	
		Start of BI 905681 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 (±10 min)	4:00[c]			X		
		7h after the end of infusion (±15 min)	8:00[c]			O		
	2	24h after start of infusion (±1 hr)	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 905681 infusion	-0:05	X	X	X	X[b]	
		Start of BI 905681 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.

g Only required in Cycle 2. The on-treatment biopsy time point may be adapted based on PK analysis.

Table 10.2: 2 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 905681	ADA	Cytokines	ECG	Tumour Biopsy
		Any time before 1st infusion						X
1 and 2	1	Before start of BI 905681 infusion	-0:05	X	X	X[a]	X[b]	
		Start of BI 905681 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 (±5 min)	1:30[c]	X				
		3h after the end of infusion (±10 min)	4:00[c]	X		X		
		7h after the end of infusion (±15 min)	8:00[c]	X		X		
	2	24h after start of infusion (±1 hr)	24:00	X		X		X[h]
	4	48:00-96:00	72:00	X				
	8	144:00-192:00	168:00	X			X[d]	
	15	Before start of BI 905681 infusion	335:55	X	X	X	X[b,d]	
		Start of BI 905681 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 (±10 min)	340:00[c]			X		
		7h after the end of infusion (±15 min)	344:00[c]			X		
	16	24h after start of infusion (±1 hr)	360:00	X		X		
	22	480:00-528:00	504:00	X				

Table 10.2: 2 (cont.) 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 905681	ADA	Cytokines	ECG	Tumour Biopsy
3 and 4	1	Before start of BI 905681 infusion	-0:05	X	X	X	X[b]	
		Start of BI 905681 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 (±10 min)	4:00[c]			X		
		7h after the end of infusion (±15 min)	8:00[c]			O		
	2	24h after start of infusion (±1 hr)	24:00			O		
	8	144:00-192:00	168:00	X				
	15	Before start of BI 905681 infusion	335:55	X		X		
		Start of BI 905681 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 (±10 min)	340:00[c]			X		
		7h after the end of infusion (±15 min)	344:00[c]			O		
	16	24h after start of infusion (±1 hr)	360:00			O		
	22	480:00-528:00	504:00	X				
Cycle 5 onwards	1	Before start of BI 905681 infusion	-0:05	X	X	X	X[b]	
		Start of BI 905681 infusion	0:00					
		Before start of BI 905681 infusion	335:55	X[g]		X		
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 cycle1 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

h Only required in Cycle 2

10.3 STATISTICAL APPENDIX INCLUDING MODEL PERFORMANCE AND DATA SCENARIOS

A BLRM with overdose control will be used to guide dose escalation in this study. After patients in each cohort have completed at least one cycle of treatment, the prior distribution will be updated through Gibbs sampling procedures with the accumulated DLT data from the MTD evaluation period (first three weeks of Schedule A and first four weeks of Schedule B). Posterior probabilities for the rate of DLTs will be summarised from BLRM. Selection of the next dose will be based on these probabilities as well as on other safety laboratory and PK data.

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 10.3:1. These scenarios reflect potential on-study data constellations and related escalation as allowed by the model. For each scenario, the probability of overdose for the current dose, as well as the next potential dose and related probabilities of under-dosing, target dose and over-dosing are shown. The actual dose chosen for the next cohort, not shown in the Table 10.3:1, 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.

For example, scenario 1 corresponds to the case where no DLT is observed at the first two dose levels, then the next permitted dose is 4.5 mg/kg/q3w.

In scenarios 2 to 6, it is assumed that no DLT is observed until the dose level of 4.5 mg/kg/q3w. Scenarios 3 to 6 focus on the case where the dose level of 6.5 mg/kg/q3w is identified as the MTD. To be more specific, in scenario 3, when 1 DLT is observed at 4.5 mg/kg/q3w, the next dose permitted by the model is the same dose level and we enroll 3 more patients at 4.5 mg/kg/q3w in scenario 4 and observed no DLT. In this case, the model advises to escalate to the next dose level of 6.5 mg/kg/q3w. Assuming 1 DLT is then observed at 6.5 mg/kg/q3w, which is demonstrated in scenario 5, the model proposed to stay at dose level of 6.5 mg/kg/q3w and enroll 3 more patients. Finally in scenario 6, assuming 1 additional DLT is observed, the criteria for MTD are met and 6.5 mg/kg/q3w is claimed to be the MTD.

In cases when DLT is not observed until the predicted efficacious dose 6.5 mg/kg/q3w, the adaptive feature of the model is fully illustrated in scenarios 7 to 10. Despite the fact that no DLTs were observed in the first three cohorts with 9 patients in total, the model reacts immediately to the data observed at 6.5 mg/kg/q3w and advises to stay at current dose in scenario with 1 observed DLT in scenario 8 and de-escalate with 2 observed DLTs in scenario 10. Further in scenario 9, one additional DLT is observed at 6.5mg/kg/q3w, the criteria of MTD are met and we claim MTD at 6.5 mg/kg/q3w.

Table 10.3:1 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	1 2.5	0 0	[redacted]	0.007	4.5	0.861	0.097	0.042
2	1 2.5 4.5	0 0 2		0.433	2.5	0.622	0.299	0.079
3	1 2.5 4.5	0 0 1		0.116	4.5	0.601	0.283	0.116
4	1 2.5 4.5 4.5	0 0 1 0		0.042	6.5	0.568	0.262	0.170
5	1 2.5 4.5 4.5 6.5	0 0 1 0 1		0.212	6.5	0.407	0.381	0.212
6	1 2.5 4.5 4.5 6.5 6.5	0 0 1 0 1 1		0.246	6.5	0.284	0.471	0.246
7	1 2.5 4.5	0 0 0		0.012	6.5	0.842	0.100	0.057
8	1 2.5 4.5 6.5	0 0 0 1		0.131	6.5	0.598	0.271	0.131
9	1 2.5 4.5 6.5	0 0 0 2		0.179	6.5	0.422	0.399	0.179
10	1 2.5 4.5 6.5	0 0 0 2		0.477	4.5	0.542	0.362	0.096

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 characteristics of the model, we assume 5 true dose-toxicity scenarios. As is shown in Table 10.3: 2, 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: High toxicity values are assumed corresponding to the respective dose levels
- Scenario 3: 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.
- Scenario 6: Extremely high toxicity values are assumed corresponding to the respective dose levels

Table 10.3: 2 Assumed true dose-toxicity scenarios (Schedule A)

P(DLT)	Dose (mg/kg/q3w)				
Scenario	1	2.5	4.5	6.5	8.5
1 (Prior)	0.081	0.118	0.165	0.214	0.254
2 (High Tox)	0.110	0.260	0.400	0.480	0.550
3 (Low Tox)	0.010	0.035	0.070	0.110	0.180
4 (Non-Logistic)	0.020	0.090	0.220	0.280	0.350
5 (Low-High)	0.030	0.080	0.160	0.350	0.470
6 (Extremely High Tox)	0.280	0.380	0.430	0.470	0.510

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 10.3: 3.

Table 10.3: 3 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	21.0	72.0	0.0	7	16.15 (3 – 33)	2.54 (1 – 8)
2	25.3	39.3	21.8	13.6	13.89 (3 – 39)	3.52 (1 – 12)
3	19.2	80.8	0	0	18.16 (9 – 51)	1.76 (1 – 7)
4	27.8	42.2	29.5	0.5	16.45 (3 – 36)	2.86 (1 – 11)
5	19.9	44.8	34.2	1.1	18.19 (3 – 45)	3.53 (1 – 10)
6	0	20.7	20.9	58.4	8.87 (3 – 30)	2.94 (1 – 11)

Scenario 1 reflects the case that the true dose-toxicity is aligned with prior means, 72.0% 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 (13.6%) 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 (80.8%). Since none of the pre-defined dose levels has a true DLT rate in the overdose range, none of the trials (0%) are stopped prematurely.

In scenarios 4 and 5, 42.2% and 44.8% of the simulated trials declared a dose as MTD with true DLT rate in the targeted dose range, respectively.

In scenario 6 (extremely high-toxicity scenario), a majority of trials (58.4%) stopped prematurely.

The mean patient numbers range from 8.87 patients (extremely high-toxicity scenario) to 18.19 patients (low-high scenario) and the maximum number of patients was 51. Therefore, the patient numbers are as expected and increase when moving away from the extremely 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.

10.4 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)

11.1 GLOBAL AMENDMENT 1

Date of amendment		15 November 2019
EudraCT number **EU number**		2019-003490-25
BI Trial number		1424-0001
BI Investigational Product(s)		BI 905681
Title of protocol		An open-label, Phase I trial to determine the maximum-tolerated dose and investigate safety, pharmacokinetics and efficacy of BI 905681 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		
Section to be changed		FLOW CHART: BI 905681 (REFMAL 638) SCHEDULE A TRIAL ASSESSMENTS
Description of change		The Follow-Up blood sample for bone biomarkers was removed. Footnote k stating that Bone biomarkers will be assessed on Cycle 1 Day 1, Cycle 2 Day 1 and then on Day 1 of every odd-numbered cycle and the EOT visit was correct.
Rationale for change		Flow Chart was revised to correct an error in the original version of the CTP.
Section to be changed		FLOW CHART: BI 905681 (REFMAL 638) SCHEDULE B TRIAL ASSESSMENTS
Description of change		The Follow-Up blood sample for bone biomarkers was removed. Footnote k stating that Bone biomarkers will be assessed on Cycle 1 Day 1, Cycle 2 Day 1 and then on Day 1 of every odd-numbered cycle and the EOT visit was correct.
Rationale for change		Flow Chart was revised to correct an error in the original version of the CTP.

Section to be changed		Section 3.1 Overall Trial Design and Plan
Description of change		**After the criterion for MTD is fulfilled, there will be no further dose escalation regardless of the SMC recommendation.** ~~The SMC may recommend stopping further dose escalation after the criterion for MTD is fulfilled. Additional patients may be included to confirm this MTD estimate (and to further evaluate PK/PDc), i.e. to confirm that the EWOC criterion is still fulfilled.~~
Rationale for change		Text was revised to ensure that if the MTD criterion is fulfilled, there is no further dose escalation regardless of the SMC recommendation.
Section to be changed		Table 4.1.1
Description of change		Dilution in ~~5% glucose~~ 0.9% sodium chloride is required
Rationale for change		Text was revised to correct an error in the original version of the CTP.
Section to be changed		Section 4.1.3 and Section 4.1.4
Description of change		The absolute maximum clinical dose must not exceed 1120 mg/dose.
Rationale for change		Text was revised to ensure that the specifications for host cell DNA and endotoxins stay within the recommended limits for the provisional dose levels for Schedule B.
Section to be changed		Section 4.1.4 Starting Dose for Schedule B
Description of change		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** ~~who~~ will also review whether the planned dosing schedule, assessments and sample collection in Schedule B remain appropriate, and may decide not to pursue testing of this schedule.
Rationale for change		Text was revised to include specific details on the provisional starting dose of Schedule B in relation to the Schedule A MTD.
Section to be changed		Section 7.1
Description of change		The BLRM recommended dose for the next dose level is the level with the posterior probability of the DLT rate falling in the target interval [0.16, 0.33] ~~among the doses fulfilling EWOC~~without skipping any dose level.
Rationale for change		The text was revised to clarify that no dose levels would be skipped.

APPROVAL / SIGNATURE PAGE

Document Number: c29037963 **Technical Version Number:2.0**

Document Name: clinical-trial-protocol-revision-01

Title: An open-label, Phase I trial to determine the maximum-tolerated dose and investigate safety, pharmacokinetics and efficacy of BI 905681 administered intravenously in patients with advanced solid tumours

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Program [redacted]	[redacted]	15 Nov 2019 09:28 CET
Author-Clinical Trial Leader		15 Nov 2019 09:47 CET
Author-Clinical Pharmacokineticist		15 Nov 2019 09:55 CET
Approval-Therapeutic Area [redacted]		15 Nov 2019 14:11 CET
Author-Trial Statistician		15 Nov 2019 17:13 CET
Approval-Clinical Trial Leader		15 Nov 2019 17:15 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**