Clinical Trial Protocol

	Document Number:	**c30222580-03**
BI Trial No.	1469-0002	
BI Investigational Medicinal Product(s)	BI 3011441	
Title	A phase I open-label trial of BI 3011441 in Japanese patients with NRAS/KRAS mutation positive advanced, unresectable or metastatic refractory solid tumours	
Lay Title	A study to test different doses of BI 3011441 in Japanese people with different types of advanced cancer (NRAS/KRAS mutation positive)	
Clinical Phase	I	
Clinical Trial Leader	[redacted] Telephone: , Fax:	
Coordinating Investigator	[redacted] Telephone:	
Version and Date	**Version:3.0**	**Date: 19 Nov 2020**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	Date: 9 Jun 2020
Revision date	Date: 19 Nov 2020
BI trial number	1469-0002
Title of trial	A phase I open-label trial of BI 3011441 in Japanese patients with NRAS/KRAS mutation positive advanced, unresectable or metastatic refractory solid tumours
Coordinating Investigator	[redacted] Telephone: [redacted]
Trial site(s)	Multi-centre trial
Clinical phase	I
Trial rationale	The present study, 1469-0002, is designed to evaluate the safety, tolerability, PK[redacted] and clinical activity of BI 3011441 as monotherapy in subjects with NRAS/KRAS mutation positive solid tumours in Japanese patients. Safety/tolerability, pharmacokinetic [redacted] profile, as well as preliminary antitumour activity, acquired in this trial will provide the basis for further development of BI 3011441 alone or in combination with other drug(s).
Trial objective(s)	The primary objective of this trial is to confirm the safety and tolerability of previously identified MTD, BI 3011441 8mg (in Caucasian FIH study) as a single agent when administered orally to adult Japanese patients with NRAS/KRAS mutation positive advanced or metastatic refractory solid tumours.
Trial endpoints	Primary endpoints • Maximum tolerated dose • Number of patients with DLTs in the MTD evaluation period. Secondary endpoints • Number of patients with DLTs during the entire on-treatment period • Number of patients with Grade ≥3 treatment-related adverse events • Number of patients with treatment related adverse events at each dose level • Pharmacokinetic parameters of BI 3011441: $C_{max(,ss)}$ and $AUC_{0\text{-}tz(,ss)}$
Trial design	Open-label monotherapy dose escalation trial of MTD determination.
Total number of patients randomised	Approximately 12

Number of patients on each treatment	Approximately 12
Diagnosis	Patients with a confirmed diagnosis of NRAS/KRAS mutation positive advanced, unresectable, or metastatic refractory solid tumours .
Main in- and exclusion criteria	**Main inclusion criteria** • Must be at least 20 years of age at screening. • Signed and dated written informed consent in accordance with GCP and local legislation prior to admission to the trial. • Pathologically documented, locally-advanced or metastatic malignancy with previously-identified activating NRAS or KRAS mutation based on local test. • Provision of archival tumor tissue, if available, to confirm retrospectively NRAS or KRAS mutation status and for biomarker assessment. • Willingness to undergo pre- and on-treatment tumour biopsies [redacted]. Patients can be enrolled without tumour biopsy upon agreement between the Investigator and the Sponsor if tumour biopsy is not feasible. • Must have either progressed despite appropriate prior standard therapies or for whom no standard therapy exists for their tumour type and disease stage. • Must have at least one target lesion that can be measured per RECIST version 1.1 • Must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. • Must show adequate organ function. **Main exclusion criteria** • Previous anticancer chemotherapy within 3 weeks of the first administration of trial drug. • Radiotherapy within 4 weeks prior to first administration of BI 3011441. • Major surgery within 4 weeks prior to start of treatment or scheduled during the projected course of the trial. • Previous treatment with a RAS, MAPK targeting agent. • Patients who have a history or current evidence/risk of retinal vein occlusion (RVO) or retinal pigment epithelial detachment or central serous retinopathy. • Patients who have visible retinal pathology that is considered a risk factor for RVO or central serous retinopathy as assessed by ophthalmic examination. • History or presence of cardiovascular abnormalities.

	• Left ventricular ejection fraction (LVEF) <50 %. • Baseline QT interval corrected for heart rate using Fridericia's formula (QTcF) >470 msec or congenital long QT syndrome • Leptomeningeal carcinomatosis. • Presence or history of uncontrolled or symptomatic brain metastases.
Test product(s)	BI 3011441
dose	4 mg, 6 mg, 8 mg per day (7 mg if necessary by the BLRM with the overdose control)
mode of administration	Per os / oral (p.o.)
Comparator product(s)	Not applicable
dose	Not applicable
mode of administration	Not applicable
Duration of treatment	Reiterated treatment cycles of 4 weeks as long as the patient has clinical benefit or until undue drug toxicity or withdrawal of consent, whichever occurs first
Statistical methods	Descriptive statistics will be used to describe safety and efficacy analyses. Dose escalation will be guided by a Bayesian logistic regression model (BLRM) with overdose control that will be fitted to binary toxicity outcomes. The estimates of the model parameters will be updated as data are accumulating using the BLRM. At the end of the dose escalation, the toxicity probability at each dose level in each arm will be calculated to determine an estimate of the MTD.

FLOW CHART

Trial period	**SCR**	**BI 3011441 monotherapy treatment period**									**EOT[q]**	**EOR[r]**	**Extended FU for progressive disease[s]**
Cycle[a]		**C1[t]**							**C2**	**C3+**			**Every 8 weeks**
Visit number	**SCR**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**1**	**1**	**EOT**	**EOR**	
Treatment day	**Up to 28 days[b]**	**1**	**2**	**3**	**8**	**15 ±1**	**16**	**22 ±3**	**1 ±2**	**1 ±2**		**30 d after treat. disc. (+1 wk)**	**±4 days**
Informed consent	x												
Inclusion / exclusion criteria	x	x											
Medical history and demographics	x												
Report planned hospitalisations	x												
Physical examination, height (screening only), and weight[c]	x	x							x	x	x	x	x
ECOG Performance score[c]	x	x				x			x	x	x	x	x
Issue patient diary[d]		Continuous											
12-Lead Electrocardiograms (triplicate) [e]	x	x				x	x		x	x	x		
LVEF[f]	x					x			x	x	x		
Vital signs	x	x	x	x	x	x	x	x	x	x	x	x	
Pregnancy test[g]	x	x							x	x	x		
Safety laboratory (haematology, biochemistry, urine, virology)[g]	x	x			x	x	x	x	x	x	x		
Safety laboratory (coagulation)[g]	x	x							x	x	x		
Ophthalmological assessment[h]	x								x	x	x		
Tumour assessment[i]	x									x	x		x
Blood sampling for pharmacokinetics[j]		x	x		x	x	x	x	x	x			
[redacted]		[redacted]											
Archival tumour tissue [l]	x												
BI 3011441 intake[m]		Continuous daily treatment until progression											
Concomitant therapy	x	x	x	x	x	x	x	x	x	x	x	x	x
All AEs/SAEs/AESIs[n]	x	x	x	x	x	x	x	x	x[u]	x	x	x	
Vital status[o]												x	x
Eligibility for next treatment cycle[p]									x	x			

a) Treatment cycles (C) are 28 days (4 weeks). Patients will continue treatment with BI 3011441 as long as they are deriving clinical benefit or until undue drug toxicity or withdrawal of consent, whichever occurs first.
b) Screening should take place within 28 days of start of trial treatment.
c) Physical examinations including the measurements of height (screening only) and weight will be done at screening, on Day 1 of each treatment cycle, at the end-of-treatment (EOT) visit, at the 30-day end of residual effect (EOR) visit, and at the follow-up (FU) visits for progressive disease. ECOG performance status will be done at screening, on Days 1 and 15 of Cycle 1, Day 1 of Cycle 2, on Day 1 of every other cycle beginning with Cycle 3, at the EOT visit, at EOR, and at FU visits for progressive disease.
d) A patient diary will be given to the patient for continuous use through the trial. It should be given to the patient at the start of each cycle. The diary collects information about BI 3011441 taken at home and provides reminders about fasting blood samples. After one week on trial medication, treatment compliance should be discussed with the patient, to ensure that the medication is being taken correctly (no compliance calculation has to be performed). Then at Visit 1 of each cycle and at EOT treatment compliance needs to be checked including compliance calculations.
e) 12-lead electrocardiograms (ECGs) will be done in triplicate before blood work or other procedures after 5 minutes of rest at screening, see section 5.2.4.
f) LVEF is measured by echocardiography at screening, Day 15 of Cycle 1, C2V1, then every 2 cycles (i.e. C4V1, C6V1, C8V1, etc.) and EOT. Additional LVEF assessments should also be done if clinically indicated.
g) Safety laboratory assessments including haematology, serum biochemistry, coagulation, pregnancy tests, urinalysis and virology (only at screening) will be performed locally. If screening laboratory tests are completed within 72 hours prior to first dose, predose samples on Day 1 of Cycle 1 will not be repeated. See Section 5.2.3 for further detail. Pregnancy tests are mandatory for women with child-bearing potential. A serum beta human chorionic gonadotropin (β-HCG) pregnancy test must be done at screening. Thereafter, this test can be done in either serum or urine on Day 1 of each cycle, at the EOT visit, and at EOR.
h) An ophthalmological assessment must be done at screening, C2V1, C3V1, C4V1 and then every 2 cycles (i.e. C6V1, C8V1, C10V1, etc.) and EOT. Ophthalmological assessment can be done separated ±2 day from visit. Additional ophthalmological assessments should also be done if clinically indicated.
i) Tumour assessments should be done according to RECIST v1.1 and should include computed tomography (CT) scans of the chest and abdomen and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g., pelvis, brain) using an appropriate method (CT scan or magnetic resonance imaging [MRI]). See Section 5.1 for detail.
j) PK sample (plasma [redacted]) will be collected at timepoint indicated in Table 10.1: 1.
k) [redacted]
l) Archival formalin-fixed paraffin-embedded (FFPE) tumour tissue from most recent timepoint (preferred less than 6 month old) should be collected. See Section 5.4 and Table 5.4.1: 1 for further details.
m) BI 3011441 intake is daily. Dosing of BI 3011441 will be determined by the SMC and communicated separately as each new cohort opens for recruitment.
n) DLTs will be collected throughout the trial and will be assessed for dose-escalation decisions following the first cycle. All serious adverse events (SAEs)/ and adverse events of special interest (AESIs) considered trial treatment related, cancers of new histology and exacerbations of existing cancer (see section 5.2.6.2.1) must be collected in the extended follow-up period.
o) Patients who discontinue trial treatment prematurely and have agreed to be contacted, should be called at least at the end of their scheduled trial participation to obtain their vital status information, please see Section 5.2.6.2.1
p) Before initiating a new treatment cycle, criteria should be checked, please see Section 4.1.4.1
q) An EOT visit should be performed for all patients who permanently discontinued trial medication. If the decision to permanently discontinue treatment is taken at a scheduled visit, the EOT visit should be performed instead of the scheduled visit (preferably within 7 days after the last treatment).
r) Residual effect period (REP) starts after last dose of trial medication and ends 30 days later. Whenever possible, a 30-day safety FU visit should take place before any other anti-cancer treatment starts.

s) Extended Follow-up for progressive disease visits for tumour assessment by imaging (CT scan or MRI) for patients who discontinue trial treatment without having progressive disease based on RECIST v1.1 should be performed every 8 weeks (±4 days) until progressive disease or another withdrawal criterion is met. At these visits, SAEs and AESIs occurring during the trial that are considered to be related to trial treatment or procedures will be followed until resolution after EOR until the individual patient's end of trial.

t) Patients will remain hospitalised for at least three days after the first administration of BI 3011441. On day four or later, the investigator will then evaluate whether it is appropriate to discharge the patient based on the patient's condition. For this evaluation, the investigator will perform the assessment of adverseevents and if necessary haematology and clinical chemistry examination.

u) X-ray for chest region will be conducted to determine presence of interstitial lung diseases on Day 1 of Cycle 2.

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AO	Aldehyde oxidase
aPTT	Activated partial thromboplastin
AST	Aspartate transaminase
AUC	Area under the concentration-time curve of the analyte in plasma
BI	Boehringer Ingelheim
BLRM	Bayesian Logistic Regression Model
BRAF	v-Raf murine sarcoma viral oncogene homolog B
CA	Competent Authority
CK	Creatine kinase
CK-MB	Creatine kinase myocardial band
CKD-EPI	Chronic Kidney Disease Epidemiology
C_{max}	Maximum measured concentration of the analyte in plasma
[redacted]	[redacted]
CRA	Clinical Research Associate
CRC	Colorectal cancer
CREE	Enzymatic serum creatinine assay
CREJ	Non IDMS standardized Jaffe
CREJIDMS	Isotype dilution mass spectrometry standardized Jaffe
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Computed Tomography
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol

CYP	Cytochrome P450
[redacted]	[redacted]
DILI	Drug Induced Liver Injury
DLT	Dose limiting toxicity
[redacted]	[redacted]
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
eDC	Electronic Data Capture
EGFR	Epidermal growth factor receptor
[redacted]	[redacted]
EOR	End of residual effect
EOT	End of Treatment
ERK	Extracellular signal-regulated kinases
EWOC	Escalation with overdose control
FFPE	Formalin-fixed paraffin-embedded
[redacted]	[redacted]
FU	Follow up
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HCO_3	Bicarbonate
[redacted]	[redacted]
IB	Investigator's Brochure
IC50	Inhibitory concentration (50%)
IDMS	Isotype dilution mass spectrometry
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
KRAS	Kirsten rat sarcoma viral oncogene homologue
LVEF	Left ventricular ejection fraction
MAO	Monoamine oxidases
MAP	Mitogen-activated protein
MAPK	Mitogen-activated protein kinase

MedDRA	Medical Dictionary for Drug Regulatory Activities
MEK	Mitogen-activated protein kinase kinase
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NRAS	Neuroblastoma RAS viral (v-ras) oncogene homolog
NSCLC	Non-small cell lung cancer
OPU	Operative Unit
[redacted]	[redacted]
p.o.	per os (oral)
PD	Pharmacodynamics
PFS	Progression-free survival
PK	Pharmacokinetics
[redacted]	[redacted]
PT	Prothrombin time
QTcF	QT interval
RAC	Accumulation Index
RAF	Rapidly Accelerated Fibrosarcoma
RAS	Rat sarcoma
RD	recommended dose
RECIST	Response Evaluation Criteria in Solid Tumours
REP	Residual effect period
RPED	Retinal Pigment Epithelial Detachment
[redacted]	[redacted]
SAE	Serious adverse event
SD	Standard deviation
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
[redacted]	[redacted]
[redacted]	[redacted]
SUSAR	Suspected unexpected serious adverse reaction
[redacted]	[redacted]
[redacted]	[redacted]
TSAP	Trial Statistical Analysis Plan

ULN	Upper limit of normal
WHO	World Health Organisation
β -HCG	beta human chorionic gonadotropin

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

The rat sarcoma (RAS)/ rapidly accelerated fibrosarcoma (RAF) / mitogen-activated protein kinase kinase (MEK)/ extracellular signal-regulated kinases (ERK) pathway (also known as the mitogen-activated protein kinase [MAPK] pathway) is one of the most important and intensively studied signaling pathways involved in the regulation of cell proliferation in normal as well as cancer cells. Signal transduction through this pathway begins with the binding of extracellular growth factors to specific trans-membrane receptors or constitutive activation of the receptor tyrosine kinase(s), leading to activation of Ras GTPase that via adaptor proteins leads to the activation of RAF kinase (B-Raf or C-Raf). Raf forms the most upstream (initiating) kinase of the pathway and is also referred to as mitogen-activated protein kinase (MAP kinase), which phosphorylates and activates the MEK that in turn phosphorylates and activates the ERK. Events such as epidermal growth factor receptor (EGFR) overexpression, EGFR mutation, Ras mutation, or B-Raf mutation often lead to activation of the MAP kinase pathway. MEK, mitogen-activated extracellular signal-regulated kinase, is a key protein kinase in this pathway, which has been shown to be activated in several tumour types such as melanoma, colorectal cancer (CRC), pancreatic cancer, non-small cell lung cancer (NSCLC), thyroid cancer, ovarian cancer, certain leukemias and, in particular, tumours with v-Raf murine sarcoma viral oncogene homolog B (BRAF), kirsten rat sarcoma viral oncogene homologue (KRAS) and neuroblastoma RAS viral (v-ras) oncogene homolog (NRAS) mutations (R19-3904). The MEK enzyme is attractive due to high selectivity for its target ERK and the central role that activated ERK plays in driving cell proliferation.
Upregulation of the RAS/RAF/MEK/ERK pathway has been implicated in approximately 30% of human cancer and the frequency of RAS mutation is high in pancreatic cancer (90%), papillary thyroid cancer (60%), colon cancer (50%), and NSCLC (30%) (R19-0761). Thus, inhibition of RAS/RAF/MEK represents a promising strategy for the discovery of a new generation of anticancer treatment.

BI 3011441 (LNP3794 and LND300110 are the [redacted] codes for Drug Product and Drug substance, respectively) is being developed as an [redacted].

1.2 DRUG PROFILE

Mode of action

[redacted]

[redacted]

Key pharmacokinetic characteristics; Non Clinical

[redacted]

Drug interactions

BI 3011441 appeared to be metabolized [redacted]

[redacted]

Key pharmacokinetic characteristics; Clinical

[redacted]

Residual Effect Period

The Residual Effect Period (REP) of BI 3011441 is 30 days. [redacted]

Data from non-clinical studies

[redacted]

Data from clinical studies

[redacted]

For a more detailed description of the BI 3011441 profile, please refer to the current Investigator's Brochure (IB, c30780360).

1.3 RATIONALE FOR PERFORMING THE TRIAL

Currently, [redacted] have been approved globally but the indication is mostly limited to the combination usage with v-Raf murine sarcoma viral oncogene homolog B (BRAF) inhibitor. The safety profile of those drugs require monitoring for potential ocular and cardiac toxicities during the course of treatment and therefore, there is an unmet medical need to develop [redacted] to have favorable safety profile in addition to targeting other cancer types.

Although the first in human (FIH) study with BI 3011441 had been completed with the identification of 8mg as an MTD in Caucasian patients, there is no data to support that this dose would be safe and tolerable for Asian patients. Furthermore, it is important to understand the safety profiles of BI 3011441 at lower dose levels, as the drug is currently planned to be [redacted].

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

This trial is for patients with no therapy options of proven efficacy, or who are not amenable to standard therapies. Anti-tumour activity was seen in BI 3011441 monotherapy in various RAS mutation positive tumour types from pre-clinical models. Moreover, the completed phase I study showed the clinical activity in RAS mutant solid tumours and therefore, it is anticipated that target patients for the study may still receive a benefit from the study treatment.

1.4.2 Risks

The potential clinically important risks based on the BI 3011441 pre-clinical data and clinical data are displayed in Table 1.4.2: 1.

The number of patients to be exposed to BI 3011441 monotherapy will take into account the characterisation of safety profile and anti-tumour activity of monotherapy. A Bayesian Logistic Regression Model (BLRM) design will be used in order to escalate the dose into 8mg still minimizing the risk of undue toxicity.

A Safety Monitoring Committee (SMC) will assess trial data to ensure overall safety of the patients treated. Based on the accumulated data, the SMC will reach a joint recommendation on the next dose level of BI 3011441 to be investigated and the sample size for the next dose-escalation cohort, and provide advice about the overall conduct of the trial.

Table 1.4.2:1 Potentially clinically important risks, their rationale and mitigation strategy

Potential risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product BI 3011441		
QT prolongation	Observed with [redacted].	Patients with history long QT syndrome, mean resting corrected QT interval (QTcF) >470 msec or patients with poorly controlled arrhythmia are excluded. Pre-planned 12-lead ECGs will be frequently performed.
Left ventricular ejection fraction (LVEF) decrease	Observed with [redacted].	Patients with LVEF <50 % are excluded. Pre-planned echocardiograms will be performed to measure LVEF.

Table 1.4.2:1 Potentially clinically important risks, their rationale and mitigation strategy (cont.)

Potential risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product BI 3011441		
Ocular toxicities	Ocular toxicities such as central serous retinopathy or vison impairment were observed in the FIH study. Observed with [redacted]	Patients with a history of retinal vein occlusion (RVO) and retinal pigment epithelial detachment are excluded. Pre-planned ophthalmologic exams will be performed to monitor it.
Drug-induced liver injury (DILI)	Rare but potentially severe event with all drugs in development.	As DILI is an adverse events of special interest (AESI), there will be timely detection, evaluation, and follow-up of pre-specified liver laboratory parameters to ensure patients´ safety.
Interstitial Lung Disease	Rare but potentially severe event observed with [redacted].	Patients with pre-existing interstitial lung disease are excluded.
Hypertension	Observed with [redacted].	Patients with uncontrolled hypertension are excluded. Vital signs will be monitored at each trial visit.
Rhabdomyolysis	Observed with [redacted].	Patients with CPK ≥ 2.5 x ULN are excluded. CPK level will be monitored.
Photosensitivity	Observed with [redacted].	Patients will be instructed to avoid direct sun light.
Trial procedures		
[redacted]	[redacted]	[redacted]

1.4.3 COVID-19 related Benefit-Risk Assessment

To date, there is no evidence suggesting an association between COVID-19 and MEK1/2 inhibition targeted by BI 3011441. Considering the currently limited data on risk factors that may increase the severity and mortality of COVID-19, there may be as yet unknown relevant risk factors in treating patients with BI 3011441. Information regarding relevant risk factors and recommendations from professional oncology organizations will be monitored as it evolves.

The protocol-defined trial procedures themselves do not impose any increased risk to study participants in developing COVID-19. The risk mitigation measures currently in place within the clinical trial protocols are a sufficient safeguard, as patients are frequently monitored with comprehensive safety evaluations.

The investigators will take the totality of information related to each single patient and the local COVID-19 situation into consideration when performing individual benefit-risk assessments on a case-by-case basis, in regards to any additional potential risks for patients receiving BI 3011441. Considering all relevant aspects relevant to the COVID-19 pandemic, the investigator will make individual benefit-risk assessments for each patient's (continued) participation in the trial. BI as the sponsor, recommends to adhere to the trial protocol as much as possible and where required, will support the investigator in their decision finding.

1.4.4 Discussion

Based on pre-clinical and clinical results, BI 3011441 showed single agent anti-tumour activity in a xenograft mouse model as well as in subjects with RAS mutant solid tumours. The therapeutic benefit or specific adverse events in patients cannot always be anticipated during the trial setup and therefore, patients should be advised and carefully monitored for the potential risk of side effects from this investigational drug.

The clinical trial sites qualified to participate in this trial will be experienced comprehensive cancer centres in treating patients with investigational drugs and with the necessary infrastructure. The Investigators and Sponsor will form a SMC. During the conduct of trial, the SMC will meet regularly and during dose escalation at minimum after all patients in each dose cohort have completed cycle 1. The Sponsor will continuously assess the risks and benefits of the trial based on accumulating clinical data from all clinical trials with BI 3011441. Any significant change in risk/benefit ratio will be communicated to Investigators and patients.

In summary, the present trial will implement a number of safety measures to mitigate possible risks. Therefore, a potential benefit is offered to patients with advanced and/or metastatic malignancies with no other approved treatment options with BI 3011441. The benefit-risk ratio of treating patients with BI 3011441 monotherapy is therefore considered to be acceptable.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The primary objective of this trial is to confirm the safety and tolerability of previsouly identified MTD, BI 3011441 8mg (in Caucasian FIH study) as a single agent when administered orally to adult Japanese patients with NRAS/KRAS mutation positive advanced or metastatic refractory solid tumours.

The MTD will be determined based on the frequency of patients experiencing DLTs during the MTD evaluation period. The MTD evaluation period is defined as first treatment cycle (28 days). At the end of the dose escalation, the BLRM will be rerun using all DLTs. This result as well as all available data will be used to define the recommended dose (RD).

The secondary objectives is to evaluate the safety and tolerability, and characterise PK of BI 3011441 as monotherapy in Japanese patients with NRAS/KRAS mutation positive advanced solid tumours

2.1.2 Primary endpoint(s)

- MTD defined as the highest dose with less than 25% risk of the true DLT rate being equal or above 33% during the MTD evaluation period. For the definition of DLTs, refer to Section 5.2.6.3
- Number of patients with DLTs in the MTD evaluation period.

2.1.3 Secondary endpoint(s)

- Number of patients with DLTs during the entire on-treatment period
- Number of patients with Grade ≥3 treatment-related adverse events
- Number of patients with treatment related adverse events at each dose level
- Pharmacokinetic parameters of BI 3011441: $C_{max(,ss)}$, and $AUC_{0\text{-}tz(,ss)}$

[redacted]

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

The trial is an open-label, non-randomised phase I trial of BI 3011441 as monotherapy to investigate the safety/tolerability, PD and PK profile at selected dose levels in Japanese patients with NRAS/KRAS mutation positive advanced or metastatic refractory solid tumours. Patients will be enrolled based on the available NRAS/KRAS mutation status previously identified by local test results performed prior to screening. The data obtained from the trial will determine the MTD estimate based on a Bayesian logistic regression model with overdose control (R13-4803). The BLRM estimates the MTD by updating estimates of the probability of observing a DLT in the MTD evaluation period for each dose level in the trial as patient information becomes available. At any time in the trial, it will not be permitted to escalate to a dose which does not fulfil the escalation with overdose control (EWOC) principle (refer to Section 7).

The provisional dose levels to be evaluated will be 4mg, 6mg and 8mg, which includes the previously established MTD of 8mg for Caucasian patients. For any dose-escalation cohort, at least 3 patients will be required (refer to Section 7). However, in the case that only 2 patients are evaluable and neither has experienced a DLT within the MTD evaluation period, then dose-escalation can occur based on these 2 patients. For determination of MTD or RD, 6 patients will be enrolled at least. A BLRM with overdose control will be performed once the enrolment of 3 patients at each dose level has been completed and these patients completed the first cycle of treatment of BI 3011441. Each cycle will consist of 28 days (4 weeks) and patients will continue the treatment until undue drug toxicity, disease progression, or withdrawal of consent, whichever occurs first. The longest treatment period will be 2 years if deemed safe and efficacious. Intra-patient dose escalation will be allowed if there is an indication from higher-dose cohorts that there is a positive-risk-benefit once the patient completed the 1st cycle of treatment including PK [redacted] sampling.

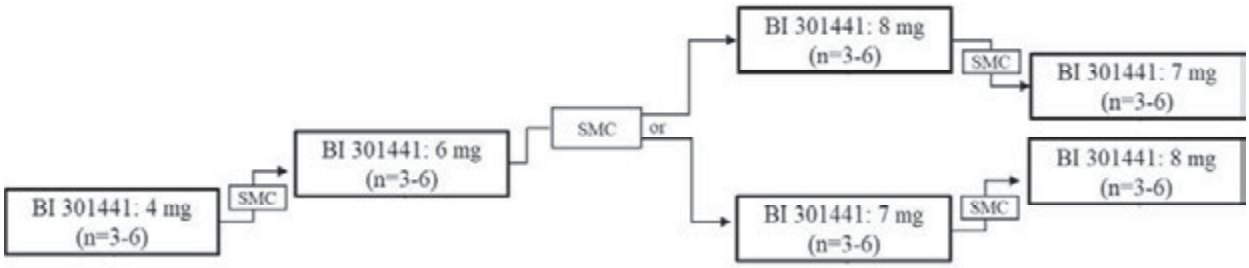


Figure 3.1: 1 Study design

The Safety Monitoring Committee (SMC, see Section 8.7) will recommend the size for the next dose escalation cohort. After all patients in a cohort have either experienced a DLT or have been observed for at least the MTD evaluation period without experiencing a DLT, the Bayesian model will be updated with the newly accumulated data. The overdose risk will then be calculated for each dose, and escalation will be permitted to all doses which fulfil the EWOC criterion and the additional 50 % escalation rule. Based on the model and on

additional information (PK, PD, patient profiles), the members of the SMC will reach a joint decision on the next dose level to be investigated.

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

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

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

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

The clinical data of BI 3011441 from the FIH study conducted in Caucasian patients allows to already define three dose levels to be investigated in this trial.
Although provisional dose levels exist, dose escalation and cohort size will be still determined based on the recommendation of the SMC, guided by a BLRM with overdose control. An escalation with overdose control design will increase the chance of treating patients at efficacious doses while reducing the risk of overdosing. This design is based on practical experience and is an efficient method due to its ability to identify the dose with a desired toxicity rate and its allocation of a greater proportion of patients to doses at, or close to, that desired dose (R13-4802, R13-4804, R13-4805). The use of Bayesian models for Phase I studies has also been advocated by the EMA guideline on small populations (R07-4856) and by the FDA (R13-4881). This trial is a single-arm trial with multiple dose cohorts and there is no control group.

3.3 SELECTION OF TRIAL POPULATION

Approximately 12 patients are planned to be included, but will be adjusted by DLT results. This trial will be conducted in Japan and provide the safety and PK[redacted] data in Japanese patients in multiple dose levels.

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

If a patient is enrolled in error (does not meet all inclusion criteria or meets one or more exclusion criteria on the day of enrolment), the sponsor should be contacted immediately.

3.3.1 Main diagnosis for trial entry

Patients with a confirmed diagnosis of NRAS or KRAS mutation positive advanced, unresectable and/or metastatic solid tumours, who have failed standard treatment(s), or for whom no therapy of proven efficacy exists, or who are not amenable to standard therapies.

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. Must be at least 20 years of age at screening.
2. Signed and dated written informed consent in accordance with GCP and local legislation prior to admission to the trial.
3. Pathologically documented, locally-advanced or metastatic malignancy with previously identified activating NRAS or KRAS mutation based on local test.
4. Provision of archival tumor tissue, if available, to confirm retrospectively NRAS or KRAS mutation status and for biomarker assessment.
5. Willingness to undergo pre- and on-treatment tumour biopsies [redacted]. Patients can be enrolled without tumour biopsy upon agreement between the Investigator and the Sponsor if tumour biopsy is not feasible (Apply only to study site which agreed to conduct biopsy).
6. Must have either progressed despite appropriate prior standard therapies or for whom no standard therapy exists for their tumour type and disease stage
7. Must have at least one target lesion that can be measured per RECIST version 1.1
8. Must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
9. Must show adequate organ function as follows:
   a) Absolute neutrophil count (ANC) ≥1.5 x 10^9/L; hemoglobin ≥9.0 g/dL; platelets ≥100 x 10^9/L without the use of hematopoietic growth factors.
   b) Total bilirubin ≤1.5 times the ULN, or ≤4 x ULN for patients who are known to have Gilbert's syndrome.
   c) 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 Chronic Kidney Disease Epidemiology [CKD-EPI] formula).
   d) AST and ALT ≤3 x ULN if no demonstrable liver metastases, or otherwise ≤5 x ULN.
10. Creatine phosphokinase is <2.5 x ULN.
11. Must have recovered from any previous therapy related toxicity to Common Terminology Criteria for Adverse Events (CTCAE) grade ≤1 at C1V1 (except for alopecia; stable sensory neuropathy must be CTCAE grade ≤2).
12. Male patients able to father a child and/or female patients of childbearing potential must be able and willing to comply with contraceptive measures i.e. use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly, prior to study entry and for the duration of study participation and for a minimum timeperiod after treatment has ended, at least 3 months.
13. Women of childbearing potential who are not surgically sterilized must have a negative serum pregnancy test completed during the Screening period.

14. Women who are nursing. Women who are nursing can be enrolled if they stop nursing. In this case, the patient cannot resume nursing until 30 days from discontinuation of study treatment.

*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 considered as a method of permanent sterilisation.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. Addition to this, even no menses for 12 months, if possibility of amenorrhea caused by anti tumor treatement can not denied, pregnancy test should be conducted as same as WOCBP.

3.3.3 Exclusion criteria

1. Previous anticancer chemotherapy within 3 weeks of the first administration of trial drug. Previous anticancer hormonal treatment or anticancer immunotherapy within 2 weeks of the first administration of trial drugs.
2. Radiotherapy within 4 weeks prior to first administration of BI 3011441 except as follows
   - Palliative radiotherapy to regions other than the chest is allowed up to 2 weeks prior to start of treatment
   - Single dose palliative radiotherapy for symptomatic metastasis within 2 weeks prior to start of treatment may be allowed but must be discussed with the sponsor.
3. Major surgery within 4 weeks prior to start of treatment or scheduled during the projected course of the trial
4. Previous treatment with a RAS, MAPK targeting agent
5. Previous treatment with any investigational agent(s) or targeted treatment within 4 weeks (28 days) prior to start of trial drug or concurrent participation in another clinical trial with an investigational device or drug.
6. 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 efficacy and safety of the study medications
7. Patients who have a history or current evidence/risk of retinal vein occlusion (RVO) or retinal pigment epithelial detachment or central serous retinopathy; for example, predisposing factors of RVO or central serous retinopathy include uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes.
8. Patients who have visible retinal pathology that is considered a risk factor for RVO or central serous retinopathy as assessed by ophthalmic examination, such as:
   - Evidence of new optic disc cupping
   - Evidence of new visual field defects
   - Intraocular pressure >21 mm Hg

History or presence of cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure NYHA classification of ≥2, unstable angina or poorly controlled arrhythmia which are considered as clinically relevant by the investigator; Myocardial infarction within 6 months prior to start of treatment. Uncontrolled hypertension is defined

as: Blood pressure measured in a rested and relaxed condition, where systolic BP >=140 mmHg, or diastolic BP >= 90 mmHg, with or without medication.

9. Left ventricular ejection fraction (LVEF) <50 %.
10. Baseline QT interval corrected for heart rate using Fridericia's formula (QTcF) >470 msec or congenital long QT syndrome
11. Previous or concomitant malignancies at other sites, except effectively treated
    - Non-melanoma skin cancers
    - Carcinoma *in situ* of the cervix
    - Ductal carcinoma *in situ*
    - Other malignancy that has been in remission for more than 3 years and is considered to be cured.
12. Leptomeningeal carcinomatosis.
13. Presence or history of uncontrolled or symptomatic brain 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.
    - Patients who have resected brain metastases, or have received radiation therapy that finished at least 4 weeks (whole brain radiation) or 2 weeks (stereotactic body radiotherapy) prior to treatment of the trial are considered eligible if they meet all of the following criteria:
    a) Residual neurological symptoms CTCAE grade ≤2
    b) Are taking stable doses of dexamethasone, if applicable
    c) Follow-up magnetic resonance imaging (MRI) shows no new lesions
14. Known pre-existing interstitial lung disease
15. Known active hepatitis B infection (defined as presence of Hep B sAg and/or Hep B DNA), active hepatitis C infection (defined as presence of Hep C RNA)
16. Active infectious disease which puts the patient at increased risk in the opinion of the investigator
17. Any history or presence of uncontrolled gastrointestinal disorders that could affect the intake and/or absorption of the study drug (e.g. nausea, uncontrolled vomiting, Crohn's disease, ulcerative colitis, chronic diarrhoea, malabsorption) in the opinion of the investigator.
18. Patients not expected to comply with the protocol requirements or not expected to complete the trial as scheduled (e.g.chronic alcohol or drug abuse or any other condition that, in the investigator's opinion, makes the patient an unreliable trial participant).

3.3.4 Withdrawal of patients from treatment or assessments

Patients may discontinue trial treatment or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications; please see sections 3.3.4.1 and 3.3.4.1.1 below.

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

Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal.

The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and Case report form (CRF). If applicable, consider the requirements for Adverse Event collection reporting (please see sections 5.2.6.2.1 and 5.2.6.2).

3.3.4.1 Discontinuation of trial treatment

An individual patient will discontinue trial treatment if:

- The patient wants to discontinue trial treatment, without the need to justify the decision.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
- The patient needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
- The patient becomes pregnant.The patient can no longer receive trial treatment for medical reasons (such as surgery, adverse events or other diseases).

BI 3011441 should be permanently discontinued in case of :

- Retinal vein occlusion (RVO)
- Symptomatic heart failure
- Interstitial lung disease/pneumonitis, regardless of grade
- Recurrent Grade 4 AEs or persistent Grade 2 to 3 AEs that do not recover to Grade 1 or less within 12 weeks
- Drug-related Grade 4 AEs.

An interruption of treatment or delayed start of treatment of more than 4 weeks or several interruptions exceeding a total of ≥28 days of BI 3011441 treatment due to SAEs/AEs will lead to permanent treatment discontinuation. However in well-justified cases if considered clinically indicated by the Investigator and aligned with the Sponsor (to be documented in writing), a patient can be re exposed to treatment.

In case of a temporary reason, trial treatment should be restarted if medically justified, please see section 4.1.4.
If new efficacy/safety information of BI 3011441 becomes available, Boehringer Ingelheim (BI) will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all patients or take any other appropriate action to guarantee the safety of the trial patients.

Even if the trial treatment is discontinued, the patients remain in the trial and, given their agreement, will undergo the procedures for early treatment discontinuation and follow-up as outlined in the Flow Chart and section 6.2.3.

3.3.4.1.1 Enrolment stopping rules

All safety information will be carefully analysed by the sponsor. Enrolment will be temporarily stopped if clinically relevant adverse events occur which meet both of the following criteria:

- Clinically relevant adverse events that:
    - are associated with evidence suggesting a reasonable possibility that the investigational drug caused the adverse event; and
    - occur at frequency or with severity that suggest that the risk-benefit profile of the study drug(s) should be reassessed.

If the SMC determines that the above criteria are met the enrolment to the trial will be temporarily stopped to allow for in-depth analysis of the safety profile of BI 3011441. The benefit-risk profile of BI 3011441 will be re-assessed by the SMC. This assessment will be used to determine if the trial should be continued as planned, permanently discontinued or whether the trial should continue with modification to the protocol. The purpose of any modifications to the protocol will be to mitigate patient risk and ensure that the benefit-risk assessment for continued investigation of BI 3011441 remains positive. The SMC will also consider and provide guidance for the management of patients who are already receiving 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 enrolment. In case the benefit-risk assessment is no longer considered to be positive, the trial will be discontinued.

3.3.4.1.2 Replacement of patients

Patients who are not evaluable for the MTD determination will be replaced, and an additional patient will be entered at the same dose level, if not decided otherwise by the SMC (e.g. because the number of evaluable patients for the current dose level is considered high enough for a dose escalation decision).

Patients who permanently discontinue treatment because of a DLT (please see section 5.2.6.3) will not be replaced.

The following patients may be replaced:

- Patients who have not received any drug after they have signed the informed consent.
- Patients who permanently discontinue treatment during the MTD evaluation period for reasons other than a DLT.
- Patients who have missed more than 8 doses of BI 3011441 during the MTD evaluation period for reasons other than a DLT.
- Patients who miss 2 or more partial or complete visits during the MTD evaluation period and (after discussion between the Sponsor and the Investigator) if the information needed to assess PK/PD and safety parameters (including evaluation for DLTs) is missing, unless they develop a DLT.
- Patient who need palliative radiotherapy during MTD determination period (e.g. first 4 weeks).

3.3.4.2 Withdrawal of consent to trial participation

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

If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site.
2. New efficacy or safety information invalidating the earlier positive benefit-risk-assessment, please see section 3.3.4.1.
3. Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

Further follow up of patients affected will occur as described in section 3.3.4.1.
The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1:1 Test product 1

Substance:	BI 3011441
Pharmaceutical formulation:	Capsules
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	0.5mg, 2 mg
Posology:	Once daily
Mode of administration:	Oral

The gelatin used for the manufacture of BI 3011441 soft capsules is manufactured from bovine bones free from skulls, spinal cord, and vertebrae from cattle over 30 months, which does not satisfy risk criteria in Japan for transmissible spongiform encephalopathy. However, appropriate acid process according to the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3), (2011/C 73/01), from the European Union are used.

4.1.2 Selection of doses in the trial

A starting dose of 4 mg of BI 3011441 is expected to be a safe starting dose as this is 50% of the MTD, which was identified in Phase 1 study with Caucasian patients. For details please refer to the Investigator's Brochure. Dose escalation steps will be guided by a BLRM. The provisional dose levels to be assigned to separate cohorts of patients are listed in Table 4.1.2: 1. Intermediate or lower dose levels may be investigated, depending on the number of DLTs observed in the trial, as long as they fulfil the EWOC criterion and if agreed upon by the SMC. For dose level 3, proposed dose is 8 mg, but depend on BLRM, 7 mg might be selected. Based on result of dose level 3, further investigation of 7 mg or 8mg will be conducted depend on BLRM.

Table 4.1.2:1 Provisional dose levels for escalation

Dose level	Proposed dose	Increment from previous dose
1	4 mg	Starting dose
2	6 mg	50 %
3-1	7 mg	16.7 %
3-2	8 mg	33.3 % (v.s 6 mg)
		14.3 % (v.s. 7 mg)

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 MTD evaluation period) for each patient in the current dose cohort will be described in detail (Including the adverse event information from patient who were excluded from DLT evaluation for reasons other than a DLT). Updated safety data on other ongoing patients, including data beyond the MTD evaluation period, will be discussed as well. Based on that, a decision on the next dose level(s) to be tested is made. Dose escalation will continue until identification of the MTD or RD, safety concerns arise, or the trial is terminated for other reasons.

4.1.3 Method of assigning patients to treatment groups

There will be no randomisation in this trial, as it is a single-arm open-label trial.

Patients will be assigned into escalating dose groups by order of admission into the trial. An interactive response technology (IRT) system is used to register participation of patients in the trial. Upon acquisition of informed consent, study sites access the IRT to register patients for screening. After assessment of all inclusion and exclusion criteria, study sites access the IRT to register each eligible patient for treatment, and the IRT system will assign the patient to the cohort which is open for recruitment.

As soon as the planned number of patients in a cohort are registered for treatment, IRT will close the screening until the next cohort is opened for recruitment or until further treatment slots become available in the current cohort. Patients who are already in screening at the time of the closure of the screening and who then meet all eligibility criteria can be registered for treatment. If more patients are eligible than planned number of patients for a cohort, it is exceptionally allowed to register more patients than planned for ethical reasons

4.1.4 Drug assignment and administration of doses for each patient

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

4.1.4.1 Administration

The different capsule strengths should not be combined in the same bottle at any time. BI 3011441 capusules must be stored in the containers provided and handled according to the labelled storage instructions and shelf life. Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines.

Patients will be advised to return any unused BI 3011441 in the dispensed bottles, in addition to returning any empty bottles. All patients will be required to complete a patient diary to document BI 3011441 intake, which must be returned to the clinic for review at each clinic visit.

BI 3011441 doses should be taken orally at approximately the same time each morning with the exception of certain trial visit days.

Whenever possible, all doses of BI 3011441 should be taken with water limited to a maximum of 100 mL per capsules and the total amount of water intake should be within the range of 300-500 mL. Capsules should be taken without food, at least 1 hour before a meal or ***1*** hours after a meal.

For all visits which plan to conduct PK sampling, patients will be asked to fast overnight (minimum of 10 hours) prior to the visit. Pre-dose laboratory samples will be collected prior to receiving the single morning dose.

Missed doses should not be made up if more than 6 hours have passed since scheduled dosing time. Missed doses must be recorded in the patient's diary.

Before initiating a new treatment cycle, all of the following criteria must be met:

- Ophthalmologic exam (if scheduled at the respective cycle visit): No evidence of Retinal Pigment Epithelial Detachment (RPED) or Retinal Vein Occlusion (RVO)
- Echocardiography (if scheduled at the respective cycle visit):
    - No evidence of an absolute decrease in LVEF of 10 percentage points or greater from screening value, to a value that is below institutional lower limit of normal (LLN).
    - No evidence of an absolute decrease in LVEF of 15 percentage points or greater whether below or above institutional LLN, even if the patient is asymptomatic.
- Absence of related clinically significant adverse events: At the planned start of a treatment cycle patients may continue therapy only after recovery to a level which would allow further therapy; i.e. CTCAE Grade 1 or pre-treatment value or considered not clinically significant (except for the following CTCAE Grade 2 AEs: neuropathy, alopecia and fatigue/asthenia).

4.1.4.2 Dose reductions and dose delays

For the assessment of the severity of adverse events (AEs), CTCAE version 5 (R18-1357) will be used. Any SAEs/AEs of ≥Grade 2 deemed intolerable by the patient or the treating physician and not responding to appropriate medical management, and any related SAEs/AEs of ≥Grade 3 will result in the interruption of treatment with BI 3011441 until resolution to baseline or Grade 1. Please see section 3.3.4.1 for the permanent IMP discontinuation criteria.

If the treatment interruption is ≤2 weeks, the patient can be re-exposed to BI 3011441 at the same dose or one dose level lower than the dose administered before the interruption as long as the re-exposure is considered clinically indicated by the Investigator. However, dose reduction is not allowed for patient who uses 4 mg, and the study medication (BI 3011441) needs to be discontinued.

In case the treatment is delayed due to an AE, the patient should visit the site at least once a week for assessment of safety laboratory and AEs. More frequent visits may be appropriate as assessed by the Investigator. Any case of a delay in treatment cycle for more than 2 weeks should be communicated to the Sponsor. The Investigator in agreement with the Sponsor will decide about further treatment of individual patient, based on known risk/benefit of BI 3011441.

A maximum of 1 dose reductions of BI 3011441 are allowed, if lower tested dose levels are available. Dose reductions will be only to doses previously explored in earlier cohorts.

In case of dose reductions, all future dose administrations will also be at the reduced dose level. If that is intolerable (as previously described), the treatment of that patient should be discontinued. Recommendations for dose reductions of BI 3011441 are given in Tables 4.1.4.2: 1, 4.1.4.2: 2, and 4.1.4.2: 3.

Table 4.1.4.2: 1 Dose modification for BI 3011441 for haematologic and non-haematologic toxicity toxicity related to treatment

Haematologic and non-haematologic toxicity	Dose modification
Grade 1	• Continue BI 3011441 at full dose, monitor as clinically indicated.
Grade 2	• Provide appropriate medical management as clinically indicated. • Consider holding BI 3011441 until resolution to Grade 1 or baseline and resume BI 3011441 at the same dose. • Deemed intolerable by the patient or the treating physician in case of continuation of BI 3011441 and not responding to appropriate medical management, interrupt BI 3011441 until resolution to baseline or Grade 1 and then, resume BI 3011441 at the reduced dose by 1 dose level.
Grade 3[a]	• Interrupt BI 3011441 until toxicity is Grade 1 or baseline, and then reduce the dose of BI 3011441 by 1 dose level. • The patient may be continued at the same dose if the toxicity is unequivocally considered to be unrelated to BI 3011441 by the Investigator in agreement with the Sponsor. • Continue monitoring as clinically indicated and provide appropriate medical management as needed.
Grade 4[a]	• Discontinue BI 3011441. • Continue monitoring as clinically indicated and provide appropriate medical management as needed.

[a] If the patient has a Grade 3 or 4 laboratory abnormality that, in the judgement of the investigator, is not considered clinically significant, dose modification is not required.

Table 4.1.4.2: 2 Dose modification for retinopathy in BI 3011441

Adverse event	Dose modification
Grade 1	• Immediately refer to the patient for ophthalomologic exam (if an ophthalmologic exam cannot be performed within 7 days, interrupt BI 3011441). • If an ophthalmologic exam is done within 7 days and no worsening, continue BI 3011441 and monitor as clinically indicated. • If retinopathy worsens to Grade 2 or 3, see below for guidance.
Grade 2 or Grade 3	• Immediately refer to the patient for ophthalomologic exam. • Interrupt BI 3011441 until resolution to baseline or Grade 1 and then, resume BI 3011441 at the reduced dose by one dose level. • Continue monitoring as clinically indicated and provide appropriate medical management as needed.
Grade 4	• Immediately refer to the patient for ophthalomologic exam. • Permanently discontinue BI 3011441. • Continue monitoring as clinically indicated and provide appropriate medical management as needed.

Table 4.1.4.2: 3 Dose modification for LVEF decrease in BI 3011441

Adverse event	Dose modification
Grade 1	• Not applicable
Grade 2 [a]	• Interrupt BI 3011441 until resolution to the normal institutional range or to within 5 percentage points of the baseline value and then, resume BI 3011441 at the reduced dose by one dose level. • Continue monitoring as clinically indicated and provide appropriate medical management as needed.
Grade 3 and 4	• Permanently discontinue BI 3011441. • Continue monitoring as clinically indicated and provide appropriate medical management as needed.

[a] An absolute decrease in LVEF of 10 percentage points or greater from baseline value to a value that is below institutional LLN value, OR an absolute decrease in LVEF of 15 percentage points or greater and lower than 20 percentage points whether below or above institutional LLN value

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This phase I trial will be handled in an open fashion by the Sponsor throughout, i.e., also for the purpose of data cleaning and preparation of the analysis. The CRF will contain information on the treatment and the dose.

4.1.5.2 Unblinding and breaking the code

Not applicable.

4.1.6 Packaging, labelling, and re-supply

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

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.
If the storage conditions are found to be outside the specified range, the Clinical Research Associate (CRA) (as provided in the list of contacts) must be contacted immediately.

4.1.8 Drug accountability

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

- Approval of the clinical trial protocol by the IRB / ethics committee.
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site.
- Approval/notification of the regulatory authority, e.g. competent authority.
- Availability of the curriculum vitae of the Principal Investigator.
- Availability of a signed and dated clinical trial protocol.

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics. Patients should be instructed to return unused investigational drug.

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

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed.

Rescue medications to reverse the actions of BI 3011441 are not available. Adverse events should be treated symptomatically and must be recorded. Concomitant medications or therapy to provide adequate supportive care may be given as clinically necessary

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Concomitant therapy, with reasons for the treatment, must be recorded in the CRF during the screening and treatment periods, starting at the date of signature of informed consent and ending after the REP. 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.

No anticancer therapy (including regular use of steroids exceeding 10 mg daily prednisone or equivalent) can be administered during treatment with BI 3011441. No other investigational drug must be used concomitantly with the study drug, and the patients are not allowed to participate concurrently in any other clinical study.

The use of concomitant medications that might lead to QT prolongation is prohibited and would require the discontinuation of the patient prior to starting the respective QT prolonging medication.

Pre-medications (e.g. antiemetics for nausea or vomiting) should not be given in cycle 1 to avoid masking the emergence of DLTs.

Prophylactic granulocyte colony stimulating factors are not allowed during the first 4 weeks of treatment

For symptom control, palliative radiotherapy is permitted for any lesion, except during the DLT evaluation period (e.g. first 4 weeks) for MTD/RD determination. If the palliative radiotherapy is necessary during the MTD determination period (e.g. first 4 weeks), then the patients will be replaced. If the palliative radiotherapy is necessary during the study, a case-by-case decision will be made together with the sponsor. Lesions that have been exposed to radiotherapy are no longer evaluable, and may not be included in the assessment of the non-target lesions and the overall assessment. Study medication needs to be interrupted during the palliative radiotherapy and maybe resumed once the patient has recovered from any radiation associated toxicity. If the medication is interrupted for more than 14 days, the decision to continue with the study medication will be made by the investigator in agreement with the sponsor.

[redacted] Table 4.2.2.1:1 provides a list of restricted medications. Alternatives with less potential for CYP450 based interactions should be considered, where available. Close monitoring for potential adverse reactions is warranted and patients should be informed about potential signs and symptoms of such adverse reactions (e.g., muscle pain). BI 3011441 was also found to be [redacted] Table 4.2.2.1:1 provides a list of restricted and permitted medications.

Table 4.2.2.1:1 Restricted medication when coadministered with BI 3011441

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Herbal preparations/medications	Not Permitted from 7 days prior to first dose of study treatment	[redacted] Dehydroepiandrosterone (DHEA), [redacted] and [redacted]

4.2.2.2 Restrictions on diet and life style

Patients should be instructed to avoid exposure to direct sunlight (including sunlamps), to use a sunblock (minimum sun-protection factor 30), and to wear clothing and sunglasses that protect against sun exposure during treatment and for 4 weeks after the last administration of BI 3011441.

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, if feasible. Grapefruit juice and Sevilla oranges and their juice are not permitted.

4.2.2.3 Contraception requirements

Women of childbearing potential and men able to father a child must use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information.

4.3 TREATMENT COMPLIANCE

Patients are requested to bring all remaining trial medication including empty package material with them when attending visits.

Based on capsules counts, treatment compliance will be calculated as shown in the formula below. Compliance will be verified by the CRA authorised by the sponsor.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of capsules actually taken} \times 100}{\text{Number of capsules which should have been taken as directed by the investigator}}$$

If the number of doses taken is not between 75-100%, staff will explain to the patient the importance of treatment compliance.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

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

The patients will be re-evaluated every 8 weeks until the earliest of progressive disease, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy or until the end of the trial. The baseline scan(s) (CT scan and/or MRI according to Investigator's decision) from screening must have been performed within 4 weeks prior to treatment with the trial drug(s) and the Investigator will record the target (5 target lesions in total and maximum 2 per organ) and non-target lesions at baseline in the patient's medical records and in the CRF before the start of treatment. The same method of assessment and the same technique must be used to characterise each reported lesion at baseline and during treatment. In case of suspected (but not otherwise confirmed) bone metastasis at screening, tumour assessment at screening should include a bone scan. If bone lesions are already known or confirmed at screening, correlative imaging (X-ray or CT scan) should be performed. Correlative imaging should then be repeated at each tumour assessment. Lesions in previously irradiated areas may not be considered measurable at baseline unless the lesions occurred after irradiation. Lesion used for biopsies should not be selected for target lesion evaluation. Tumour assessment will be performed at screening (as close as possible to the treatment start and no more than 28 days before the start of trial treatment), at week 8 and every 8 weeks thereafter, and at the EOT visit (if not performed within the last 4 weeks).

If the patient discontinues the trial medication for another reason than progression, the tumour assessment according to RECIST v1.1 will continue every 8 weeks until the last follow-up needed according to protocol (progression, death, lost to follow-up, end of the trial).

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified in the Flow chart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.

Measurement of height and body weight will be performed at the time points specified in the Flow chart.

During the physical examination, the patient should be assessed for possible adverse events.

The results must be included in the source documents available at the site.

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the Flow Chart, prior to blood sampling and trial treatment administration.

This includes body temperature, systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute), and saturation of percutaneous oxygen. All except body temperature need to be taken in a seated position after 5 minutes of rest. Oxygen saturation will be measured, if needed. The results must be included in the source documents available at the site.

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.3: 1. For the sampling time points please see the Flow Chart. All analyses will be performed locally. Patients do not have to be fasted for the blood sampling for the safety laboratory tests.

Clinically relevant abnormal findings as judged by the Investigator will be reported as adverse events (please refer to Section 5.2.6).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1.4 and the DILI Checklist provided in the ISF). The amount of blood taken from the patient concerned will be increased due to this additional sampling.

Table 5.2.3:1 Safety laboratory tests

Haematology	Haemoglobin, red blood cell count, haematocrit, mean corpuscular volume, white blood cell count, and differential blood count (preferably expressed in absolute values), and platelets.
Biochemistry	Glucose, sodium, potassium, chloride, calcium, creatinine, phosphate, venous bicarbonate (HCO_3), AST, ALT, alkaline phosphatase, lactate dehydrogenase, lipase, bilirubin (direct and indirect bilirubin in case of elevated total bilirubin values), total protein, albumin, urea nitrogen, uric acid and creatinine kinase (CK; if CK is elevated, then myoglobin and creatine kinase myocardial band (CK-MB) [cardiac] should also be measured; if a patient has signs/symptoms of myocardial ischemia and CK elevation, then CK-MB ,Troponin I or Tshould also be reactively tested). Note: Creatinine can be assessed by any of these methods: CREE (enzymatic serum creatinine assay), CREJIDMS (isotype dilution mass spectrometry (IDMS) standardized Jaffe), or CREJ (non IDMS standardized Jaffe).
Coagulation	Activated partial thromboplastin time (aPTT) or prothrombin time (PT) (expressed either in seconds or as percentage)
Urine	Urine (pH, glucose, erythrocytes, leukocytes, protein, and nitrite) will be analysed by dipstick (semi-quantitative measurements).

Table 5.2.3:1 Safety laboratory tests (cont.)

Pregnancy test	A beta human chorionic gonadotropin (β-HCG) pregnancy test in serum will be performed for women of childbearing potential at screening. Thereafter, this test may be done in serum or urine on Day 1 of each cycle, at the EOT visit, and at the 30-day safety follow-up visit.
Virology (screening)	Hepatitis B (HBs-Ag, and if HBs-Ag is negative anti-HBs, anti-HBc antibodies and HBV DNA will be measured) and hepatitis C (PCR)

If laboratory safety investigations have been performed >72 hours prior to the first trial treatment, the results of the new safety laboratory investigations performed within 72 hours of first treatment must be available to reconfirm eligibility.

5.2.4 Electrocardiogram

Standard 12-lead (I, II, III, aVR, aVL, aVF, V1 - V6) resting electrocardiograms (ECGs) will be digitally recorded in triplicate (3 single ECGs within a maximum period of 5 minutes) and performed for each patient at various time points during the trial according to the appropriate Flow Chart and Appendix 10.1. This will include triplicate readings at every PK sampling time point during Cycle 1 on Days 1, 15, and 16.

All ECGs will be obtained after the patient has been resting supine for at least 5 minutes prior to the indicated times. All ECGs should be recorded with the patient in the same physical position.

Electrocardiogram machines will be provided to facilitate central retrospective readings. Before trial start, the trial sites will be trained for the proper use of the equipment and transfer of the electronic data to the vendor. While all ECGs will be transmitted to the central vendor, they will be analysed only after PK analysis points to a t_{max}.

ECGs may be repeated for quality reasons and the repeated recording used for analysis. If necessary, additional ECGs may be recorded for safety reasons.

The ECG recordings must be analysed and checked for abnormality by the Investigator (or designated physician) who will also calculate the QTcF value for each time point as the mean of the 3 ECGs. Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as adverse events and will be followed up and/or treated as medically appropriate. CTCAE version 5.0 will be used for the grading of prolonged QTcF intervals. Dated and signed printouts of ECG with findings should be documented in patient's medical record.

In case of related ECG changes and whenever the Investigator deems necessary, additional ECG monitoring will be performed in the respective and later courses of treatment. To allow for a heart rate correction of QT intervals the QT intervals will be matched to the preceding RR intervals using at least QTcF (Fridericia's formula $QTcF = QT/RR^{-1/3}$) and QTcB (Bazett's formula $QTcB = QT/RR^{-1/2}$).

In case of QTcF prolongation to >500 ms (mean of 3 ECGs) AFTER receiving therapy, the Investigator will initiate further ECG monitoring and diagnostics (e.g., check electrolytes and check concomitant therapy that may be contributing to QTcF prolongation) and if required provide adequate treatment according to medical standards. The patient will be discharged from the investigational site only after resolution of ECG findings as assessed by the Investigator.

In case of occurrence of symptoms suggestive of arrhythmia related to QTcF prolongation, a cardiologic evaluation will be performed, and treatment will be provided according to medical standards at the discretion of the Investigator.

In order not to confuse an ECG recording, PK samples should be taken after performing the ECG.

Centralised ECG evaluation
Abnormalities detected during centralised ECG evaluation will not necessarily qualify as AEs. In case of clinically relevant abnormalities (e.g., heart blocks or large changes in interval duration) the ECG core laboratory may contact the Investigator and vice versa. Centrally assessed ECGs will comply with the ICH E14 guidance document and supplements (R05-2311, R13-0801, R13-4095) as well as the FDA requirements for annotated digital ECGs (R09-4830).

5.2.5 Other safety parameters

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

Ophthalmological assessments
Patients are required to have a standard ophthalmologic exam performed by an ophthalmologist at baseline, at each defined timepoint (see Flow Chart) and as clinically indicated. The exam will include indirect fundoscopic examination, visual acuity, visual field examination, tonometry and slit lamp examination with special attention to retinal abnormalities that are predisposing factors for RVO or retinopathy.

In addition, it is recommended that patients have baseline color fundus photographs to document baseline appearance. In patients with clinical suspicion of RVO or retinopathy, additional color fundus photographs are recommended, and fluorescein angiography and/or optical coherence tomography are recommended.

Echocardiography
Echocardiography will be performed to assess cardiac ejection fraction and other abnormalities if applicable as indicated in the Flow Chart. Additional echocardiography assessments may be performed if clinically indicated.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

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

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

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

- Worsening of the underlying disease or of other pre-existing conditions, see section 5.2.6.2.4 for further detail.
- Changes in vital signs, ECG, physical examination, laboratory test results, ophthalmological assessment and echocardiography if they are judged clinically relevant by the investigator.

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

5.2.6.1.2 Serious adverse event

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

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

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

Patients may be hospitalized for administrative reasons during the trial, including hospitalisation for respite care. These as well as hospitalisations/surgical procedures which

were planned before the patient signed informed consent need not be reported as SAEs if they have been documented at or before signing of the informed consent and have been performed as planned (the condition requiring hospitalisation/surgical procedure has not changed/worsened after signing informed consent)

5.2.6.1.3 AEs considered "Always Serious"

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as defined above.

The latest list of "Always Serious AEs" can be found in the electronic data capture (eDC) system. A copy of the latest list of "Always Serious AEs" will be provided upon request. These events should always be reported as SAEs as described in section 5.2.6.2.
Every new occurrence of cancer of new histology must be classified as a serious event regardless of the time since the discontinuation of the trial medication and must be reported as described in section 5.2.6.2, subsections "**AE Collection**" and "**AE reporting to sponsor and timelines**".

5.2.6.1.4 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see section 5.2.6.2.2.

The following are considered as AESIs:

Dose-limiting toxicities
DLTs are considered to be AESIs, and must be reported as such. The definition of DLTs is presented in Section 5.2.6.3.

Potential severe drug-induced liver injury (DILI)
A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by the

- following alterations of hepatic laboratory parameters: For patients with normal aminotransaminase levels at baseline:
  - An elevation of AST and/or ALT ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN either measured in the same blood draw sample, or in samples drawn within 30 days of each other; or
  - Aminotransferase (ALT and/or AST) elevations ≥10 fold ULN.
- For patients with abnormal aminotransaminase levels between >1 and <3 x ULN at baseline:

- An elevation of AST and/or ALT ≥3 fold the baseline value combined with an elevation of bilirubin ≥2 fold ULN or ≥2 fold the baseline value (if bilirubin is elevated at baseline) in the same blood sample, or in samples drawn within 30 days of each other ; or
- Aminotransferase elevations ≥5 fold the baseline value.

- For patients with abnormal aminotransaminase levels between ≥3 and ≤5 x ULN at baseline:
  - An elevation of AST and/or ALT ≥2 fold the baseline value combined with an elevation of bilirubin ≥2 fold ULN or ≥2 fold the baseline value (if bilirubin is elevated at baseline) in the same blood sample, or in samples drawn within 30 days of each other; or
  - Aminotransferase elevations ≥3 fold the baseline value.

These lab findings constitute a potential hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the ISF. For further details, see figure 5.2.6.1.4: 1 below.

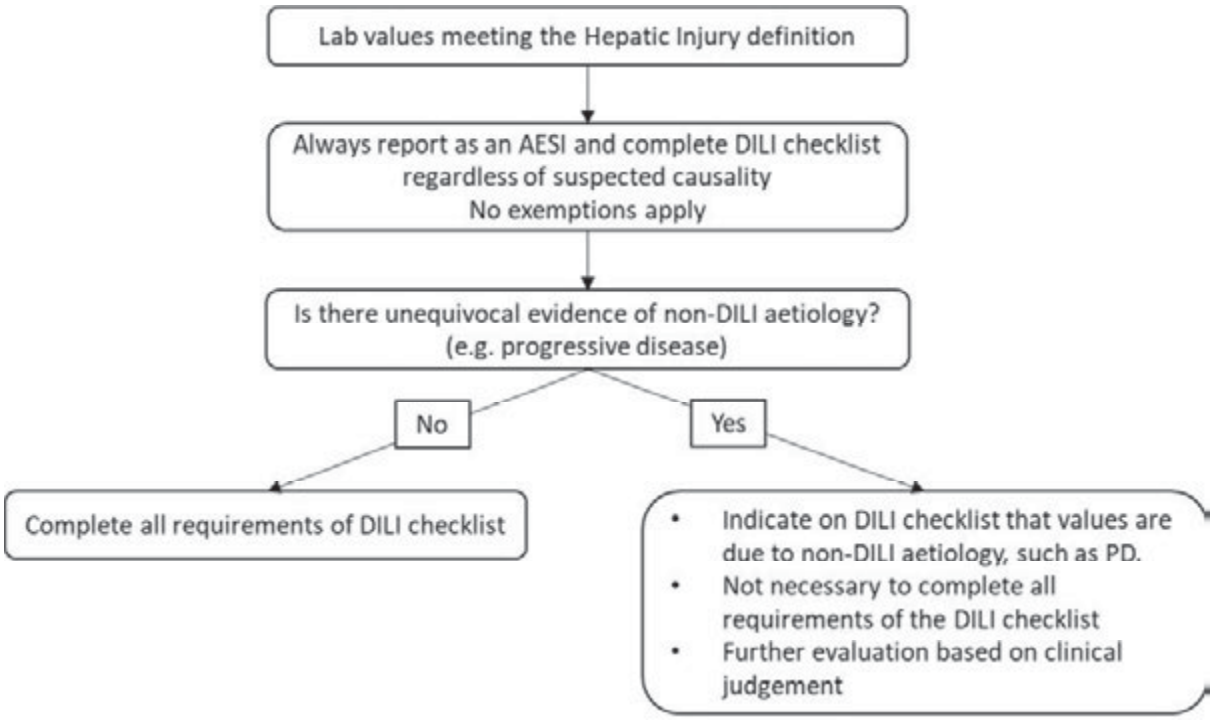


Figure 5.2.6.1.4: 1 Hepatic injury reporting

5.2.6.1.5 Intensity (severity) of AEs

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

5.2.6.1.6 Causal relationship of AEs

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

relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

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

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

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

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

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

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

- From signing the informed consent onwards until the EOR all AEs (non-serious and serious) and all AESIs.
- After EOR until the individual patient's end of trial:
  cancers of new histology and exacerbations of existing cancer, all trial treatment related SAEs and all trial treatment related AESIs.

- After the individual patient's end of the trial:
  the investigator does not need to actively monitor the patient for new AEs but should 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 5.2.6.2.2), but not on the CRF.

The rules for Adverse Event Reporting exemptions still apply, please see section 5.2.6.2.4.

Vital Status Data Collection
Patients who discontinue trial medication prematurely, who agree to be contacted further but do not agree to physical visits, should be followed up as described in section 3.3.4.1, withdrawal from trial treatment. From then on 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.

5.2.6.2.2 AE reporting to the sponsor and timelines

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

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

5.2.6.2.3 Pregnancy

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

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; in the event that consent cannot be obtained, information will be collected and reported in accordance with regulatory requirements. 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 Studies (Part B).
The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (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 Studies and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

5.2.6.2.4 Exemptions to AE reporting

Collection and reporting of progressive disease

The outcome "disease progression" is used to assess trial endpoints for the analysis of efficacy and will be recorded on the appropriate page of the eCRF.

Disease progression will not be considered as an 'always serious' AE for this study. Only if disease progression meets standard seriousness criteria (see Section 5.2.6.1.2, *Serious adverse event*), will it be recorded on the AE page in the eCRF as well as on the BI SAE form, and the SAE reporting process will be followed. The exemption to reporting disease progression as an AE or SAE applies when disease progression is observed on imaging in an asymptomatic patient with no clinical signs of disease progression.

However if there is evidence suggesting a causal relationship between the investigational drug and the progression of the underlying malignancy, the event must be recorded as an SAE on the AE page in the eCRF and reported as an SAE on the SAE Form.

Clinical symptoms and/or signs of disease progression 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 as SAEs on the BI SAE form and SAE reporting procedures will be followed. If signs and symptoms are attributable to a diagnosis, reporting the diagnostic term is preferable (e.g. pulmonary embolism rather than dyspnoea; intestinal obstruction rather than abdominal pain).

Lab values meeting the potential severe DILI definition in section 5.2.6.1.4 must always be reported as AESI, even if the most likely cause is disease progression. No exemption to AE reporting applies.

Exempted events are reviewed at appropriate intervals by the Sponsor and the SMC.

5.2.6.3 Dose limiting toxicities

DLTs will be recorded throughout the trial. Any DLT must be reported to the Sponsor by the Investigator or designee within 24 hours of first knowledge using the same procedure as SAE reporting. Only DLTs occurring in the first 4 weeks (the first cycle) of treatment are considered for dose-escalation decisions made by the SMC. DLTs observed during the MTD

evaluation period will be considered for MTD determination. In addition, DLT(s) observed during the ophthalmological assessment and echocardiographic assessment of Cycle 2 Day 1 will be considered for MTD determination. However, all AEs and SAEs meeting criteria of DLT observed in all treatment cycles will be considered for determining a RD.

Any of the following AEs will be classified as DLTs if assessed as possibly related to BI 3011441, i.e., unless unequivocally due to underlying malignancy or an extraneous cause and will be reviewed by the SMC.

Haematologic

- CTCAE Grade 4 neutropenia (<500/mm$^{3)}$ lasting >7 days without documented infection.
- CTCAE Grade ≥3 neutropenia (<1000/mm^3) with documented infection.
- CTCAE Grade ≥3 febrile neutropenia, where Grade 3 febrile neutropenia is defined as ANC <1000/mm^3 and a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100°F) for more than one hour; Grade 4 neutropenia is defined as life-threatening consequences or urgent intervention indicated; and Grade 5 neutropenia is defined as a fatal neutropenia
- CTCAE Grade 3 thrombocytopenia (≥25,000/mm^3 and <50,000/mm^3) associated with bleeding
- CTCAE Grade 4 (<25,000/m^3) thrombocytopenia
- Thrombocytopenia or anaemia requiring transfusion per local or international guidelines.

Non-haematologic

- Grade ≥3 non-haematologic (not laboratory) toxicities despite the use of adequate medical interventions and/or prophylaxis as dictated by local institutional clinical practices, the clinical trial protocol, and/or the judgment of the Investigator. The following exceptions apply:
    - In a patient with pre-existing fatigue at baseline, Grade 3 fatigue will only be considered as a DLT if it lasts for more than 7 days despite adequate medical interventions and baseline fatigue was no more than Grade 1.
    - Grade 3 nausea or Grade 3 vomiting will be defined as a DLT when it persists at Grade 3 longer than 48 hours despite adequate medical intervention
    - Grade ≥3 diarrhea will be defined as a DLT only when hospitalisation is required, and the event persists at Grade ≥3 for more than 48 hours despite adequate medical intervention.
    - Hypertension will be defined as a DLT only when a patient was enrolled with controlled hypertension as per the exclusion criteria, and systolic blood pressure has increased >=160 mm Hg or diastolic blood pressure increased >=100 mm Hg, which cannot be controlled by hypertensive medication and which requires a dose reduction / discontinuation of study drug.
- Any Grade 3 or Grade 4 non-haematologic laboratory value if:
    - Medical intervention is required to treat the patient, except Grade 3 electrolyte abnormality that lasts <72 hours, is not clinically complicated and resolves spontaneously or responds to conventional medical intervention, or
    - The abnormality leads to hospitalisation, or
    - The abnormality persists for >1 week, and considered significant enough to be qualified as DLT in the opinion of the Investigator, and confirmed by the SMC.

- An absolute decrease in LVEF of 10 percentage points or greater from screening value to a value that is below institutional LLN value, OR an absolute decrease in LVEF of 15 percentage points or greater whether below or above institutional LLN, even if the patient is asymptomatic, will be defined as a DLT if:
    - After holding the trial drug and obtaining a follow-up echocardiography within 4 weeks, LVEF has not returned within the normal institutional range or to within 5 percentage points of the screening value; OR
    - After holding the trial drug and obtaining a follow-up echocardiography within 4 weeks, LVEF has returned within the normal institutional range or to within 5 percentage points of the screening value, but on re-challenge there is second decline of an absolute decrease in LVEF of 10 percentage points or greater from screening value, whether above or below institutional LLN.
- Symptomatic heart failure
- Any retinopathy ≥ Grade 2
- Retinal vein occlusion of any grade.
- Interstitial lung disease/pneumonitis of any grade
- Hepatic injuries assessed as related to trial drug and which meet the AESI criteria for hepatic injury in Section 5.2.6.1.4
- Treatment pause of BI 3011441 for ≥14 days, or dose reduction in Cycle 1 due to treatment-related AEs
- Any treatment-related ≥ Grade 2 toxicity that persists and results in a more than 2 weeks delay of administration of BI 3011441 on Cycle 2 Day 1
- Any treatment-related AE that would require permanent discontinuation of BI 3011441.

Any other toxicity considered significant enough to be qualified as DLT in the opinion of the Investigators, and confirmed by the SMC, will be reported as a DLT.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Blood [redacted] samples will be collected for the purose of PK analysis. Further information about sampling is provided in section 5.3.2. Actual data and clock times of PK sampling will be recoreded in CRF.
The planned PK analyses will require blood [redacted] samplings at the time points indicated in the Flow Chart and Table 10.1: 1. Correct, complete and legible documentation of drug administrations and PK sampling times, as well as adequate handling and identification of PK samples, are mandatory to obtain data of adequate quality of the PK analysis.

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis

General aspects for all analytes

At a minimum, the sample tube labels should list BI trial number, patient number, visit, and planned sampling time. Further information such as matrix and analyte may also be provided.

After completion of the trial, the plasma samples may be used for further methodological investigations (e.g., for stability testing or assessment of metabolites). However, only data related to the analyte and/or its metabolite(s) 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 clinical trial report (CTR) is archived.

BI 3011441

For quantification of drug in plasma, blood for each analyte will be drawn into a K_2-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in Appendix 10.1.

Two plasma aliquots will be obtained and stored in an upright position at approximately -20°C or below at the trial site until shipment. Details on sample handling, processing and shipments are described in the lab manual.

5.3.2.2 Urine sampling for pharmacokinetic analysis

[redacted]

Details on sample handling, processing and shipments are described in the lab manual.

After completion of the trial, the urine samples may be used for further methodological investigations (e.g., for stability testing or assessment of metabolites). However, only data related to the analyte and/or its metabolite(s) 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 CTR has been archived.

[redacted]

5.4 ASSESSMENT OF BIOMARKER(S)

[redacted]

5.4.1 Methods of sample collection

5.5 BIOBANKING

NA

5.6 OTHER ASSESSMENTS

NA

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are in accordance with measurements in Phase I oncology trials and will be performed in order to monitor safety aspects and to determine efficacy and PK parameters in an appropriate way.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

The visit schedule is in detail described in the Flow Chart for all patients enrolled into this trial. Unscheduled visits can be performed as necessary and assessments will be performed as required at the discretion of the Investigator.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

See the Flow Chart and Section 5 for details on the procedures performed at each visit.

6.2.1 Screening period(s)

Screening Period

All patients will need to sign the informed consent form (ICF). Only patients who have tested positive for activating NRAS/KRAS mutations by prior local analysis conducted in an international or country-specific certified laboratory (e.g. CAP/CLIA or ISO) are eligible for the trial. An archival tumour tissue sample will be submitted to the central laboratory to retrospectively confirm the NRAS/KRAS mutation status (see Section 5.4).

Demographic information (sex, year of birth, race) will be obtained, based on information in the patients' medical records.
Examinations and assessments per Flow Chart will be conducted and patients' medical history will be collected. Inclusion and exclusion criteria must be assessed (see Sections 3.3.2 and 3.3.3). Baseline images must be available as outlined in the Flow Chart.

Concomitant diagnoses and/or therapies present during trial participation (between first ICF and the first follow-up visit) will be recorded in the CRF. Medical history of the tumour disease will be obtained and reported in the CRF:

- The date of first histological diagnosis
- The primary tumour site
- The number and location of metastatic sites
- Previous treatment for the tumour disease, including any surgery, radiotherapy, and/or systemic therapy, including start and end dates and the outcome.

Examinations during the screening period also include electrocardiography, echocardiography, and an eye exam.

Re-screening will be allowed once for unexpected reason such as schedule conflict. Re-screened patients will receive a new patient number. In case of re-screening any procedures that fall outside the required screening window as defined in Flow Chart must be repeated.

A repeat testing during the screening period for items not meeting the eligibility criteria is basically not allowed.

6.2.2 Treatment period(s)

Treatment visits are specified in the Flow Chart and must be conducted as scheduled and outlined there. Treatment cycles are 4 weeks (28 days) in duration.

All planned visit dates are calculated from the start of Day 1 (Visit 1) of Cycle 1. 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. All subsequent visits must adhere to the scheduled programme of visits for all cycles of treatment. Hospitalisation for administrative reasons (e.g. for the first days of Cycle 1) will not be considered as SAE. PK blood sampling timepoints are outlined in Appendix 10.1 and biomarker sampling is detailed in Section 5.4.

Imaging visits must adhere to the schedule provided in the Flow Chart at all times, unless they are scheduled for suspected progressive disease.

6.2.3 Follow-up period and trial completion

6.2.3.1 End of treatment visit and EOR

The EOT visit will be performed as soon as possible (within 7 days) after permanent discontinuation of all trial medications for any reason or as soon as possible after the Investigator became aware that the trial medication had been terminated. The assessments of the EOT visit will then be performed instead at the next planned visit. If the patient finishes active treatment without having progressive disease, tumour assessment/imaging must be performed at the time of treatment discontinuation, unless it has been done within the past 4 weeks.

The EOR will be performed 30 (+7) days after permanent discontinuation of all trial medications and is primarily to collect follow-up safety information as required by regulatory authorities. For the majority of patients, progression will already be documented at this point.

6.2.3.2 Extended follow-up period

For patients who did not discontinue treatment due to progressive disease, additional follow-up visits after the 30-day safety follow-up visit will be performed every 8 weeks to continue tumour imaging until progressive disease or another withdrawal criterion is met.

The follow-up for progression period will end at the time that one of the following events is met:

- Disease progression based on RECIST 1.1
- Start of a new anti-cancer therapy
- Lost to follow-up
- Death
- End of whole trial as specified in Section 8.6.

The following will be obtained and/or performed during the follow-up visits for progression.

- For each reportable SAE/AESI, the Investigator should provide the information with regard to concomitant medication and the medication administered to treat the AE on the

appropriate CRF pages and the SAE form including trade name, indication and dates of administration
- Perform physical examination
- Record performance score/status (e.g., ECOG)
- Perform tumour assessment and imaging
- Treatment and date with any subsequent anti-cancer drug / therapy including the name and type of the anti-cancer drug and/or best supportive care (if applicable)
- Outcome (date of and reason for death [if applicable], in case the patient had progressive disease the actual date of progressive disease shall be recorded).

6.2.3.3 Trial completion for an individual patient

A patient is considered to have completed the trial in case any of the following applies:
- Completion of planned follow-up period
- Lost to follow-up
- Refusal to be followed-up
- Death.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

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

The model is given as follows:
logit (π_d) = log(α) + β*log(d/d*),
where logit (π) = log (π/(1-π)).
π_d represents the probability of having a DLT in the MTD evaluation period at dose d, d* = 8 mg is the reference dose, allowing for the interpretation of α as the odds of a DLT at dose d*, and θ = (log(α), log(β)) with α, $\beta > 0$ is the parameter vector of the model. The estimated probability of a DLT at each dose level from the model will be summarized using the following intervals:

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

The BLRM-recommended dose for the next cohort is the level with the highest posterior probability of the DLT rate falling in the target interval [0.16, 0.33) among the doses fulfilling EWOC. Applying the EWOC criterion, it should be unlikely (<25% posterior probability) that the DLT rate at that dose will exceed 0.33. However, the maximum allowable dose increment for the subsequent cohort will be no more than 50 % for each dose level.

The MTD may be considered reached if one of the following criteria is fulfilled:

1. The posterior probability of the true DLT rate in the target interval [0.16 – 0.33) of the MTD is above 0.5, OR
2. At least 12 patients have been treated in the dose escalation phase of the trial, of which at least 6 at the MTD.

The SMC may recommend stopping the dose escalation phase after the criterion for MTD is fulfilled. Further patients may be included to confirm this MTD estimate. If no DLT is observed at a dose of which the efficacy is considered sufficient, the SMC may decide to include an additional number of patients at this dose level and to declare this dose as the dose recommended for further testing
Since a Bayesian approach is applied, a prior distribution f(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:
For the current trial, relevant information in the form of human data was available. Therefore, the three mixture components were established as follows:

1. The MAP prior using the historical data for LPN3794, modified to include grade 2 retinopathy as DLT, can be found in Table 7.1:1

Table 7.1:1 Historical data for LPN3794 (modified to include grade 2 retinopathy as DLT)

Trial	Dose (mg)	N of patients with DLTs during MTD evaluation period / N of patients
LPN3794 (including grade 2 retinopathy as DLT)	2	0/1
(including grade 2 retinopathy as DLT)	4	0/1
	6	0/3
	8	3/9
	10	2/5
	16	1/1

This yields μ_1 = (-0.94, 0.61). The standard deviations were set such that large uncertainty about the parameter means is reflected, and the correlation was set to 0, thus yielding $\sigma_{1,11}$ = 0.91, $\sigma_{1,22}$ = 0.91 and ρ_1 = -0.08, respectively. The prior weight a_1 for the first component was chosen as 0.8.

2. 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 2 mg would equal 0.10, and the median DLT at the anticipated MTD of 8 mg would equal 0.70. These assumptions yield μ_2 = (0,85 , 0.79). The standard deviations and correlations were set identical to the weakly informative prior, i.e. $\sigma_{2,11}$ = 2, $\sigma_{2,22}$ = 1 and ρ_2 = 0, respectively. The prior weight a_2 for the second component was chosen as 0.1.

3. 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 2 mg would equal 0.005, and the median DLT at the anticipated MTD of 8 mg would equal 0.1. These assumptions yield μ_3 = (-2.20, 0.80), i.e. basically a flat curve. The standard deviations and correlations were set to $\sigma_{3,11} = 2$, $\sigma_{3,22} = 1$. The correlation was set to 0, i.e. $\rho_3 = 0$. The prior weight a_3 for the third component was chosen as 0.1.

A summary of the prior distribution is provided in Table 7.1:2. Additionally, the prior probabilities of DLTs at different doses, as well as the corresponding probability of under-, targeted and over toxicity, are shown in Table 7.1:3. 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 2.8 patients at 4 mg. A detailed evaluation of the model using hypothetical data scenarios and operating characteristics is provided in the statistical Appendix 10.2.

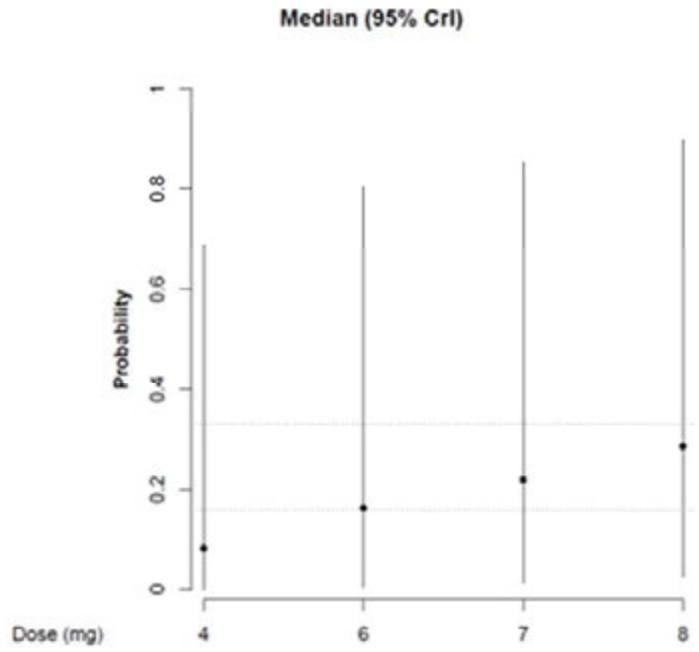
Table 7.1:2 Summary of prior distribution

Prior Component	Mixture Weight	Mean Vector	SD Vector	Correlation
1: MAP prior	0.800	(-0.94, 0.61)	(0.91,0.91)	-0.08
2: High Tox.	0.100	(0.85,0.79)	(2,1)	0
3: Low Tox.	0.100	(-2.20,0.80)	(2,1)	0

Table 7.1:3 Prior probabilities of DLTs at selected doses

Dose	Probability of true DLT rate in			Quantiles				
	[0-0.16)	**[0.16-0.33)**	**[0.33-1)**	**Mean**	**SD**	**2.5%**	50%	**97.5%**
4 mg	0.682	0.189	0.128	0.147	0.182	0.000	0.081	0.688
6 mg	0.492	0.274	0.233	0.224	0.205	0.003	0.164	0.804
7 mg	0.370	0.320	0.310	0.272	0.213	0.012	0.218	0.853
8 mg	0.248	0.330	0.422	0.329	0.220	0.024	0.285	0.897

Figure 7.1:1 Prior medians and 95% credible intervals



7.2 NULL AND ALTERNATIVE HYPOTHESES

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

7.3 PLANNED ANALYSES

7.3.1 General considerations

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

7.3.2 Primary endpoint analyses

In order to identify the MTD, the number of evaluable patients with DLTs during the MTD evaluation period at each dose level must be presented. Replaced patients will be excluded from the determination of MTD.
The main analysis of the MTD will use the BLRM model described above using DLT data from the MTD evaluation period.
For the analysis of tolerability and safety, please refer to Section 7.3.5.

7.3.3 Secondary endpoint analyses

The number of patients with DLTs at each dose level during the on-treatment period will be analyzed descriptively in terms of a frequency table.
The number of patients with CTCAE Grade ≥ 3 treatment-related adverse events observed during the on-treatment period will be analyzed descriptively in terms of a frequency table.
The number of patients with treatment related adverse events at each dose level will be analyzed descriptively in terms of a frequency table.

[redacted]

7.3.5 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the residual effect period (REP), a period of 30 days after the last dose of trial medication, will be assigned to the on-treatment period for evaluation.

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the REP (Section 1.2) Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the MedDRA at database lock.
Laboratory data will be analyzed 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.
Other safety analyses (AESIs, centrally evaluated ECG, etc.) will be specified in detail in the TSAP.

7.3.6 Other Analyses

The pharmacokinetic parameters listed in Section 2.1.3 will be calculated according to the internal BI standard operating procedure (SOP). PK analyses will be performed using validated software programs, normally, Phoenix WinNonlin (Pharsight®) with applications validated for the respective purpose. Graphs and tables will be generated using validated customised SAS® macros or appropriate graphic software.

7.3.7 Interim Analyses

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

[redacted]

7.4 HANDLING OF MISSING DATA

No imputation will be performed on missing efficacy data. Missing baseline laboratory values will be imputed with the respective values from the screening visit. No other imputations will be performed on missing data unless otherwise specified in the TSAP. Every effort will be made to obtain complete information on all adverse events, with particular emphasis on DLTs.

Handling of missing PK data will be performed according to the internal BI SOP. [redacted]

7.5 RANDOMISATION

No randomisation will be performed. Patients will be assigned to escalating dose groups by order of admission into the trial.

7.6 DETERMINATION OF SAMPLE SIZE

No formal statistical power calculations to determine sample size were performed for these parts of the trial. Approximately 12 patients (including at least 6 patients at MTD) are expected for dose escalation based on the number of dose levels/cohorts that are tested. Fewer or more patients might be needed based on the recommendation of the SMC. However, the actual number of patients will depend on the number of dose cohorts tested. Detailed information of simulation study to evaluate operating characteristics of the BLRM will be provided in section 10.2.

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

The trial will be carried out in accordance with the Medical Devices Directive (93/42/EEC) and the harmonised standards for Medical Devices (ISO 14155, current version).

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as “protocol deviation”.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.
The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalisation of the Clinical Trial Report. 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 investigator or delegate must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible.

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

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

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

8.2 DATA QUALITY ASSURANCE

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

Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.

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

8.3 RECORDS

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

8.3.1 Source documents

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

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

The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least one documented attempt to

retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

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

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

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.
Exemptions from expedited reporting are described in section 5.2.6.2.4, if applicable.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the WHO GCP handbook.

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:

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

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

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

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

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.
The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed").
The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with

the trial medication until 30 days after LPLT at their site. **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.
Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.
Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

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

A SMC composed of participating investigators and members of the BI trial team will be established to review individual and aggregated safety and efficacy data to determine the safety profile and risk/benefit ratio and recommend next dose level/does escalation/de-escalation/modification/next cohort size, and appropriateness of further enrolment. Details of the SMC responsibilities and procedures are described in the SMC charter. Regarding SMC please see also sections 2.1, 3.1, 3.2, 4.1 and 7.1 of the clinical trial protocol.

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 web portal Clinergize to access documents provided by the sponsor.

BI has appointed a Clinical Trial Leader (CT Leader), responsible for coordinating all required activities, in order to

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

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

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

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

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

9. REFERENCES

9.1 PUBLISHED REFERENCES

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R19-0761 Liu F, Yang X, Geng M, Huang M. Targeting ERK, an Achilles' heel of the MAPK pathway, in cancer therapy. Acta Pharm Sin B 8 (4), 552-62 (2018).

R19-3904 Burotto M, Chiou VL, Lee JM, Kohn EC. The MAPK pathway across different malignancies: a new perspective. Cancer 120, 3446 - 3456 (2014)

9.2 UNPUBLISHED REFERENCES

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10. APPENDICES

10.1 TIME SCHEDULE FOR PHARMACOKINETIC (PK) SAMPLING

Table 10.1: 1 Time schedule for PK blood [redacted] sampling and ECG

Cycle	Visit	Day	Time Point [hh:min]	CRF Time /PTM	Event		
					Drug administr.	PK Blood and ECG	[redacted]
1	1	1	Just before drug administration	-0:05		X	[redacted]
			0:00	0:00	X		[redacted]
			0:30	0:30		X	[redacted]
			0:45	0:45		X	[redacted]
			1:00	1:00		X	[redacted]
			1:30	1:30		X	[redacted]
			2:00	2:00		X	[redacted]
			2:30	2:30		X	[redacted]
			3:00	3:00		X	[redacted]
			4:00	4:00		X	[redacted]
			6:00	6:00		X	[redacted]
			8:00	8:00		X	[redacted]
			10:00	10:00		X	[redacted]
			12:00	12:00		X [a]	[redacted]
	2	2	Just before drug administration	23:55		X	[redacted]
	4	8	Just before drug administration	167:55		X	
	5	15	Just before drug administration	335:55		X	
			0:00	336:00	X		[redacted]
			0:30	336:30		X	[redacted]
			0:45	336:45		X	[redacted]
			1:00	337:00		X	[redacted]
			1:30	337:30		X	[redacted]
			2:00	338:00		X	[redacted]
			2:30	338:30		X	[redacted]
			3:00	339:00		X	[redacted]
			4:00	340:00		X	[redacted]
							[redacted]
			6:00	342:00		X	[redacted]
			8:00	344:00		X	[redacted]
			10:00	346:00		X	[redacted]
			12:00	348:00		X [a]	[redacted]

Table 10.1: 1 Time schedule for PK blood [redacted] sampling and ECG (cont.)

Cycle	Visit	Day	Time Point [hh:min]	CRF Time /PTM	Event		
					Drug administr.	PK Blood and ECG	[redacted]
	6	16	Just before drug administration	359:55		X	[redacted]
	7	22	Just before drug administration	503:55		X	
2	1	1	Just before drug administration	-0:05		X	
3	1	1	Just before drug administration	-0:05		X	
4	1	1	Just before drug administration	-0:05		X	

a) An optional 12-hour postdose PK blood sample should be collected if the patient is willing.

b) [redacted]

10.2 STATISTICAL APPENDIX INCLUDING MODEL PERFORMANCE AND DATA SCENARIOS

A Bayesian logistic regression model with overdose control will be used to guide dose escalation in this trial. The BLRM is introduced in Section 7.1, which also specifies the prior for the model. 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. 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 and laboratory data.
The purpose of this statistical appendix is to present performance metrics (operating characteristics) that illustrate the precision of the design in estimating the MTD under various dose-toxicity relationships through computer simulation. These results are summarized in Table 10.2:3. In addition, recommendations of the next dose level by the BLRM with overdose control principle are also provided under various hypothetical outcome scenarios in early cohorts to show how it facilitates on-trial dose-escalation decisions (see Table 10.2:1). For simplicity reasons, a cohort size of 3 patients who are all evaluable is assumed.

Hypothetical data scenarios
Hypothetical data scenarios are shown in Table 10.2:1. These scenarios reflect potential on-study data constellations and related escalation as allowed by the model. It is assumed that each cohort has exactly three patients who are all evaluable. For each scenario, the probability of overdose for the current dose, as well as the next potential dose and related probabilities of under-dosing, target dose, and over-dosing are shown.
For example, scenario 1 represents the case that no DLT is observed in the first three patients at the starting dose of 4 mg. In this case, the next optimal dose, i.e. the dose with the highest probability of being in the target interval, is 7 mg. Since the escalation is restricted to a maximum of 50 % from the previous dose per protocol, the next dose to be tested in the trial would be 6 mg.
Scenario 4 is the case that one DLT is observed in the first three patient at the starting dose of 4mg and no DLT is observed in second three patient at 4mg; in this case the model recommend to escalate 6 mg . Scenario 5 is the case that one DLT is observed in the first three patient at the starting dose of 4 mg and one DLT is observed in second three patient at 4 mg; in this case the model recommend to 4 mg. Scenario 6 represents the case that 3 patients have been treated at 4 mg and 3 patients at 6 mg, none of them with a DLT. In this case, the model recommends to escalate to 8 mg.
Scenarios 16 to 22 are the cases where doses of 4 mg and 6 mg have been completed with no DLT and the BLRM recommends 8mg to be tested next. More specifically, scenarios 18, 21 and 22 are the cases that dose of 8 mg have been completed and BLRM recommend to reduce to 7mg. Scenario 19, 20 illustrate a case where escalation has proceeded up to the highest dose of 8 mg, where the MTD could be declared at 8 mg.
Scenarios 23 to 26 are the cases that 1 DLT out of 6 patients in 4mg cohort and no DLT in 3 patients in 6 mg cohort, BLRM recommends 7 mg to be tested next. In scenarios 23, the next optimal dose, i.e. the dose with the highest probability of being in the target interval, is 8 mg. In such cases, SMC will suggest whether to open up 8mg cohort or keep treating patients at 7mg. In scenarios 25, the next optimal dose, i.e. the dose with the highest probability of being in the target interval, is 8 mg. In such cases, SMC will suggest whether to open up 8 mg

cohort or claiming 7 mg as MTD according to BLRM. Scenario 26 illustrates a case when we can claim 7 mg as MTD according to BLRM.
Scenarios 27, 28, 30 and 31 are the cases that no DLT out of 3 patients in 4mg cohort and one DLT in 6 patients in 6 mg cohort, BLRM recommends 7 mg to be tested next. In scenarios 27 and 29, the next optimal dose, i.e. the dose with the highest probability of being in the target interval, is 8 mg. In scenarios 28, the next optimal dose, i.e. the dose with the highest probability of being in the target interval, is 7 mg. Scenario 30 illustrates a case when we can claim 7 mg as MTD according to BLRM. Scenario 31 illustrates a case when we can claim 6 mg as MTD according to BLRM.
Scenarios 32 to 36 are the cases that 1 DLT out of 6 patients in 4mg cohort, no DLT in 3 patients in 6 mg cohort and no DLT in 3 patients in 7 mg cohort BLRM recommends 8 mg to be tested next.
Scenarios 37 to 41 are the cases that 1 DLT out of 6 patients in 4mg cohort, no DLT in 3 patients in 6 mg cohort and one DLT in 6 patients in 7 mg cohort BLRM recommends 8 mg to be tested next.
Scenarios 42 to 46 are the cases that no DLT out of 3 patients in 4mg cohort, one DLT in 6 patients in 6 mg cohort and no DLT in 3 patients in 7 mg cohort BLRM recommends 8 mg to be tested next.

Table 10.2:1 Hypothetical data scenarios

Scenario	Dose (mg)	# Patients	# DLT	Current Dose : P (OD)	Next recommended dose *	Next dose:		
						P (UD)	P (TD)	P (OD)
1	4 mg	3	0	0.026	6 mg [7 mg]	0.636 [0.486]	0.270 [0.339]	0.095 [0.175]
2	4 mg	3	1	0.194	4 mg	0.442	0.365	0.194
3	4 mg	3	2	0.569	NA			
4	4 mg	6	1	0.065	6 mg	0.309	0.459	0.233
5	4 mg	6	2	0.249	4 mg	0.273	0.478	0.249
6	4 mg 6 mg	3 3	0 0	0.027	8 mg	0.440	0.375	0.185
7	4 mg 6 mg	3 3	0 1	0.153	6 mg	0.427	0.420	0.153
8	4 mg 6 mg	3 6	0 1	0.049	7 mg	0.377	0.480	0.143
9	4 mg 6 mg	3 6	0 2	0.178	6 mg	0.304	0.518	0.178

Table 10.2:1 Hypothetical data scenarios (cont.)

10	4 mg 6 mg	3 6	0 3	0.397	4 mg	0.484	0.400	0.116
11	4 mg 6 mg	3 6	0 4	0.658	4 mg	0.318	0.449	0.233
12	4 mg 6 mg	6 3	1 0	0.096	7 mg	0.335	0.474	0.192
13	4 mg 6 mg	6 3	1 1	0.243	6 mg	0.215	0.542	0.243
14	4 mg 6 mg	6 6	1 1	0.125	7 mg	0.212	0.553	0.235
15	4 mg 6 mg	6 6	1 2	0.288	4 mg	0.504	0.424	0.072
16	4 mg 6 mg 8 mg	3 3 3	0 0 0	0.058	8 mg	0.604	0.338	0.058
17	4 mg 6 mg 8 mg	3 3 3	0 0 1	0.234	8 mg	0.281	0.485	0.234
18	4 mg 6 mg 8 mg	3 3 3	0 0 2	0.500	7 mg	0.304	0.481	0.214
19	4 mg 6 mg 8 mg	3 3 6	0 0 0	0.023	8 mg	0.731	0.245	0.023
20	4 mg 6 mg 8 mg	3 3 6	0 0 1	0.106	8 mg	0.443	0.451	0.106
21	4 mg 6 mg 8 mg	3 3 6	0 0 2	0.274	7 mg	0.453	0.464	0.083
22	4 mg 6 mg 8 mg	3 3 6	0 0 3	0.501	7 mg	0.287	0.519	0.195

Table 10.2:1 Hypothetical data scenarios (cont.)

23	4 mg 6 mg 7 mg	6 3 3	1 0 0	0.076	8 mg [7 mg]	0.364 [0.483]	0.484 [0.442]	0.152 [0.076]
24	4 mg 6 mg 7 mg	6 3 3	1 0 1	0.209	7 mg	0.234	0.557	0.209
25	4 mg 6 mg 7 mg	6 3 6	1 0 1	0.092	8 mg [7 mg]	0.247 [0.368]	0.560 [0.540]	0.193 [0.092]
26	4 mg 6 mg 7 mg	6 3 6	1 0 2	0.225	7 mg	0.174	0.602	0.225
27	4 mg 6 mg 7 mg	3 6 3	0 1 0	0.052	8mg [7 mg]	0.335 [0.534]	0.492 [0.413]	0.173 [0.052]
28	4 mg 6 mg 7 mg	3 6 3	0 1 1	0.177	7 mg	0.278	0.546	0.177
29	4 mg 6 mg 7 mg	3 6 6	0 1 1	0.224	8 mg [7 mg]	0.222 [0.404]	0.554 [0.530]	0.224 [0.066]
30	4 mg 6 mg 7 mg	3 6 6	0 1 2	0.199	7 mg	0.200	0.602	0.199
31	4 mg 6 mg 7 mg	3 6 6	0 1 3	0.363	6 mg	0.263	0.589	0.148
32	4 mg 6 mg 7 mg 8 mg	6 3 3 3	1 0 0 0	0.065	8 mg	0.510	0.425	0.065
33	4 mg 6 mg 7 mg 8 mg	6 3 3 3	1 0 0 1	0.178	8 mg	0.258	0.563	0.178

Table 10.2:1 Hypothetical data scenarios (cont.)

34	4 mg 6 mg 7 mg 8 mg	6 3 3 6	1 0 0 0	0.023	8 mg	0.637	0.340	0.023
35	4 mg 6 mg 7 mg 8 mg	6 3 3 6	1 0 0 1	0.077	8 mg	0.380	0.544	0.077
36	4 mg 6 mg 7 mg 8 mg	6 3 3 6	1 0 0 2	0.207	8 mg	0.188	0.605	0.207
37	4 mg 6 mg 7 mg 8 mg	6 3 6 3	1 0 1 0	0.100	8 mg	0.366	0.534	0.100
38	4 mg 6 mg 7 mg 8 mg	6 3 6 3	1 0 1 1	0.226	8 mg	0.177	0.597	0.226
39	4 mg 6 mg 7 mg 8 mg	6 3 6 6	1 0 1 0	0.041	8 mg	0.490	0.468	0.041
40	4 mg 6 mg 7 mg 8 mg	6 3 6 6	1 0 1 1	0.109	8 mg	0.272	0.619	0.109
41	4 mg 6 mg 7 mg 8 mg	6 3 6 6	1 0 1 2	0.236	8 mg	0.139	0.625	0.236
42	4 mg 6 mg 7 mg 8 mg	3 6 3 3	0 1 0 0	0.074	8 mg	0.495	0.431	0.074

Table 10.2:1 Hypothetical data scenarios (cont.)

43	4 mg 6 mg 7 mg 8 mg	3 6 3 3	0 1 0 1	0.200	8 mg	0.240	0.560	0.200
44	4 mg 6 mg 7 mg 8 mg	3 6 3 6	0 1 0 0	0.025	8 mg	0.615	0.360	0.025
45	4 mg 6 mg 7 mg 8 mg	3 6 3 6	0 1 0 1	0.082	8 mg	0.369	0.549	0.082
46	4 mg 6 mg 7 mg 8 mg	3 6 3 6	0 1 0 2	0.232	8 mg	0.162	0.606	0.232

* Model recommendation is higher than allowed by additional rules in the CTP. Dose in brackets represents next dose with taking into account the CTP-specific rules.

Operating characteristics

Operating characteristics are a way to assess the long-run behaviour of a model by illustrating the precision of the design in estimating the MTD. Under an assumed true dose-toxicity curve, metrics such as the probability of recommending a dose with true DLT rate in the target interval can be approximated via simulation. Table 10.2:2 describes 6 assumed true dose-toxicity scenarios which were used to assess the operating characteristics of the model. These scenarios reflect a wide range of possible cases as follows:

- Scenario 1: aligned with prior means
- Scenario 2: high-toxicity scenario
- Scenario 3: low-toxicity scenario
- Scenario 4: non-logistic dose-toxicity scenario
- Scenario 5: low-toxicity followed by high-toxicity
- Scenario 6: too-toxicity scenario

Table 10.2:2 Assumed true dose-toxicity scenarios

Scenario		Dose (mg)			
		4 mg	6 mg	7mg	8 mg
1: Prior	P(DLT)	0.147	**0.224**	**0.272**	**0.329**
2: High Tox		**0.22**	0.34	0.40	0.45
3: Low Tox		0.04	0.11	0.13	**0.16**
4: Non-Logistic		0.1	**0.2**	**0.25**	**0.3**
5: Low-High		0.04	**0.2**	0.40	0.45
*6:Too Tox		0.42	0.68	0.75	0.81

Bold numbers indicate true DLT rates in the target interval [0.16, 0.33].
* For Scenario 6, 2mg dose with 32% true DLT probability was added to the simulation condition in order for the R package to run (which needs at least one provisional dose level with true DLT probability in the target range).
For each of these scenarios, 1000 trials were simulated. Each cohort consisted of 3 patients
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 10.2:3.

Table 10.2:3 Simulated operating characteristics

Scenario	% of trials declaring a MTD with true DLT rate in				# Patients	# DLTs
	under dose	target dose	overdose	Stopped	Mean (Min-Max)	Mean (Min-Max)
1	19.4	66.3	0	14.3	15.3 (3-33)	3.4 (1-9)
2	0	25.2	32.2	42.6	11.6 (3-30)	3.4 (1-11)
3	26.2	72.6	0	1.2	16.8 (3-42)	1.9 (1-7)
4	11.7	76.7	0	11.6	13.6 (3-33)	2.7 (1-9)
5	14.4	48.7	35.1	1.8	15.9 (3-36)	3.7 (1-11)
6	0	20.8	12.8	66.4	8.6 (3-24)	3.7 (2-12)

In Scenario 1, which reflects the case that the true dose-toxicity is aligned with prior means, 66.3% of the simulated trials declared the dose 4 mg as MTD with true DLT rate under the targeted dose range.
Scenario 2 (high-toxicity scenario) shows, that when the true DLT rate is high, i.e. the majority dose levels with true DLT rate above the target interval, The probability of observing a DLT at 6 mg is 0.34 and therefore very close to the upper bound of the target range. This accounts for 17.7% out of 32.2% where we declared a dose as MTD in the overdose interval. 42.6% of the trials were stopped without declaring a MTD since all dose levels were too toxic. This is an expected situation for a high-toxicity scenario.
Scenario 3 shows that when the true DLT rate is low, 72.6% of the simulated trials declared the dose 4 mg as MTD with true DLT rate under the targeted dose range, and 26.2% of the simulated trials declared a MTD in the underdose interval.
Scenario 4 represents a case where the assumed true dose-toxicity curve does not follow a logistic shape. In this scenario, 76.7% of trials declared MTDs with true DLT rate in the target interval, and only a few trials declared MTDs with true DLT rate in the underdose interval. This illustrates that the model is not sensitive to model misspecification.
Scenario 5 shows that when the true DLT rate is low-high, 48.7% of the simulated trials declared a dose as MTD with true DLT rate in the targeted dose range.
Scenario 6 shows that when the true DLT rate is super high, 66.4% of simulated trials stopped, since none of the doses is considered tolerable anymore. This is an expected situation for a super high-toxicity scenario.

The mean patient numbers range from 8.6 patients (Scenario 6) to 16.8 patients (Scenario 3) and the maximum number of patients was 42. Therefore, the patient numbers are as expected and increase when moving away from the high-toxicity scenario.
By reviewing the metrics presented in Table 10.2:3, it can be seen that the model is not sensitive to different scenarios of truth. In general, this model is conservative due to the overdose control criteria. In all scenarios, the probabilities of recommending a dose with true P(DLT) ≥ 33% as MTD are much smaller than probabilities of recommending a dose with true P(DLT) between 16% and 33% as MTD.

On-study recommendations based on the model are consistent with the clinical decision making process, and should be considered in conjunction with other available clinical information by the BI clinical trial team and trial investigators in deciding the dose levels to be tested in order to determine the MTD estimate.

R version 3.5.1 and JAGS were used for data scenarios and simulations.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		22 Jul 2020
EudraCT number **EU number**		NA
BI Trial number		1469-0002
BI Investigational Medicinal Product(s)		BI 3011441
Title of protocol		A phase I open-label trial of BI 3011441 in Japanese patients with NRAS/KRAS mutation positive advanced, unresectable or metastatic refractory solid tumours
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		Flow chart
Description of change		LVEF measurement added on Day 15 of Cycle 1. Footnote t) which is explaining hospitalisation period during Cycle 1 and u) which is about additional X-ray were added.
Rationale for change		Based on comment from authority to make sure patient safety.
Section to be changed		Section 3.3.2 and 3.3.4.1
Description of change		Inclusion criteria 13, 14, footnote and treatment discontinuation condition was added to explain more clearly about WOBCP definition and handling for related to pregnancy and nursing.
Rationale for change		Based on comment from authority to be clearer about handling.
Section to be changed		Section 4.1.1
Description of change		Explanation about gelatin used for BI 3011441 was added.
Rationale for change		Based on comment from authority.
Section to be changed		Section 4.1.2 and 5.2.6.3
Description of change		DLT condition for MTD evaluation has updated to avoid underestimate of DLT.
Rationale for change		Based on comment from authority to make sure patient safety.

Section to be changed		Section 5.2.2
Description of change		Measurement of saturation of percutaneous oxygen was added.
Rationale for change		To detect ILD earlier.
Section to be changed		Section 5.2.3
Description of change		Testing for HBV detection was corrected based on local guideline.
Rationale for change		Based on comment from authority to make sure patient safety.
Section to be changed		Section 5.4
Description of change		Additional explanation about disclosure of biomarker analyses result to patient and handling of data and sample after withdrawal were added.
Rationale for change		Based on comment from authority.

11.2 GLOBAL AMENDMENT 2

Date of amendment		19 Nov 2020
EudraCT number **EU number**		NA
BI Trial number		1469-0002
BI Investigational Medicinal Product(s)		BI 3011441
Title of protocol		A phase I open-label trial of BI 3011441 in Japanese patients with NRAS/KRAS mutation positive advanced, unresectable or metastatic refractory solid tumours
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		Flowchart
Description of change		Footnote h) was updated to increase allowance for ophthalmological assessment.
Rationale for change		Based on comment from priniciple investigator.
Section to be changed		Section 1.2
Description of change		Drug interaction information was updated based on most recent information. Description of safety information from previous study was updated based on recent IB.
Rationale for change		Same as above

Section to be changed		Section 1.4.2
Description of change		Description was simplified and moved to Table 1.4.2:1 based on internal consideration
Rationale for change		Same as above
Section to be changed		Section 1.4.3
Description of change		New section about COVID-19 related Benefit-Risk Assessment was added.
Rationale for change		Due to internal requirement
Section to be changed		Section 3.3.3
Description of change		Exclusion criteria 8 was upodated to add more detail definition about hypertension.
Rationale for change		To make exclusion criteria clear
Section to be changed		Section 3.3.4.1.1
Description of change		Enrolment stopping rule was updated.
Rationale for change		Due to internal requirement
Section to be changed		Section 4.2.2.1
Description of change		Updated based on recent drug interaction information.
Rationale for change		Same as above
Section to be changed		Table 5.2.3:1
Description of change		Desnription about myoglobin and cratine kinase was updated.
Rationale for change		Based on request from Risk Management Physician.
Section to be changed		Section 5.2.6
Description of change		DILI definition was updated based on internal process update.
Rationale for change		Due to internal requirement
Section to be changed		Section 5.2.6.2.4
Description of change		Exemptions to AE reporting was updated based on internal process update.
Rationale for change		Due to internal requirement
Section to be changed		Section 5.2.6.3
Description of change		DLT definition about hypertension was updated based to make condition clearer.
Rationale for change		Same as above.

12. REFERENCES FOR CTP AUTHORS

NA

APPROVAL / SIGNATURE PAGE

Document Number: c30222580 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol-version-03

Title: A phase I open-label trial of BI 3011441 in Japanese patients with NRAS/KRAS mutation positive advanced, unresectable or metastatic refractory solid tumours

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
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