Boehringer Ingelheim

Clinical Trial Protocol

	Document Number:	**c27190653-05**
EudraCT No. **EU Trial No.**	Not applicable	
BI Trial No.	1379-0006	
BI Investigational Medicinal Product(s)	BI 891065 BI 754091	
Title	An open label, Phase I study of BI 891065 monotherapy and combination therapy of BI 891065 and BI 754091 in Asian patients with advanced solid tumours	
Lay Title	A study to test different doses of BI 891065 alone and in combination with BI 754091 in Asian patients with different types of advanced cancer (solid tumours)	
Clinical Phase	I	
Clinical Trial Leader	[redacted] Telephone: + [redacted] Fax: + [redacted]	
Coordinating Investigator	[redacted] Telephone: + [redacted]	
Status	Final Protocol (Revised Protocol (based on global amendment 4))	
Version and Date	**Version: 5.0**	**Date: 30 Apr 2021**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	02 Jul 2019
Revision date	30 Apr 2021
BI trial number	1379-0006
Title of trial	An open label, Phase I study of BI 891065 monotherapy and combination therapy of BI 891065 and BI 754091 in Asian patients with advanced solid tumours
Coordinating Investigator	[redacted] Telephone: +[redacted]
Trial site(s)	Multi-centre trial conducted in Asia
Clinical phase	I
Trial rationale	The trial is required to evaluate the safety of BI 891065 monotherapy and combination therapy of BI 891065 and BI 754091 in Asian patients for the later phase clinical development in Asian populations.
Trial objective(s)	The main objectives of this trial are: Part A (monotherapy part) • To determine the Maximum tolerated dose (MTD) and/or the recommended dose (RD) of BI 891065 monotherapy in Asian patients with advanced solid tumours • To document the safety and tolerability, and characterise pharmacokinetics (PK) of BI 891065 as monotherapy in Asian patients with advanced solid tumours In Part B (combination therapy part) • To determine the MTD and/or the RD of BI 891065 in combination with a fixed dose of BI 754091 at 240 mg in Asian patients with advanced solid tumours • To document the safety and tolerability, and characterise PK of the combination therapy of BI 891065 and BI 754091 in Asian patients with advanced solid tumours
Trial endpoints	Part A (monotherapy part) Primary: • Maximum tolerated dose (MTD) • Number of patients with Dose Limiting Toxicities (DLTs) in the MTD evaluation period and thereafter

	Secondary: • PK parameters of BI 891065 in cycle 1: $C_{max(,ss)}$, AUC_{0-24} and $AUC_{\tau,ss}$ of BI 891065 Part B (combination therapy part) Primary: • Maximum tolerated dose (MTD) • Number of patients with Dose Limiting Toxicities (DLTs) in the MTD evaluation period Secondary: • PK parameters of BI 891065 and BI 754091 in cycle 1: $C_{max(,ss)}$, AUC_{0-24} and $AUC_{\tau,ss}$ of BI 891065 C_{max} and AUC_{0-504} of BI 754091
Trial design	Open label, uncontrolled, non-randomised, dose-escalation design
Total number of patients randomised	Approximately 21
Number of patients on each treatment	Approximately 21
Diagnosis	Patients with a confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumours
Main in- and exclusion criteria	Main inclusion criteria: • Patients with a confirmed diagnosis of advanced, unresectable and/or metastatic solid tumours, who have failed standard treatment, or for whom no therapy of proven efficacy exists, or who are not amenable to standard therapies • Eastern Cooperative Oncology Group (ECOG) performance status: 0 to 1 • Presence of at least one measureable lesion according to response evaluation criteria in solid tumours (RECIST) 1.1 Main exclusion criteria: • Presence of active invasive cancers other than the one treated in this trial within 5 years prior to screening • HIV, HBV, or HCV infection • Inadequate organ function or bone marrow reserve as demonstrated by laboratory values • Active, known or suspected autoimmune disease • History (including current) of interstitial lung disease or pneumonitis within 5 years • Serious concomitant disease or medical condition affecting compliance with trial requirements • Patients with brain metastases • Patients receiving systemic treatment with any immunosuppressive medication within 1 week prior to treatment start

Test product(s)	BI 891065 BI 754091 (Part B only)
dose	**Part A**: BI 891065: starting dose 100 mg once daily **Part B**: BI 891065: starting dose 200 mg per day BI 754091: fixed dose of 240 mg every three weeks
mode of administration	BI 891065: p.o. BI 754091: i.v. infusion
Comparator product(s)	Not applicable
dose	Not applicable
mode of administration	Not applicable
Duration of treatment	Administration will continue until progressive disease (PD), unacceptable toxicity, or other withdrawal criteria.
Statistical methods	In Parts A and B, dose escalation is guided by Bayesian Logistic Regression Models (BLRMs) with overdose control that will be fitted to binary toxicity outcomes. The estimate of parameters will be updated as data are accumulated using the BLRMs. At the end of the dose escalation, the toxicity probability at each dose level will be calculated to determine an estimate of the MTD and/or the RD. Descriptive analysis (summary statistics) will be used to describe the safety and efficacy endpoints.

FLOW CHART

Trial period	**Screening**	**Treatment period (Cycle = 21 days)***								**Post-Treatment Period***		
Cycle[a]		**Cycle 1[t]**							**Cycle 2 onwards**	**End-of-Treatment (EOT) Visit[v]**	**30-day Safety follow-up**	**Follow-up for PD[p]**
Visit number		**1a**	**1b**	**1c**	**2**	**3**	**4**	**5**	**1**			
Day; visit window [days]	**-14 to -1 unless otherwise specified[s]**	**1**	**2**	**3 (Part A only)**	**8 (±1)**	**12 (±1)**	**15[u]**	**16[u]**	**1 (±2)**	**Within 7 (+7) days after decision of discontinuation**	**30 (+7) days after last dose**	**At least every 12 weeks**
Informed consent	X											
Inclusion / exclusion criteria	X	X										
Medical history and demographics	X											
Physical examination, height (screening only), and weight	X	X							X	X	X	
ECOG Performance status	X	X							X	X	X	
Vital signs (BP, PR, BT and SpO_2)[b]	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG (Triplicate)[c]	X	X	X				X	X				
12-Lead ECG (single, local assessment only)[c]									X	X		
Ejection fraction (only if clinically indicated)[d]	X											
Pregnancy test[e,f]	X	X							X	X	X	
Haematology and biochemistry[e]	X	X			X		X		X	X		
Coagulation test[e]	X	X							X	X		
Urinalysis[e]	X	X			X		X		X	X		
Virology test[g]	X											
Blood, urine sampling for BI 891065 pharmacokinetics[h]		X	X	X	X	X	X	X	X (C2)			

Trial period	**Screening**	**Treatment period (Cycle = 21 days)***								**Post-Treatment Period***		
Cycle[a]		**Cycle 1[t]**							**Cycle 2 onwards**	**End-of-Treatment (EOT) Visit[v]**	**30-day Safety follow-up**	**Follow-up for PD[p]**
Visit number		**1a**	**1b**	**1c**	**2**	**3**	**4**	**5**	**1**			
Day; visit window [days]	**-14 to -1 unless otherwise specified[s]**	**1**	**2**	**3 (Part A only)**	**8 (±1)**	**12 (±1)**	**15[u]**	**16[u]**	**1 (±2)**	**Within 7 (+7) days after decision of discontinuation**	**30 (+7) days after last dose**	**At least every 12 weeks**
(Part B only) Blood sampling for BI 754091 pharmacokinetics[i]		X	X		X	X	X		X[i]	X	X	
(Part B only) Blood sampling for anti-drug antibodies (ADAs)[j]		X					X		X[j]	X	X	
Alpha-1 acid glycoprotein (AGP)		X							X (C2)			
Blood sampling for Cytokines[k]		X	X		X		X		X (C2)	X		
Blood sampling for Coproporphyrin[l]		X	X	X			X	X				
Blood sampling for PGx[m]		X										
(Part B only) Tumour biopsy[n]		X							X (C2)			
BI 891065 intake[o]		Continuous dosing of once or twice daily, with exceptions for PK assessment										
(Part B only) BI 754091 infusion		X							X			
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Check of disease progression[p]												X
Review Patient Diary	X	X	X	X	X	X	X	X	X	X		
(Part B only) Chest X-ray[e,q]	X	X							X	X		
Tumour assessment[r]	X (-28 to -1)	Every 6 weeks ±3 days for 24 weeks (then every 9 weeks ±3 days thereafter)										

* After implementation of protocol version 05, the patient will have assessments as medically indicated to monitor the safety at the discretion of the investigator. These assessments may include: ECG, safety lab, and vital signs at a frequency decided by the investigator. The study treatment is administered as continuous daily dosing and the administration information will be documented in the eCRF. Tumour assessment will be performed according to standard of care based on medical opinion of the investigator. The results of any assessments will be documented in the source data, but will not be collected in the eCRF. The blood sampling for cytokines at the EOT visit is not required. Findings which qualify as an (S)AE will be reported in the eCRF and in case of an SAE, on the SAE form (timelines and distribution requirements for SAEs apply).

The data collection is required only for the following items:
- Adverse events
- Concomitant medications that are used to treat adverse events
- Drug dispensing
- Dose changes
- At each cycle visit: visit date and medication compliance to BI 891065
- At EOT visit: visit date, end of treatment – BI 891065, and subject retention
- At safety follow-up visit: visit date and end of study page
- Death details (if applicable)

a Treatment cycles are 21 days (3 weeks). Patients will continue treatment with the study drug(s) until they meet any of the discontinuation criteria (CTP section 3 "withdrawal from study treatment"). All circumstances for withdrawal of trial treatment are presented in section 3.3.4.1.

b Vital signs (blood pressure, pulse rate, body temperature, and arterial oxygen saturation rate [SpO_2] measured by non-invasive pulse oximeter) are checked at every visit prior to blood sampling and trial treatment. The measurement of SpO_2 is required in Part B only.

c Triplicate 12-lead electrocardiograms (ECGs) will be done for local and central assessments as outlined in section 5.2.4 in cycle 1 at the time points specified in section 10.3 and whenever the Investigator deems it necessary. ECG machines will be provided to facilitate central readings. From cycle 2 onwards, single ECGs will be done for local assessment on visit 1 before the study drug administration.

d Refer to section 3.3.3 for details on which patients require an ejection fraction assessment (e.g., echocardiogram (ECHO)/multi-gated acquisition (MUGA) scan).

e For haematology, clinical biochemistry, coagulation test, urinalysis, pregnancy test and chest X-ray, if screening tests for these items are performed within 3 days prior to the initiation of treatment, they do not need to be repeated on Cycle 1 Day 1.

f Pregnancy tests are mandatory for women with child-bearing potential. A serum (or plasma) beta human chorionic gonadotropin (β-HCG) pregnancy test must be done at screening. Thereafter, either a serum (or plasma) or urine pregnancy test will be done on Day 1 of each cycle, at the EOT visit, and at the 30-day safety FU visit.

g HBV, HCV, and HIV testing should be performed at screening (see section 5.2.3.6 for HBV and HCV test requirements). In Part A, these tests are exempted if test results obtained in routine clinical practice within 6 months before the informed consent date are available. In part B, HBV and HCV tests are mandatory but HIV testing is not mandatory if test results obtained in routine clinical practice within 6 months before the informed consent date are available.

h Pharmacokinetic (PK) sampling for BI 891065 (blood and urine) will be done during Cycles 1 and 2 (see tables in section 10.3). Patients will be asked to fast overnight (minimum of 10 hours) prior to the following intensive PK days

- Cycle 1 day 1
- Cycle 1 day 15

Urine samples are taken in Part A in once daily (q.d.) dosing schedule cohorts only.

i Pharmacokinetic (PK) sampling for BI 754091 will be done in Part B only in Cycles 1, 2, 3, 4, 8, 12, 16, and at the EOT and 30-day safety FU visits (see tables in section 10.3).

j Blood samples to test for anti-drug antibodies (ADAs) will be collected from all patients in Part B pre-treatment on Day 1 and 15 of Cycle 1, pre-treatment to Cycles 3, 4, 8, 12, 16, and at the EOT and 30-day safety FU visits (see tables in section 10.3).

k Blood samples for the quantification of cytokines will be taken during Cycle 1 on Day 1 pre-treatment and at 1, 3 and 8 hours post treatment, on Day 2 (no treatment day) at 24 hours after first drug intake on the previous day, and pre-treatment on Days 8, 15, and C2D1, as well as at the EOT visit (see tables in section 10.3).

l Coproporphyrin plasma level will be assessed as biomarker to assess the potential inhibition of OATP1B1/B3. Plasma sampling for CPI and CPIII is detailed in section 10.3.

m To perform the pharmacogenetic analysis, patients will provide a blood sample for DNA isolation at Visit 1 of Cycle 1 (C1V1) or at a later visit during treatment. Refer to section 5.4.4.

n The following tumour biopsies will be mandatory for all patients in Part B of the trial:

- One fine needle biopsy must be freshly taken between screening and first trial drug treatment.
- One fine needle biopsy from the same lesion on treatment as soon as possible after the 21-day observation period is completed and the patient has been on the uninterrupted and unchanged dose of BI 891065 for at least two continuous weeks. Biopsy collection should be delayed until these conditions are met. If it is absolutely impossible to obtain a biopsy from the same lesion, another lesion may be chosen.

o BI 891065 is taken either once daily (q.d.) or twice daily (b.i.d.), depending on the assigned treatment regimen. BI 891065 doses should be taken orally at approximately the same time each morning (and evening for patients with b.i.d. dosing). There are exceptions depending on the part (Part A or Part B) and dosing regimen (q.d. or b.i.d.):

- Part A q.d. dosing: a dose will be skipped on cycle 1 day 2
- Part A b.i.d. dosing: following doses will be skipped in cycle 1 – day 1 evening, day 2 morning and evening, and day 15 evening
- Part B q.d. dosing: no exceptions
- Part B b.i.d. dosing: following doses will be skipped in cycle 1 – day 1 evening and day 15 evening

p The follow-up visits for progression will be performed for patients whose disease has not progressed by the 30-day follow-up visit, at least once every 12 weeks (preferably in person, but if the patient cannot visit the study sites, collecting information by telephone is accepted) until PD, introduction of a new anti-cancer treatment, death, loss to follow-up, withdrawal of consent, or end of the whole trial (section 6.2.3.3).

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

r Tumour assessments should be done according to RECIST v1.1 and iRECIST and should include 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 MRI). The same radiographic procedure must be used throughout the trial. 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. Assessments will be performed by the Investigator at screening and once every 6 weeks ±3 days for the first 24 weeks of treatment, once every 9 weeks ±3 days thereafter, at the EOT visit (if not performed within the previous 4 weeks), and at the discretion of the Investigator. The timing of on-treatment imaging assessments is not affected by delays in treatment cycles. Copies of the imaging may be collected by the sponsor or designee. Tumour assessments performed prior to informed consent as part of routine clinical practice will be accepted if they meet the requirements of the protocol and are performed within 28 days prior to the first administration of study drug(s).

s Screening should take place within 14 days of start of study treatment unless otherwise specified (e.g., virology tests and tumour assessment for which results obtained in routine clinical practice are accepted). However, it may be extended as outlined in section 6.2.1.1.

t Patients will remain hospitalised for at least three days after the first administration of BI 891065. 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 adverse events and if necessary haematology and clinical chemistry examination.

u Visits 4 and 5 can be shifted one day before or after (i.e., there's an allowance window of +/- 1 day), but these visits should be performed on two consecutive days.

v An EOT visit should be performed for all patients who permanently discontinue trial medication, preferably within 7 days and no later than 14 days after the decision of discontinuation. However, if the assessments specified for EOT have been performed within 7 days prior to the decision of discontinuation, these assessments do not need to be repeated. If the decision to permanently discontinue treatment is taken at a scheduled visit, the EOT visit should be performed instead of the scheduled visit.

TABLE OF CONTENTS

TITLE PAGE 1

CLINICAL TRIAL PROTOCOL SYNOPSIS 2

FLOW CHART 5

TABLE OF CONTENTS 10

ABBREVIATIONS 15

1. INTRODUCTION 19

1.1 MEDICAL BACKGROUND 19
1.2 DRUG PROFILE 20
1.2.1 BI 891065 (SMAC mimetic) 20
1.2.2 BI 754091 (anti-PD-1 mAb) 21
1.2.3 Combination of BI 891065 and BI 754091 21
1.3 RATIONALE FOR PERFORMING THE TRIAL 23
1.4 BENEFIT - RISK ASSESSMENT 23
1.4.1 Benefits 23
1.4.2 Risks 23
1.4.3 Discussion 25

2. TRIAL OBJECTIVES AND ENDPOINTS 27

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS 27
2.1.1 Main objectives 27
2.1.2 Primary endpoint(s) 27
2.1.3 Secondary endpoint(s) 28

[redacted]

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION 31

3.1 OVERALL TRIAL DESIGN AND PLAN 31
3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S) 32
3.3 SELECTION OF TRIAL POPULATION 32
3.3.1 Main diagnosis for trial entry 33
3.3.2 Inclusion criteria 33
3.3.3 Exclusion criteria 34
3.3.4 Withdrawal of patients from treatment or assessments 36
3.3.4.1 Discontinuation of trial treatment 36
3.3.4.2 Withdrawal of consent to trial participation 37
3.3.4.3 Discontinuation of the trial by the sponsor 37

4. TREATMENTS 38

4.1 INVESTIGATIONAL TREATMENTS 38
4.1.1 Identity of the Investigational Medicinal Products 38

4.1.2 Selection of doses in the trial and dose modifications 38
4.1.2.1 Starting dose of BI 891065 38
4.1.2.2 Dose of BI 754091 39
4.1.3 Dose-finding scheme 40
4.1.4 Method of assigning patients to treatment groups 40
4.1.5 Drug assignment and administration of doses for each patient 41
4.1.5.1 Administration of BI 891065 41
4.1.5.2 Administration of BI 754091 42
4.1.6 Dose modifications (pause, delay, dose reduction, and discontinuation) 42
4.1.7 Dose limiting toxicities 44
4.1.8 Blinding and procedures for unblinding 45
4.1.9 Packaging, labelling, and re-supply 45
4.1.10 Storage conditions 46
4.1.11 Drug accountability 46
4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS 47
4.2.1 Other treatments and emergency procedures 47
4.2.1.1 Permitted concomitant medications 47
4.2.1.2 Caution for concomitant medication and/or food 47
4.2.2 Restrictions 48
4.2.2.1 Restrictions regarding concomitant treatment 48
4.2.2.2 Restrictions on diet and life style 50
4.2.2.3 Contraception requirements 51
4.3 TREATMENT COMPLIANCE 51
4.3.1 BI 891065 51
4.3.2 BI 754091 51

5. ASSESSMENTS 52

5.1 ASSESSMENT OF EFFICACY 52
5.1.1 Tumour assessments 52
5.2 ASSESSMENT OF SAFETY 53
5.2.1 Physical examination 53
5.2.2 Vital signs 53
5.2.3 Safety laboratory parameters 53
5.2.3.1 Haematology 53
5.2.3.2 Biochemistry 54
5.2.3.3 Coagulation 54
5.2.3.4 Urinalysis 54
5.2.3.5 Pregnancy test 54
5.2.3.6 Virology 54
5.2.3.7 Alpha-1 acid glycoprotein 55
5.2.4 Electrocardiogram 55
5.2.5 Other safety parameters 56
5.2.5.1 ECOG performance status 56
5.2.5.2 Ejection fraction 56
5.2.5.3 Chest X-ray (Part B only) 56
5.2.6 Assessment of adverse events 57

5.2.6.1 Definitions of AEs 57
5.2.6.2 Adverse event collection and reporting 63
5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS 64
5.3.1 Assessment of pharmacokinetics 64
5.3.2 Methods of sample collection 65
5.3.2.1 Plasma sampling for BI 891065 pharmacokinetics and for coproporphyrin 65
5.3.2.2 Plasma sampling for BI 754091 pharmacokinetics 65
5.3.2.3 Urine sampling and analysis for pharmacokinetics of BI 891065 66
[redacted]
5.4 ASSESSMENT OF BIOMARKER(S) 67
5.4.1 Methods of sample collection 67
[redacted]
5.4.3 Storage period of samples 68
5.4.4 Pharmacogenomic biomarkers 68
5.5 BIOBANKING 68
5.6 OTHER ASSESSMENTS 69
5.6.1 Immunogenicity testing 69
5.7 APPROPRIATENESS OF MEASUREMENTS 69
6. INVESTIGATIONAL PLAN 70
6.1 VISIT SCHEDULE 70
6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS 70
6.2.1 Screening 70
6.2.1.1 Screening Period 71
6.2.1.2 Baseline Conditions 71
6.2.1.3 Medical History 71
6.2.1.4 Concomitant medications 72
6.2.2 Treatment period(s) 72
6.2.3 Follow-up period and trial completion 72
6.2.3.1 End-of-treatment (EOT) visit 72
6.2.3.2 30-day safety follow-up visit (end of residual-effect period) 72
6.2.3.3 Follow-up visits for PD (extended follow-up period) 72
6.2.3.4 Trial completion for an individual patient 73
6.2.3.5 Study procedures modification after implementation of protocol version 5 73
7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE 75
7.1 STATISTICAL DESIGN – MODEL 75
7.1.1 Part A 75
7.1.2 Part B 78

7.2 NULL AND ALTERNATIVE HYPOTHESES 82
7.3 PLANNED ANALYSES 82
7.3.1 General considerations 83
7.3.1.1 Patient analysis sets 83
7.3.1.2 Pharmacokinetics 84
7.3.2 Primary endpoint analyses 84
7.3.2.1 Part A 84
7.3.2.2 Part B 84
7.3.3 Secondary endpoint analyses 84
[redacted]
7.3.5 Safety analyses 85
7.3.6 Interim Analyses 85
7.4 HANDLING OF MISSING DATA 86
7.5 RANDOMISATION 86
7.6 DETERMINATION OF SAMPLE SIZE 86

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE 87

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT 87
8.2 DATA QUALITY ASSURANCE 88
8.3 RECORDS 88
8.3.1 Source documents 89
8.3.2 Direct access to source data and documents 90
8.3.3 Storage period of records 90
8.4 EXPEDITED REPORTING OF ADVERSE EVENTS 90
8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY 90
8.5.1 Collection, storage and future use of biological samples and corresponding data 91
8.6 TRIAL MILESTONES 91
8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL 91

9. REFERENCES 93

9.1 PUBLISHED REFERENCES 93
9.2 UNPUBLISHED REFERENCES 96

10. APPENDICES 98

10.1 IMMUNE-RELATED ADVERSE EVENTS OF SPECIAL INTEREST 98
10.2 MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS 101
10.3 TIME SCHEDULE FOR ECG, BLOOD AND URINE SAMPLING FOR PK, AND BLOOD SAMPLING FOR BIOMARKER 108
10.4 STATISTICAL APPENDICES 112
10.4.1 Part A 112
10.4.2 Part B 116
10.5 IRECIST RESPONSE ASSESSMENT 121
10.5.1 Confirming progression 121
10.5.2 New lesions 121

11. DESCRIPTION OF GLOBAL AMENDMENT(S) 125

11.1 GLOBAL AMENDMENT 1 125
11.2 GLOBAL AMENDMENT 2 130
11.3 GLOBAL AMENDMENT 3 131
11.4 GLOBAL AMENDMENT 4 140

ABBREVIATIONS

ADA	Anti-Drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
AGP	Alpha-1 Acid Glycoprotein
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area under the Curve
BCRP	Breast Cancer Resistance Protein
β-HCG	Beta Human Chorionic Gonadotropin
BI	Boehringer Ingelheim
b.i.d.	Twice a day, Twice daily
BLRM	Bayesian Logistics Regression Model
CA	Competent Authority
CK	Creatine Kinase
CKD-EPI	Chronic Kidney Disease Epidemiology
C_{max}	Maximum Concentration
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organisation
CRS	Cytokine release syndrome
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical Trial Protocol
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid

ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EF	Ejection Fraction
EOT	End of Treatment
EWOC	Escalation With Overdose Control
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBc	Hepatitis B core
HBs	Hepatitis B surface
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IAP	Inhibitor of apoptosis
iCPD	Confirmed Immune Progression
iCR	Immune Complete Response
IDMS	Isotope Dilution Mass Spectroscopy
IEC	Independent Ethics Committee
IL	Interleukin
ILD	Interstitial Lung Disease
IRB	Institutional Review Board
iPD	Immune Progressive Disease
iPR	Immune Partial Response
irAE	Immune related Adverse Event
IRT	Interactive Response Technology
iUPD	Unconfirmed Immune Progression
iSD	Immune Stable Disease
ISF	Investigator Site File
i.v.	intravenous
LC	Liquid Chromatography

LC-MS/MS	Liquid Chromatography Tandem Mass Spectrometry
mAb	Monoclonal Antibody
MAP	Meta-Analytic Predictive
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic Resonance Imaging
MS	Mass Spectroscopy
MSI	Microsatellite Instability
MTD	Maximum Tolerated Dose
MUGA	Multi-Gated Acquisition Scan
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
NSCLC	Non-Small Cell Lung Cancer
OR	Objective Response
p.o.	per os (oral)
PD	Progressive disease
PD-1	Programmed-cell-death-protein-1
PD-L1	Programmed-cell-death ligand-1
P-gp	P-glycoprotein
PK	Pharmacokinetics
PT	Prothrombin Time
PR	Partial Response
q.d.	Once a day, Once daily
QTcF	Corrected QT interval by Fredericia
RD	Recommended Dose
RECIST	Response Evaluation Criteria In Solid Tumours
REP	Residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SD	Stable Disease
SMAC	Second Mitochondrial Activator of Caspases
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
SpO_2	Arterial oxygen saturation

SUSAR	Suspected Unexpected Serious Adverse Reactions
$t_{1/2}$	Half Life Time
TSH	Thyroid Stimulating Hormone
t_{max}	Timepoint of Maximum Plasma Concentration
TMB	Tumour Mutation Burden
TNFα	Tumour necrosis factor alpha
TNM	Tumour, Node, Metastasis
TSAP	Trial Statistical Analysis Plan
ULN	Upper Level of Normal
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

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

Inhibitors of apoptosis (IAP) proteins are critical regulators of cell death and survival, and thus attractive targets for the development of novel anticancer drugs. Degradation of IAP following treatment with second mitochondrial activator of caspases (SMAC) mimetics lowers the threshold of apoptosis and therefore may be potentially beneficial for treatment of cancer. The SMAC protein is an endogenous antagonist of X-linked IAP (XIAP), cellular IAP 1 (cIAP1), and cIAP2. In the last decade, intense research efforts have resulted in the design and development of several small-molecule SMAC-mimetics now in clinical trials for cancer treatment (R16-1600). Clinical studies revealed the potency of SMAC-mimetics to cause IAP depletion at clinically achievable blood levels and some evidence of antitumour activity (complete response [CR], disease stabilization, and tumour regression) when SMAC-mimetics were used as monotherapy (R16-0378; R16-0671; R16-0871; R16-4718; R16-4805; R16-4958). However, the therapeutic potential of these compounds will likely be fully exploited in rational combination protocols by taking advantage of synergistic drug effects (R16-0379).

The normal role of the immune system is to protect the body against the invasion of foreign antigens such as bacteria, viruses, and parasites as well as the body's own malfunctioning cells. Once a mounted immune response (adaptive or innate) completes its task of eliminating the threat, the immune system deploys the immune checkpoint program to dampen the immune response and minimise collateral immune-mediated damage to healthy tissue. Programmed cell death protein-1 (PD-1) and programmed death ligand-1 (PD-L1) pathway is one of the major immune checkpoint master switches. Treatment of patients with advanced melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma, and many other tumour types with anti-PD-1 (nivolumab or pembrolizumab) or anti-PD-L1 (atezolizumab, durvalumab and avelumab) Monoclonal Antibodies (mAbs) results in highly durable responses in approximately 15% to 30% of patients (R15-3588; R15-3715; R15-3776; R15-3778; R15-6023; R16-0663; R16-0864; R16-0876; R16-1225; R16-1588; R16-3547). The majority of patients do not respond and require more effective treatments.

1.2 DRUG PROFILE

1.2.1 BI 891065 (SMAC mimetic)

The SMAC mimetic, BI 891065, is a new chemical entity with a molecular weight of 704 g/mol that is being developed as film-coated tablets for oral administration. BI 891065 is characterised by a medium bioavailability in rats (37%) with low plasma clearance. Excretion of [^{14}C]BI 891065 applied to rats was rapid with more than 90% of dosed radioactivity excreted in the faeces within 48 hours.

BI 891065 showed a high and similar protein binding in investigated animal species and human plasma. Considerable and comparatively long-lasting (yet reversible) exposure of radioactivity to ocular tissues and relevant yet rather short-lived exposure of radioactivity to the integumentary system was observed.

BI 891065 is an *in vitro* inhibitor of various cytochrome P450 (CYP) enzymes that play a role in drug metabolism, with 2C8 being the most susceptible. No irreversible inhibition of the CYP enzymes was observed. BI 891065 was shown to be an *in vitro* inducer of CYP1A2. BI 891065 inhibited P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and MATE2-K. BI 891065 potently inhibits cIAPs protein function with selectivity for cIAP1 versus cIAP2 and XIAP. Binding of BI 891065 to the BIR3 domain of cIAP1 induces auto-ubiquitination and subsequent degradation by the proteasome.

Based on the nonclinical studies summarised in the BI 891065 Investigator's Brochure (c14463420), the nonclinical safety profile of BI 891065 is considered to be acceptable for the intended oncological indications. Clinical side effects in adult patients may be related to a tumour necrosis factor alpha (TNFα)-mediated release of pro-inflammatory cytokines.

Several SMAC-mimetics have been investigated in patients with various malignancies. In general, they were well tolerated, and the majority of adverse events (AEs) were mild to moderate, fatigue and gastrointestinal AEs being most frequently reported. Adverse events of higher grade considered drug related, serious, or dose-limiting included cytokine release syndrome, elevations of liver enzymes, elevations of pancreatic enzymes, facial nerve palsy, lymphocytopenia, and pneumocystis jirovecii pneumonia (R16-0671; R16-0871; R16-4718; R16-4805; R16-4958; R17-0287). Thus, close safety monitoring and precautions to mitigate the risk for severe cytokine release syndrome, elevations of liver or pancreatic enzymes, monitoring of lymphocytes, and facial nerve palsy will be implemented.

As of March 2019, the first-in-man trial of BI 891065 (1379-0001) is being conducted in Western countries. The trial consists of three parts, BI 891065 monotherapy dose escalation part, BI 891065 and BI 754091 (anti-PD-1 mAb) combination dose escalation part, and BI 891065 and BI 754091 combination expansion part. In the monotherapy dose escalation part, dose levels ranging from 5 mg to 400 mg were tested and no dose limiting toxicity (DLT) was reported in a total of 25 treated patients. Currently the combination dose escalation part is ongoing.

1.2.2 BI 754091 (anti-PD-1 mAb)

BI 754091 is a humanised IgG4Pro isotype anti-PD-1 mAb being developed as an i.v. infusion for the treatment of cancer. BI 754091 has highly human frameworks and a low predicted immunogenicity score. The BI 754091 molecule has a molecular weight of approximately 148 kilodaltons. The antibody is composed of 2 heavy chains (446 amino acids each) and 2 light chains (218 amino acids each). The 4 polypeptide chains of the antibody are linked together by disulfide bonds. Each heavy chain contains one consensus sequence for N-linked glycosylation.

BI 754091 shows strong anti-tumour effects in several mice tumour models with some mice showing a CR. Single and repeat dosing studies showed that BI 754091 was well tolerated (as judged by body weight changes and clinical signs) and resulted in significant tumour growth inhibition (≥83%) (BI 754091 Investigator's Brochure; c07895879).

As of March 2019, BI 754091 is under clinical development and the status of clinical trials are as follows:

- The first-in-man trial of BI 754091 (1381-0001) is being conducted in Western countries. The trial consists of a dose escalation part and an expansion part. In the dose escalation part, dose levels ranging from 80 mg to 400 mg were tested and no DLT was reported. 240 mg was selected as the recommended dose for the expansion part and following clinical trials. As of the data cut-off point of 01 November 2018, 50 patients were treated in total (dose escalation cohorts and expansion cohorts) and the objective response rate was 12% (6 patients with partial response).
- There is an ongoing clinical trial of BI 754091 in Asia (1381-0004). This trial consists of several parts including a dose-finding part for BI 754091 monotherapy. BI 754091 as single agent of 240 mg was administered to six Japanese patients, and no DLT was reported.
- BI 754091 is also being tested in combination with other investigational products in several clinical trials.

1.2.3 Combination of BI 891065 and BI 754091

The rationale for combining BI 891065 and anti-PD-1 is the "one-two-punch" combination model. The first punch is given to the tumour cells directly by the SMAC mimetic BI 891065 in combination with cell death triggers released by the immune system or by the tumour cells themselves (e.g., TNFα), while the second punch leading to decisive, tumour knock-out occurs only after concomitant blockade of the co-inhibitory receptor PD-1 that restores T-cell activity. The killing of tumour cells mediated by SMAC-mimetic may lead to immunogenic cell death (R16-0468; R16-4658), followed by activation of dendritic cells and ultimately increased T-cell infiltration. Thus, the SMAC-mimetic/PD-1 combination may be effective in tumours with low T-cell infiltrate as suggested by an increased efficacy in syngeneic mouse models that respond poorly to anti-PD-1 monotherapy. In these models, complete tumour regression with high response rates (80% to 90%) can be achieved upon combination of BI 891065 and an anti-PD-1 mAb.

The SMAC mimetics induce rapid degradation of cIAP1, which leads, amongst others, to the activation of the alternative NF-Kb pathway within subsets of immune cells, and stimulation of cytokine secretion. Changes in cytokine levels, as contributors to the 'first punch' will be monitored in peripheral blood.

SMAC-mimetics have been shown to have an immunomodulatory function mediating the induction of systemic cytokines (e.g., Interleukin-6, TNFα etc.) and chemokines (e.g., MCP-1) when administered to animals or humans (R16-0671 and Boehringer Ingelheim [BI] in-house data).

To assess the potential of the combination of BI 891065 (SMAC-mimetic) and BI 754091 (anti-PD-1 mAb) to cause cytokine release different from that induced by the administration of BI 891065, a combination study was conducted in cynomolgus monkeys, the animal species used for the non-clinical program of the monoclonal antibody BI 754091. This study did not provide evidence for a clinically relevant change in the cytokine release profile of BI 891065.

Combination of BI 891065 with BI 754091 did not affect the pharmacokinetics (PK) of BI 754091 in cynomolgus monkeys. Under the conditions of this study, BI 891065 at 15 mg/kg/day was well tolerated in the cynomolgus monkey in the presence or absence of BI 754091 dosed at 10 mg/kg.

For a more detailed description of BI 891065 and BI 754091 profiles, please refer to the current Investigator's Brochures (c14463420 and c07895879).

At a data cut-off date of 29 March 2019, 3 patients have been treated in a single cohort (BI 891065 200 mg + BI 754091 240 mg). No patient has experienced an SAE, death on study, an AE leading to treatment discontinuation or a ≥ Grade 3 AE. One patient has experienced non-serious irAEs (hyperthyroidism and pruritus, both grade 1) which were not treated nor did they lead to dose modification of study drugs.

At the same cut-off date (29 March 2019) seven patients (out of 25, 28 %) in the monotherapy portion (Part A) and two patients (out of 3, 66 %) in the combination therapy portion (Part B) of study 1379-0001 had elevated bilirubin based on safety laboratory measurements. The blood bilirubin increases appeared to be dose-dependent. There were no concomitant abnormalities in other parameters like AST, ALT, Alkaline phosphatase and LDH which could not be explained otherwise (e.g. underlying disease). All increased bilirubin values were maximum Grade 2 and did not lead to dose-reduction or discontinuation of study drug. Aetiology and clinical significance are still under investigation.

Of note, after the data cut-off date, a non-serious immune-related adverse reaction of pneumonitis grade 2 was reported which was considered as a DLT as per Clinical Trial Protocol (CTP) in the highest dose combination cohort (BI 891065 400 mg + BI 754091 240 mg). The event started 16 days after first study drug administration and the patient responded well to high-dose steroids.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Most patients with locally advanced or metastatic tumours will succumb to their disease, justifying the substantial need for novel therapeutic strategies to improve the outcome for these patients. Immune checkpoint inhibition has been shown to be a promising therapeutic strategy. Despite encouraging clinical results with immune checkpoint inhibitors, up to 80% of treated patients do not respond to current checkpoint inhibitor monotherapy (R15-3588; R15-3778).

Preclinical studies generated evidence of a tumour regression effect of the combination of second mitochondrial activator of caspases (SMAC) mimetic BI 891065 and programmed-cell-death-protein-1 (PD-1) antagonists. In particular, the strong combinatorial effect observed in several syngeneic models in combination with anti-PD-1 supports the combination with PD-1 inhibitors. The PD-1 inhibitor BI 754091 will serve as a combination partner for the SMAC-mimetic BI 891065.

Further clinical development of BI 891065 is planned in combination with BI 754091. This requires phase I clinical investigation of BI 891065 monotherapy in Caucasian and Asian patients. In particular, establishment of clinical safety of BI 891065 monotherapy unaffected by a combination treatment is needed. The first-in-human clinical trial of BI 891065 monotherapy and combination of BI 891065 and BI 754091 (trial 1379-0001) is being conducted in Western countries. This trial (trial 1379-0006) is intended to assess the safety, efficacy and PK of BI 891065 monotherapy and combination of BI 891065 and BI 754091 in Asian patients to establish a safe combination dose for the clinical development in Asia.

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. BI 891065 and BI 754091 inhibit tumour growth and induce tumour regression in pre-clinical models. Based on pre-clinical results, BI 891065 showed single agent anti-tumour activity in several tumour models. Furthermore, the inhibitory effects of the combination of both compounds have been demonstrated in tumour models and may translate into clinical benefit in cancer patients.

1.4.2 Risks

Table 1.4.2: 1 displays the anticipated side effects of the study drugs, based on the mechanism of action, observed clinical data from ongoing studies, and published clinical data for drugs targeting SMAC mimetic and PD-1.

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

Potential risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product BI 891065		
Unexpected adverse events and laboratory abnormalities	Due to limited clinical experience of this drug.	Close monitoring, including implementation of safety monitoring committee (SMC).
Cytokine release syndrome (CRS)	Mode of action of the drug may cause CRS because it promotes release of cytokines. (No safety relevant increases of cytokines measured were observed in the first in human trial 1379-0001 (as of 29 March 2019))	To keep patients hospitalised for 3 days after the first administration of BI 891065. Provide recommendation for the management of CRS in the clinical trial protocol. Cytokine levels are measured.
Photosensitivity	SMAC mimetics may sensitize neoplastic as well as non-neoplastic cells to radiation. Preliminary data for BI891065 from a standard phototoxicity assay in 3T3 mouse fibroblasts seem to confirm this hypothesis.	Patients should be instructed to avoid of exposure to direct sunlight (including sunlamps), to use a sunblock and to wear clothing and sunglasses that protect against sun exposure during treatment and for 4 weeks after the last administration of BI 891065.
Drug-induced liver injury (DILI)	Rare but can be a potentially severe event, thus under constant surveillance by sponsors and regulators for all drugs in development.	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients' safety.

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

Potential risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product BI 754091		
Unexpected adverse events and laboratory abnormalities	Due to limited clinical experience of this drug.	Close monitoring, including implementation of safety monitoring committee (SMC).
Immune-related adverse events (irAEs)	irAEs are associated with immune mediated mode of action and can be potentially severe.	Recommendations for the management of irAEs are provided according to international guidelines and product labels of approved PD-1 inhibitors.
Infusion related reactions	As with any mAb, hypersensitivity reactions to study medication administration are possible and they are potentially severe.	Patients with history of severe hypersensitivity reactions to other mAbs are excluded. Recommendations for the management of infusion related reactions are given in section 5.2.6.1.4.
Drug-induced liver injury (DILI)	Rare but can be a potentially severe event, thus under constant surveillance by sponsors and regulators for all drugs in development.	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients' safety.
Trial procedures		
Tumour biopsy related AEs (Part B only)	Tumour biopsies are mandatory in Part B. There are known risks associated with biopsies such as pain or bleeding.	The risks are clearly explained in the informed consent document.
Other risks		
NA		

1.4.3 Discussion

Both BI 891065 and BI 754091 are currently tested in early phase clinical trials. In general, the observed safety data from the ongoing clinical trials have been consistent with the anticipated safety profiles of these compounds. No DLTs were reported in preceding trials of BI 891065 and BI 754091 in single agent setting. Pre-clinical results showed that BI 891065 exhibited anti-tumour activity as single agent in several tumour models. Target engagement

(cIAP degradation in Peripheral Blood Mononuclear Cells) was observed in patients in the dose escalation part of trial 1379-0001. At a dose of 100 mg BI 891065, cIAP1 degradation in blood (mode of action biomarker) of >60% was observed in 2 out of 3 patients. Based on the pre-clinical data, as well as clinical data obtained with BI 754091, the inhibitory effects of PD-1 by BI 754091 may translate into clinical benefit in cancer patients.

A Bayesian Logistic Regression Model (BLRM) design will be used in order to escalate the dose into a range where efficacy or target engagement are expected while still minimizing the risk of undue toxicity.

The starting doses of this trial was selected based on the available data from preceding trials, and are considered to minimise the exposure of patients to sub-therapeutic doses.

Patients will remain under surveillance for 10 hours after the first administration of BI 891065 (i.e., until the blood sampling for PK on day 1 is completed). All trial sites will have emergency resuscitation services and access to intensive care.

Specific attention will be given to immune-mediated adverse events (irAEs), infusion-related reactions, and cytokine release syndrome (CRS). Infusion-related reactions or CRS, amongst others, are defined as adverse events of special interest (AESI) and have to be reported according to the rules defined for serious AE (SAE)-reporting.

A Safety Monitoring Committee (SMC) will be established for the assessment of the trial data to ensure the overall safety of the patients and for making dose escalation decisions and defining the recommended dose (RD) for further development.

In summary, the present trial will implement a number of safety measures to mitigate potential risks. A potential benefit is offered to patients with advanced and/or metastatic malignancies by SMAC-mimetic monotherapy and even more by the combination of a SMAC mimetic with a PD-1 inhibitor. Therefore, treatment with both compounds is considered to have the potential to provide patients with clinical benefit at an acceptable risk.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The primary objective of this trial is:

Part A
- To determine the Maximum tolerated dose (MTD) and/or the recommended dose (RD) of BI 891065 monotherapy for further development in Asian patients with advanced solid tumours

Part B
- To determine the MTD and/or the RD of BI 891065 in combination with a fixed dose of BI 754091 at 240 mg for further development in Asian patients with advanced solid tumours

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

The MTD will be determined based on the frequency of patients experiencing DLTs during the MTD evaluation period. The MTD evaluation period is defined as first treatment cycle (21 days). At the end of the dose escalation, the BLRM will be rerun using DLTs from all treatment cycles. This result as well as all available data will be used to define the RD.

The secondary objectives are:

Part A
- To document the safety and tolerability, and characterise pharmacokinetics (PK) of BI 891065 as monotherapy in Asian patients with advanced solid tumours

Part B
- To document the safety and tolerability, and characterise PK of the combination therapy of BI 891065 and BI 754091 in Asian patients with advanced solid tumours

2.1.2 Primary endpoint(s)

- Maximum tolerated dose (MTD).

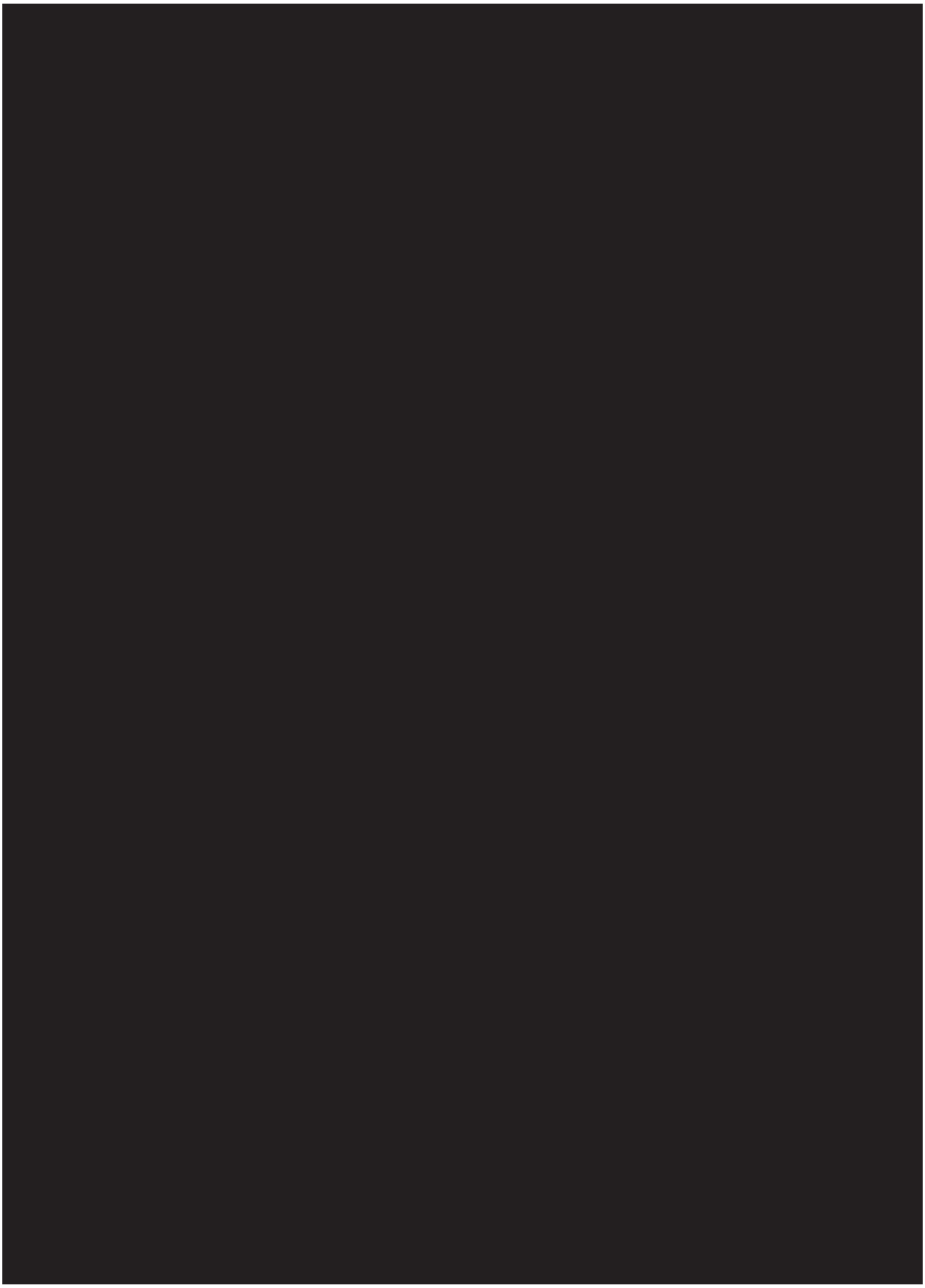
- Number of patients with Dose Limiting Toxicities (DLTs) in the MTD evaluation period and thereafter.

A BLRM employing the EWOC principle will be used during the escalation phase for selection of doses and for estimation of the MTD. Cohorts of patients will receive escalating doses of BI 891065 single agent or combination of BI 891065 and BI 754091 until the MTD is reached or the highest planned dose has been tested (see section 4.1.3). Each cohort will consist of newly enrolled patients. Estimation of the MTD will be based upon the estimation of the probability of a DLT in the MTD evaluation period in the set of evaluable patients for MTD (section 3.3.4.1).

2.1.3 Secondary endpoint(s)

Part A
- The following pharmacokinetics (PK) parameters of BI 891065 will be calculated in cycle 1:
  - $C_{max(,ss)}$, AUC_{0-24} and $AUC_{\tau,ss}$ of BI 891065

Part B
- The following PK parameters of BI 891065 and BI 754091 will be calculated in cycle 1:
  - $C_{max(,ss)}$, AUC_{0-24} and $AUC_{\tau,ss}$ of BI 891065;
  - C_{max} and AUC_{0-504} of BI 754091



3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a Phase I, open-label, non-randomised, multicentre trial of BI 891065 given as single agent (Part A) and in combination with BI 754091 (Part B). The data obtained from the trial will determine the MTD estimate for each Part based on a Bayesian logistic regression model (BLRM) 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 EWOC principle (refer to section 7). Dose-escalation will be restricted to a maximum of 100 % from the previous dose.

In Part A, successive cohorts of patients will receive increasing doses of BI 891065. The starting dose of BI 891065 is 100 mg once daily. The dose escalation continues until the MTD is reached, or the safety in the highest planned dose level (400 mg total daily dose of BI 891065) is confirmed. Depending on the occurrence of DLTs or other relevant safety information, SMC may decide to decrease the dose of BI 891065. For any dose-escalation cohort, at least three patients will be enrolled. SMC may decide enrolment of further patients. However, in the case that only two patients are evaluable (i.e. one patient is not evaluable) and neither has experienced a DLT within the MTD evaluation period, then dose-escalation can occur based on these two patients.

A Safety Monitoring Committee decides 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 BLRM 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 100 % escalation rule. Based on the model and on other available information, 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 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 are enrolled at a lower dose level.

The SMC may decide to stop the dose escalation phase after the criterion for MTD is fulfilled, or the safety in the highest planned dose level is confirmed in the absence of an MTD. Further patients may be included to confirm this MTD estimate, i.e., to confirm that the EWOC criterion is still fulfilled.

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

In Part B, successive cohorts of patients will receive escalating daily dose of BI 891065 in

combination with a fixed dose of BI 754091 at 240 mg once every 3 weeks. The planned starting dose of BI 891065 in Part B is 200 mg, and this cohort will commence after the safety of the same dose level in Part A is confirmed. Other doses may be investigated depending on the safety data obtained from Part A and from the preceding first-in-human trial (1379-0001). SMC will make the decision based on recommendation from BLRM as well as other safety information. BLRM with overdose control will be implemented in Part B incorporating all available information of BI 891065 and BI 754091 to quantify the probability of observing a DLT once patient information becomes available.

The dose escalation will continue until any of the following occurs:
1. the MTD is reached
2. the safety in the highest planned dose level (400 mg) is confirmed
3. the safety at the highest dose tolerated in Part A is confirmed (applicable when this dose is less than 400 mg).

In Part B the dose escalation will follow the approach as described for Part A.

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

This trial is a single-arm trial with multiple dose cohorts and there is no control group. This is a standard design in Phase I trials in Oncology clinical trials where the assessment of MTD, safety and PK are the main objectives.

A Bayesian Logistic Regression Model (BLRM) will be used to guide the dose-finding, in order to escalate the dose into a dose range where efficacy or target engagement may be seen while still minimizing the risk of undue toxicity.

A SMC will be established to ensure the patient safety (for details, see section 8.7). The SMC will monitor the safety data on an ongoing basis, interpret the DLT risk estimate provided by BLRM, and make decisions regarding the dose level to be investigated, the MTD and/or RD, and the necessity of trial plan modifications in case of emerging safety issues.

3.3 SELECTION OF TRIAL POPULATION

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.

Approximately 21 patients (12 in Part A, 9 in Part B) are planned to be included. This trial will be conducted in Japan and Taiwan. Japanese patients will be recruited in all treatment cohorts, and Taiwanese patients will be recruited in the highest planned dose in Part A and all cohorts in Part B (for details, please refer to section 4.1.3). This design provides the

safety/PK data in Japanese patients in multiple dose levels, and also gives the safety/PK data in Taiwanese patients.

3.3.1 Main diagnosis for trial entry

Patients with a confirmed diagnosis of advanced, unresectable and/or metastatic solid tumours, who have failed standard treatment, 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.

The grade of adverse events mentioned in this protocol is based on Common terminology criteria for adverse events (CTCAE) version 5.0 (R18-1357).

3.3.2 Inclusion criteria

1. Of legal age (according to local legislation) at screening. No upper limit.
2. Signed and dated written informed consent in accordance with International Council on Harmonisation (ICH) Good Clinical Practice (GCP) and local legislation prior to admission to the trial.
3. Male or female patients. Women of childbearing potential (WOCBP)[1] and men able to father a child must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly, starting with the screening visit and through 6 months after the last dose of study treatment. A list of contraception methods meeting these criteria is provided in the patient information. The requirement of contraception does not apply to women of no childbearing potential and men not able to father a child, but they must have an evidence of such at screening.
4. Eastern Cooperative Oncology Group (ECOG) performance status: 0 to 1
5. Patients with a confirmed diagnosis of advanced, unresectable and/or metastatic solid tumours, who have failed standard treatment, or for whom no therapy of proven efficacy exists, or who are not amenable to standard therapies.
6. Presence of at least one measureable lesion according to RECIST 1.1.
7. Life expectancy of at least 12 weeks after the start of the treatment according to the Investigator's judgement
8. For Part B: Patients must have at least 1 tumour lesion amenable to biopsy, and must be willing to undergo a biopsy prior to first treatment and after 3 weeks while on therapy.
9. For Part B: Patients with following cancer types: bladder, colon, breast, NSCLC, ovarian, pancreatic, renal, esophagogastric, sarcoma, prostate, and melanoma.

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

3.3.3 Exclusion criteria

1. Major surgeries (major according to the Investigator's assessment) performed within 12 weeks prior to the first administration or planned within 12 months after screening (e.g., hip replacement), or moderate surgeries (moderate according to the Investigator's assessment) performed within 4 weeks prior to the first administration.
2. Presence of active invasive cancers other than the one treated in this trial within 5 years prior to screening, except for appropriately treated basal cell carcinoma of the skin, or *in situ* carcinoma of uterine cervix, or other local tumours considered cured by local treatment
3. Patients who must or wish to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial
4. Previous administration of BI 891065 or other SMAC mimetic/IAP inhibitor
5. Patients who have been treated with any other anticancer drug or investigational drug, within 4 weeks or within 5 half-life periods (whichever is shorter) prior to first administration of BI 891065
6. Persistent toxicity from previous treatments that has not resolved to ≤ Grade 1 (except for alopecia and Grade 2 neuropathy due to previous treatments)
7. Active, known or suspected autoimmune disease except vitiligo or resolved asthma/atopy
8. (Part B only) Patients removed from previous anti-PD-1 or anti-PD-L1 therapy because of a severe immune-related adverse event (irAE)
9. History (including current) of interstitial lung disease or pneumonitis within 5 years
10. Any of the following cardiac criteria:
    - Mean resting corrected QT interval (QTcF) >480 msec
    - Any clinically important abnormalities (as assessed by the investigator) in rhythm, conduction, or morphology of resting Electrocardiograms (ECGs), e.g., complete left bundle branch block, third degree heart block
    - Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years-of-age, or any concomitant medication with known or possible risk of QT interval prolongation
    - Patients with an ejection fraction (EF) of either <50% or less than the lower limit of normal of the institutional standard will be excluded, whichever is lower. Only in cases where the Investigator (or the treating physician or both) suspects cardiac disease with negative effect on the EF, will the EF be measured during screening using an appropriate method according to local standards to confirm eligibility (e.g., echocardiogram [ECHO], multi-gated acquisition scan [MUGA]). A historic measurement of EF no older than 6 months prior to first administration of study drug can be accepted provided that there is clinical evidence that the EF value has not worsened since this measurement in the opinion of the Investigator or of the treating physician or both.
11. Inadequate organ function or bone marrow reserve as demonstrated by the following laboratory values:
    - Absolute neutrophil count (ANC) <1.5 x 10^9/L (<1500/mm^3)
    - Platelet count <100 x 10^9/L (<100,000/mm^3)
    - Haemoglobin <9.0 g/dL

- Alanine transaminase (ALT) >3 times the upper limit of normal (ULN) if no demonstrable liver lesion(s) (primary or metastases) or >5 times ULN in the presence of liver lesion(s)
- Aspartate aminotransferase (AST) >3 times the ULN if no demonstrable liver lesion(s) or >5 times ULN in the presence of liver lesion(s)
- Total bilirubin >1.5 times ULN, except for patients with Gilbert's syndrome who are excluded if total bilirubin >3.0 times ULN or direct bilirubin >1.5 times ULN
- Serum creatinine > 1.5 x ULN (measured by enzymatic assay, Isotope dilution mass spectroscopy [IDMS] standardised Jaffe assay, or non-IDMS Jaffe assay). If serum creatinine is > 1.5 x ULN, patient is eligible if concurrent estimated glomerular filtration rate (eGFR) is ≥ 30 mL/min/1.73m^3 (measured or calculated by Chronic Kidney Disease Epidemiology [CKD-EPI] formula)

12. Human immunodeficiency virus (HIV) infection. Test results obtained in routine diagnostics are acceptable if done within 6 months before the informed consent date.
13. Any of the following laboratory evidence of hepatitis virus infection.
    - Positive results of hepatitis B surface (HBs) antigen
    - Presence of hepatitis B core (HBc) antibody together with hepatitis virus B (HBV) Deoxyribonucleic acid (DNA)
    - Presence of hepatitis virus C (HCV) antibody together with HCV Ribonucleic acid (RNA)

    In Part A, test results obtained in routine clinical practice are acceptable if done within 6 months before the informed consent date.
14. Known relevant hypersensitivity to the trial drugs or their excipients based on the investigator's assessment
15. Serious concomitant disease or medical condition affecting compliance with trial requirements or which are considered relevant for the evaluation of the efficacy or safety of the trial drug, such as cardiac, neurologic, psychiatric, infectious disease or active ulcers (gastro-intestinal tract, skin) or laboratory abnormality that may increase the risk associated with trial participation or trial drug administration, and in the judgment of the Investigator would make the patient inappropriate for entry into the trial.
16. Chronic alcohol or drug abuse or any condition that, in the Investigator’s opinion, makes them an unreliable trial patients, unlikely to complete the trial, or unable to comply with the protocol procedures
17. Women who are pregnant, nursing, or who plan to become pregnant during the trial. Women who are nursing can be enrolled if they stop nursing. In this case, the patient cannot resume nursing even after discontinuation of study treatment.
18. Untreated brain metastasis(es) that may be considered active. Patients with previously treated brain metastases may participate provided they are stable (i.e., without evidence of PD by imaging for at least 4 weeks prior to the first dose of trial treatment, and any neurologic symptoms have returned to baseline), and there is no evidence of new or enlarging brain metastases
19. Patients with known leptomeningeal disease
20. Patients receiving systemic treatment with any immunosuppressive medication within 1 week prior to treatment start (steroids of max. 10 mg/day prednisolone equivalent per day are allowed, topical and inhaled steroids are not considered as immunosuppressive).

3.3.4 Withdrawal of patients from treatment or assessments

Patients may discontinue trial treatment or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications; please see sections 3.3.4.1 and 3.3.4.2 below.

Every effort should be made to keep the patients in the trial: if possible on treatment, or at least to collect important trial data. Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal.
The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and 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 trial assessments. Refer to section 4.2.2.1 for prohibited concomitant medications.
- Progressive disease according to RECIST v1.1 and/or iRECIST. Refer to section 5.1.1 for details and exceptions.
- The patient can no longer receive trial treatment for medical reasons (such as surgery, other diseases, or pregnancy).
- The patient experiences an AE requiring treatment discontinuation as listed in section 4.1.6.

Even if the trial treatment is discontinued, the patient remains in the trial and will undergo the procedures for the end of treatment visit and follow-up visits as outlined in the Flow Chart and section 6.2.3.

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

Patients meeting the following criteria will be considered non-evaluable for DLT. If less than two patients are evaluable for DLT in a cohort, the non-evaluable patients will be replaced;
- Patient withdrawal for a reason other than DLT before completing the first treatment cycle
- Patients who have reduced BI 891065 dose level during the first treatment cycle, unless they develop a DLT

- Patient who can't be assessed for safety due to missed visits in the first cycle of treatment and who does not experience DLTs
- Patient who misses >5 doses of BI 891065 during the first treatment cycle for reasons other than treatment-related AEs and who does not experience DLTs
- (Part B only) Patients who have received less than 50% of the BI 754091 initial dose, unless they develop a DLT

Patients who miss one visit during the first treatment cycle may be replaced after discussion between the sponsor and the investigator if the information that needs to be collected during this visit is not available and makes the patient non-evaluable for determining DLT. All other patients who withdraw, including all patients who are withdrawn from the trial due to a DLT, and all patients who withdraw after the first treatment cycle, will not be replaced.

If a patient should become pregnant during the trial, the study treatment must be immediately stopped. The patient will be followed up until delivery or termination of pregnancy (see Section 5.2.6.2.3 for information on pregnancy forms). The data of the patient will be collected and reported in the electronic case report form (eCRF) until the last patient's last visit and any events occurring thereafter will be reported in the BI drug safety database.

3.3.4.2 Withdrawal of consent to trial participation

Patients may withdraw their consent to trial participation at any time without the need to justify the decision.
If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site.
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial.
3. Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

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

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 BI 891065

Substance:	BI 891065
Pharmaceutical formulation:	Film-coated tablets
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	5 mg, 20 mg, 50 mg, 100 mg tablets
Posology:	Once daily (q.d.) or twice daily (b.i.d.), individual dose depending on dose escalation
Method and route of administration:	Oral

Table 4.1.1: 2 BI 754091

Substance:	BI 754091
Pharmaceutical formulation:	Solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	20 mg/mL (vial with 15 mL filling volume)
Posology:	Infusion on day 1 of 21-day cycles
Method and route of administration:	Intravenous infusion

4.1.2 Selection of doses in the trial and dose modifications

4.1.2.1 Starting dose of BI 891065

In Part A, BI 891065 will be tested at a starting dose of 100 mg once daily. In case of DLTs in 100 mg cohort, a lower dose level may also be investigated. Twice daily dosing may also be investigated.

The starting dose was selected based on the data obtained in clinical trial 1379-0001 monotherapy dose-escalation part. As of the end of January 2019, BI 891065 was administered at dose range of 5 mg to 400 mg in 25 patients as single agent. In these patient cohorts, DLTs were not reported at any dose level tested, and the MTD was not reached. There was no treatment related SAE. There was an isolated increase in total bilirubin in 7 patients (28%) which appears to be dose-dependent. All bilirubin increases were maximum Grade 2 and did not lead to dose-reduction or discontinuation of study drug. Twice daily dosing will be explored, aiming to reduce peak plasma concentrations compared to single dosing of the same daily dose, which may reduce occurrences of bilirubin increase, and may allow for better tolerability of similar total daily doses compared to once daily dosing, and potentially higher daily doses. Etiology and clinical significance are currently under further investigation. Otherwise there were no abnormal lab trends identified which could not be explained by underlying disease. To obtain sufficient dose-PK relationship data in Asian patients, the starting dose of this trial is set at a lower dose than the highest dose in trial 1379-0001.

In Part B, the starting dose of BI 891065 will be 200 mg per day, in combination with BI 754091 240 mg once every three weeks. The SMC may recommend to start at a lower dose level depending on the MTD or occurrence of DLTs in Part A. In case of DLTs in the starting dose cohort of Part B, a lower dose level may also be investigated. Twice daily dosing will also be investigated.

4.1.2.2 Dose of BI 754091

The dose of BI 754091 will be fixed at 240 mg once every three weeks. The dose of BI 754091 was selected based on the data from preceding trials, including a first-in-human Phase I trial in Western patients (Trial 1381-0001) and a Phase I trial in Asian patients (Trial 1381-0004).

In the dose escalation part of trial 1381-0001, dose levels of 80 mg, 240 mg, and 400 mg every 3 weeks were investigated and three patients were assigned at each cohort. None of them experienced DLTs and the MTD was considered not reached. The RD for further development was determined to be 240 mg based on the results of in vitro binding testing, clinical safety data and the result of a receptor occupancy testing in trial 1381-0001. The preliminary data showed 100% PD-1 receptor occupancy in peripheral blood in all on-treatment patient samples compared to baseline throughout one treatment cycle, which also supports that the selected dose of 240mg administered every 3 weeks should be adequate.

The clinical safety is further supported by the data from trial 1381-0004 dose-finding part, where six Japanese patients received BI 754091 monotherapy 240 mg every 3 weeks and none of them experienced DLTs (Median number of treatment cycles: 4.5, range 2-8).

4.1.3 Dose-finding scheme

The dose is planned to be tested in cohorts at pre-defined provisional dose levels. The provisional dose levels to be assigned to different cohorts of patients are listed in Tables 4.1.3: 1 and 4.1.3: 2. Intermediate or lower dose levels may be investigated if agreed in the SMC, depending on the number of DLTs observed in the trial. The highest planned dose of BI 891065 is 400 mg per day.

Table 4.1.3: 1 Example of dose escalation in Part A

Dose level	Proposed daily dose of BI 891065*	Participating countries
1	100 mg	Japan
2	200 mg**	Japan
3	400 mg**	Japan and Taiwan

*The total daily dose will be given in q.d. or b.i.d. dosing schedule.
**Actual dose level and dosing schedule for a cohort will be communicated separately as determined by the SMC. Intermediate or lower dose level(s) may be investigated depending on the latest DLT rate estimate.

Table 4.1.3: 2 Example of dose escalation in Part B

Dose level	Proposed daily dose of BI 891065*	Proposed dose of BI 754091 (every three weeks)	Participating countries
1	200 mg**	240 mg	Japan and Taiwan
2	400 mg**	240 mg	Japan and Taiwan

* The total daily dose will be given in q.d. or b.i.d. dosing schedule.
**Actual dose level and dosing schedule for a cohort will be communicated separately as determined by the SMC. Intermediate or lower dose level(s) may be investigated depending on the latest DLT rate estimate.

4.1.4 Method of assigning patients to treatment groups

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

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.

4.1.5 Drug assignment and administration of doses for each patient

4.1.5.1 Administration of BI 891065

BI 891065 tablets 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 need to be instructed to return any unused BI 891065 in the dispensed bottles, in addition to returning any empty bottles.

All patients will be required to complete a Dosing Diary, which must be returned to the clinic for review at each clinic visit. The fasting status on the PK days should be recorded in the patient diary and collected in the eCRF (section 5.3.1). The diary should be given to patients before cycle 1 day 1.

Refer to Flow Chart and section 10.3 for information about sampling that is required prior to dose administration.

BI 891065 is taken either q.d. or b.i.d., depending on the assigned treatment regimen. Refer to Flow Chart for exceptions of dosing schedule where study drug is skipped.

Patients will be asked to fast overnight (minimum of 10 hours) prior to the morning dose on the following intensive PK days:

- Cycle 1 Day 1
- Cycle 1 Day 15

Refer to section 10.3 for details.

When BI 891065 and BI 754091 are to be administered on the same day, BI 891065 will be administered approximately 30 minutes following the end of infusion of BI 754091, based on the safety assessments made by the Investigator.

Whenever possible, all doses of BI 891065 should be taken with water, limited to a maximum of 240 mL.

Missed doses of BI 891065 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 Dosing Diary, and then should be recorded in the eCRF.

4.1.5.2 Administration of BI 754091

Vials of BI 754091 will be diluted and administered via i.v. infusion according to the details in the Instruction for Pharmacists.

4.1.6 Dose modifications (pause, delay, dose reduction, and discontinuation)

AEs that are immune related should be managed according to the Guidelines for irAE management (as outlined in Appendix 10.2).

For Grade 4 AE/SAEs that are not immune related, study drug should be withdrawn. However, if it can be excluded with high certainty that the event was related to study medication, study drug should be paused, and resumption of study drug may be allowed after discussion with the Sponsor.

For Grade 3 AE/SAEs that are not immune related, study drug should be paused.

For Grade 2 AEs/SAEs that are not immune related but are deemed intolerable by the patient or the treating physician and not responding to appropriate medical management, the physician should decide if a pause of treatment is warranted considering relevant variables such as perceived relatedness to study drug.

If, after a treatment pause of ≤12 weeks, the non-immune related SAE/AE resolves to baseline or Grade 1 and the physician thinks it is clinically appropriate to restart study drug, then the physician may choose to restart BI 891065 at one dose lower than the dose administered before the pause (except for patients who are receiving the lowest dose allowed) according to Table 4.1.6: 1 and Table 4.1.6: 2, and BI 754091 at the same fixed dose of BI 754091. Up to two dose reductions of BI 891065 are allowed per patient. If the AE/SAE prompting interruption has unequivocally been excluded to be drug related, reintroduction of BI 891065 at the same dose as prior to the pause may be considered.

There will be no dose reductions or escalations of BI 754091 in any one patient. However, in the event of an infusion-related reaction ≤ Grade 2, the infusion rate of BI 754091 may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. In patients experiencing infusion-related reactions ≤ Grade 2, subsequent infusions may be administered at 50% of the initial rate. If an infusion-related reaction is Grade 3 or higher in severity at any point during the study, treatment with BI 891065 and BI 754091 will be permanently discontinued.

As a general rule for Part B, both drugs (BI 891065 and BI 754091) will be stopped, paused, or re-exposed together. Exemptions have to be justified and aligned with the Sponsor in writing.

If exemption to the dose reduction and pause (e.g., to restart the treatment at the same dose level) is considered, it should be discussed and agreed with the sponsor in advance in writing.

Table 4.1.6: 1 Dose reduction recommendations for BI 891065 in q.d. dosing (up to two dose reductions are allowed per patient)

BI 891065 dose before the pause	BI 891065 dose at restart
400 mg	200 mg
200 mg	100 mg
100 mg	50 mg (lowest dose allowed)

Table 4.1.6: 2 Dose reduction recommendations for BI 891065 in b.i.d. dosing

BI 891065 dose before the pause	BI 891065 dose at restart
200 mg x 2	100 mg x 2
100 mg x 2	50 mg x 2 (lowest dose allowed)

If an intermediate dose which is not listed in the table is investigated, a dose reduction guideline for that dose will be provided separately

There will be no dose reductions or escalations of BI 754091. Modifications of infusion rate are described in section 5.2.6.1.4.

The study treatment should be permanently discontinued if any of the following adverse events occur:

- A pause of treatment or delayed start of treatment of more than 12 weeks due to AEs
- Grade 3 or 4 CRS
- Interstitial lung disease (ILD) of any grade
- (For Part B only) Immune related AEs requiring permanent study drug discontinuation as described in Guidelines for Management of Immune-Related AEs (section 10.2):
  - encephalitis, aseptic meningitis, transverse myelitis, or Guillain-Barre syndrome of any grade
  - acquired thrombotic thrombocytopenic purpura of any grade
  - myocarditis of any grade
  - myasthenia gravis, peripheral neuropathy or autonomic neuropathy of grade ≥3
  - myositis grade 2 with objective findings (see below), any myositis grade ≥3
  - hepatitis grade ≥3 (transaminase >5 times ULN or total bilirubin >3 times ULN), recurrent hepatitis grade ≥2
  - nephritis grade ≥3, persisting grade 2 nephritis unresponsive to initial steroid therapy or worsening, and recurrent nephritis grade ≥2
  - pneumonitis grade ≥3,
  - rash, bullous dermatoses, severe cutaneous adverse reaction, Stevens Johnson Syndrome, toxic epidermal necrolysis of grade 4, and recurrent rash grade ≥3
  - colitis grade 4, and recurrent colitis of any grade
  - uveitis, iritis, episcleritis of grade ≥3

  - autoimmune-hemolytic anemia grade ≥2
  - haemolytic uremic syndrome grade ≥3
  - immune thrombocytopenia grade 4
  - any recurrent irAE grade ≥3
  - inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or
  - persistent Grade 2-3 AEs that do not recover to Grade 1 or less within 12 weeks.
- Grade ≥3 infusion related reactions
- AEs of Grade ≥2 deemed intolerable by the patient or the treating physician and not responding to medical management within 12 weeks
- Grade 3 to 4 AEs that are classified as immune-related by the Investigator but are not listed in section 10.1 if they do not resolve to Grade ≤ 1 or baseline with immunosuppressive therapy within 2 weeks.
- ≥Grade 4 drug-related AEs.

Other criteria leading to permanent discontinuation of study treatment are presented in Section 3.3.4.1.

4.1.7 Dose limiting toxicities

Dose-limiting toxicities (DLTs) will be recorded throughout the trial. Any DLT must be reported to the sponsor within 24 hours of first knowledge. Only DLTs occurring during cycle 1 will be used for MTD determination. All relevant safety information (including DLTs occurring at any time) will be considered when selecting the RD.

Severity of AEs will be graded according to CTCAE Version 5.0. Any of the following AEs will be classified as DLTs following review by the Investigators and the sponsor, unless unequivocally due to underlying malignancy or an extraneous cause.

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

Non-haematological toxicities:
- AST or ALT >3 times ULN and concurrent total bilirubin >2 times ULN without initial findings of cholestasis (e.g., findings consistent with Hy's law or the FDA definition of potential DILI, see section 5.2.6.1.4)
- ≥Grade 4 AST or ALT of any duration
- Any ≥Grade 3 non-haematologic toxicity with the following exceptions:

  - Grade 3 irAE that resolves to ≤ Grade 1 or to baseline with immunosuppressive therapy within 2 weeks
  - Grade 3 fatigue that persists ≤7 days
  - Grade 3 rash that resolves to ≤ Grade 1 within 2 weeks
  - Grade 3 or 4 elevation in serum amylase and/or lipase that is not associated with clinical or radiographic evidence of pancreatitis
  - Grade 3 electrolyte abnormality that lasts <72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical intervention
  - Grade 3 nausea or vomiting that lasts <48 hours, and resolves to ≤ Grade 1 either spontaneously or with conventional medical intervention
  - Alopecia
  - Grade 3 endocrine disorders (thyroid, pituitary, and/or adrenal insufficiency) that are managed with or without systemic corticosteroid therapy and/or hormone replacement therapy, and the patient is asymptomatic.
  - Grade 3 tumour flare syndrome
- Grade 2 pneumonitis of any duration
- Grade 2 related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks or requires systemic treatment
- Treatment pause of BI 891065 for ≥7 days 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 754091 on Cycle 2 Day 1
- Any AEs that require dose reduction will be assessed by SMC and may be considered as DLTs unless the SMC considers the dose reduction as not strictly medically warranted
- Permanent treatment discontinuation according to section 4.1.6

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

Late DLTs are AEs that meet the same grading criteria as DLT criteria but occur after the first cycle of study treatment. In order to assess the recommended dose, the BLRM will be rerun using all DLTs up until 90 days after the first administration of the last patient.

4.1.8 Blinding and procedures for unblinding

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

4.1.9 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 GMP. Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

For details of packaging and the description of the label, refer to the ISF.

4.1.10 Storage conditions

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

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

4.1.11 Drug accountability

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

- Approval of the CTP by the Institutional Review Board (IRB) / Independent Ethics Committee (IEC),
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority (CA),
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated CTP,

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics. 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 CTP and reconcile all investigational medicinal products received from the sponsor. At the time of return to the sponsor, the investigator or designee must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no other mandatory treatments to be used in this trial or special emergency procedures to be followed. Recommendations for the management of immune-related AEs can be found in section 10.2.

Rescue medications to reverse the actions of BI 891065 or BI 754091 are not available. Therefore, potential side effects of BI 891065 or BI 754091 have to be treated symptomatically (relevant information is available in section 5.2.6.1.4).

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 residual effect period (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.

4.2.1.1 Permitted concomitant medications

- If medically feasible, patients taking regular medication should be maintained on it throughout the trial.
- Pre-medication is not required, but may be utilised following the first dose of study medication. This includes medications for the management of nausea, diarrhoea, and vomiting for which the patient must be treated according to institutional standards.
- Supportive care and other medications that are considered necessary for the patient's well-being may be given at the discretion of the Investigator.
- Blood transfusions are allowed at any time during the trial, except to meet inclusion criteria. There must be at least 4 weeks between a patient's last transfusion and the screening laboratory assessment. Exceptions to this will be considered by the Sponsor on a case-by-case basis.

4.2.1.2 Caution for concomitant medication and/or food

BI 891065 is a substrate of CYP3A4. In ongoing overseas trial of 1379-0001, the exposure (C_{max}, AUC) tended to increase in two patients who took moderate CYP3A4 inhibitor from 25 patients at 5 to 400 mg dose cohort. Caution is necessary for the intake of CYP3A4 inhibitor (ex. clarithromycin, erythromycin, fluconazole, itraconazole, verapamil, ketoconazole, and diltiazem) or grapefruits and their juices, because the possibility cannot be excluded for the increase of plasma concentration.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

- No other investigational therapy or anticancer agent should be given to patients. If such agents are required for a patient, then the patient must first be withdrawn from the trial.
- Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor-alpha blockers are prohibited. Use of immunosuppressive medications for the management of investigational product-related AEs or in patients with contrast allergies is acceptable, and does not necessarily warrant immediate treatment discontinuation. In addition, use of inhaled, topical, intranasal corticosteroids or local steroid injections (e.g., intra-articular injection) is permitted. Temporary uses of corticosteroids for concurrent illnesses (e.g., food allergies, computed tomography [CT] scan contrast hypersensitivity) are acceptable. For the treatment of CRS, supportive therapy including steroids and/or interleukin 6 receptor (IL6R) antagonists (R15-0031) may be used as clinically indicated.
- Pre-medications should not be given in cycle 1 to avoid masking the emergence of DLTs.
- Live attenuated vaccines are prohibited from informed consent until 30 days after the last dose of investigational product.
- Herbal preparations/medications are not allowed throughout the trial. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications at least 7 days prior to first dose of study treatment.
- Patients already receiving erythropoietin at the time of screening for the trial may continue it, provided they have been receiving it for more than one month at the time trial treatment is started. Prophylactic erythropoietin should not be started during the first 3 weeks of treatment, but may be started thereafter. In Japan, no erythropoietin product is approved for anaemia associated with cancer chemotherapy.
- Prophylactic granulocyte colony stimulating factors are not allowed during the first 3 weeks of treatment.
- For symptom control, palliative radiotherapy is permitted for any lesion, except during the first 3 weeks as it could interfere with the DLT evaluation for MTD/RD determination. If a patient need palliative radiotherapy during the first 3 weeks 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.

BI 891065 was found to be an inhibitor of various CYP450 enzymes *in vitro*. A drug-drug interaction with other medications metabolized by these enzymes cannot be excluded. Caution should be exercised when combining BI 891065 with substrate drugs of CYP450 enzymes (1A2, 2C8, 2C9, 2C19, 2D6, 3A4). 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 from statins). BI 891065 was also

found to be an inhibitor of the drug transporters P-gp and BCRP *in vitro*. Caution should be exercised when combining BI 891065 with P-gp and BCRP substrates.

Table 4.2.2.1: 1 provides the restrictions information for substrate drugs of CYP450 enzymes, P-gp and BCRP.

Table 4.2.2.1: 1 Restrictions on concomitant treatment with substrate drugs of CYT450 enzymes, P-gp and BCRP

Type of medication	Instruction	Example of medication
Sensitive CYP1A2, CYP2C8, CYP2C9 and CYP2C19, CYP2D6, CYP3A4 substrates with a high probability of exposure increase in combination with BI 891065	Permitted if strictly indicated and with judicious dosing	Buspirone, Lovastatin, Simvastatin and Nisoldipine
Sensitive CYP1A2, CYP2C8, CYP2C9 and CYP2C19, CYP2D6, CYP3A4 substrates with a medium probability of exposure increase in combination with BI 891065	Permitted if strictly indicated and with judicious dosing	Atorvastatin, Tacrolimus, Cisapride, Terfenadine, Midazolam, Saquinavir, Rifabutin, and Sertraline
Sensitive CYP1A2, CYP2C8, CYP2C9 and CYP2C19, CYP2D6, CYP3A4 substrates with a low probability of exposure increase in combination with BI 891065	Permitted if strictly indicated and with judicious dosing	Alfentanil, Amodiaquine, Felodipine, Loperamide, Maraviroc, Methadone, Montelukast, Nifedipine, Nimodipine, Pioglitazone, Repaglinide, Trazodone, Triazolam, Verapamil and Zolpidem.
P-gp substrates (partly with narrow therapeutic margin)	Not Permitted	Dabigatran etexilate Digoxin
P-gp substrates and in addition involvement of CYP3A4 with narrow therapeutic margin	Permitted if strictly indicated and with judicious dosing	Apixaban Rivaroxaban
P-gp and BCRP substrates with a probability of exposure increase in combination with BI 891065	Permitted if strictly indicated and with judicious dosing	Fexofenadine, Verapamil and Rosuvastatin

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 891065.

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 with the following caveats:

- Fasting requirements on PK days are described in section 4.1.5.1

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

The investigational products should only be used as directed in this protocol.

4.3.1 BI 891065

Patients are requested to bring all remaining BI 891065 including empty package material with them when attending visits. Details of treatment with investigational product for each patient will be recorded in the eCRF.

The trial personnel at the investigational site will account for all drugs dispensed and for appropriate destruction.

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

$$\text{Treatment compliance (\%)} = \frac{\text{Number of tablets actually taken} \times 100}{\text{Number of tablets that should have been taken}}$$

If the number of doses taken is not between 80% to 100%, site staff will explain to the patient the importance of treatment compliance.

4.3.2 BI 754091

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

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 Tumour assessments

Tumour response will be evaluated at the site according to RECIST Version 1.1 (R09-0262) and/or iRECIST (R17-0923).

The assessment by the Investigator and/or the local radiologist will be the basis for continuation or discontinuation of the trial in an individual patient (in addition to safety).

The baseline scan(s) (CT scan and/or magnetic resonance imaging [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 patients will be re-evaluated every 6 weeks for the first 24 weeks, then every 9 weeks thereafter, and at the end of treatment (EOT) visit (if not performed within the previous 4 weeks). The same method of assessment and the same technique must be used to characterise each reported lesion at baseline and during treatment. Lesions in previously irradiated areas may not be considered measurable at baseline unless the lesions appeared for the first time or have re-grown after irradiation.

If the patient stops treatment with the trial medication for a reason other than progression, the tumour assessment according to RECIST v1.1 and iRECIST will be performed with a frequency according to local standard and the information will be collected at the follow-up visits for PD (section 6.2.3.3).

Patients will be allowed to stay on treatment in the case of initial PD according to RECIST version 1.1, if the Investigator feels that the patient is clinically stable. As a rule, the treatment will be discontinued when a patient is considered to be confirmed progressive disease according to iRECIST (iCPD). However, the patient may still continue to receive treatment if the Investigator and sponsor agree that the patient is deriving clinical benefit. In this case, the rationale to continue the treatment beyond iCPD should be provided in the CRF.

Duplicates of the images will be collected and stored by a BI-appointed representative, and may be used for further review, if deemed appropriate, e.g., the images may be used for further analysis to explore the potential for enhanced and improved baseline and on-treatment markers/patterns of early efficacy based on comprehensive quantitative CT metrics (i.e., radiomics features, assessed in standard-of-care medical imaging data).

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified in the flowchart. 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.

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 flowchart, prior to blood sampling, or after a sufficient period of rest (usually 5 minutes is sufficient, but a longer rest may be required if there are any problems at the blood sampling).

This includes systolic and diastolic blood pressure, pulse rate (electronically or by palpation count for 1 minute), body temperature, and arterial oxygen saturation (SpO_2) by non-invasive pulse oximetry. SpO_2 is required in Part B only. The results must be included in the source documents available at the site.

5.2.3 Safety laboratory parameters

For the sampling time points please see the Flow Chart. All analyses will be performed locally and the respective reference ranges will be provided in the ISF. 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.

5.2.3.1 Haematology

The standard haematology panel will consist of: haemoglobin, red blood cell count, haematocrit, mean corpuscular volume, reticulocytes, white blood cell count, and differential blood count (preferably expressed in absolute values), and platelets.

5.2.3.2 Biochemistry

The standard biochemistry panel will consist of glucose (serum or plasma), sodium, potassium, chloride, calcium, phosphate, serum creatinine (measured by enzymatic assay, Isotope dilution mass spectroscopy [IDMS] standardised Jaffe assay, or non-IDMS Jaffe assay), AST, ALT, alkaline phosphatase, lactate dehydrogenase, gamma glutamyl transferase, bilirubin (total, direct, and indirect bilirubin), haptoglobin, total protein, albumin, urea or urea nitrogen, uric acid and creatine kinase (CK). If CK is elevated, then CK-MB [cardiac], Troponin (either I or T), and myoglobin should be reactively tested.

A thyroid panel (Thyroid Stimulating Hormone [TSH], free T4, and free T3) will be done in Part B at the time of each standard biochemistry panel.

If symptoms of pancreatitis are observed, amylase and lipase should be tested at the discretion of the Investigator.

5.2.3.3 Coagulation

Activated partial thromboplastin time (aPTT) or prothrombin time (PT) (expressed either in seconds or as percentage) will be tested.

5.2.3.4 Urinalysis

Urine (pH, glucose, erythrocytes, leukocytes, protein, and nitrite) will be analysed by dipstick (semi-quantitative measurements).

5.2.3.5 Pregnancy test

A beta human chorionic gonadotropin (β-HCG) pregnancy test in serum (or plasma) will be performed for women of childbearing potential at screening. Thereafter, this test may be done in serum (or plasma) or urine.

5.2.3.6 Virology

HBV, HCV, and HIV testing should be performed at screening. In Part A these tests are exempted if test results obtained in routine clinical practice within 6 months before the informed consent date are available. In part B, HBV and HCV tests are mandatory but HIV testing is not mandatory if test results obtained in routine clinical practice within 6 months before the informed consent date are available.

The required test items are as follows:
For HBV: HBs antigen and HBc antibody tests are performed. HBV-DNA test is required only for patients with HBc antibody positive results.

For HCV: HCV antibody test is performed. HCV-RNA test is required only for patients with HCV antibody positive results.

5.2.3.7 Alpha-1 acid glycoprotein

One plasma sample will be taken for alpha-1 acid glycoprotein (AGP) analysis at the beginning of Cycles 1 and 2 at the time of the safety laboratory tests (prior to BI 891065 administration).

5.2.4 Electrocardiogram

Standard 12-lead (I, II, III, aVR, aVL, aVF, V1 - V6) resting ECGs will be digitally recorded at various time points throughout the trial. The Flow Chart outlines which visits will require ECGs, and section 10.3 outlines which time points require triplicate ECGs to be done along with certain PK samples.

All ECGs will be obtained after the patient has been resting supine for at least 10 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 readings. Before study start, the study sites will be trained for the proper use of the equipment and transfer of the electronic data to the vendor. All ECGs outlined in section 10.3 will be transmitted to the central vendor.

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 also 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. Particular attention must be paid to T wave inversions. It is not mandatory to wait for central evaluation of ECGs to make clinical decisions, and all treatment related decisions should be based on the investigator's assessment. 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.

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. The ECGs will be recorded using dedicated equipment provided by a vendor. The ECGs will be sent for evaluation by a central vendor. Data from this central review will be taken for retrospective data analysis. 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 for triplicate 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.

The centralised ECG evaluation will include the semi-automatic determination of the RR, PR interval, QRS complexes, and QT intervals.

All interval measurements in one patient will be performed on the same lead. The intervals will be measured from four cardiac cycles (beats) in lead II. If lead II shows a flat T wave or is not measurable for any reason, lead V5 will be used, or if that lead is not measurable, then lead I will be used.

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

5.2.5.1 ECOG performance status

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

5.2.5.2 Ejection fraction

The ejection fraction should be measured only if clinically indicated using echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan. Refer to section 3.3.3 for details on which patients require an ejection fraction assessment.

5.2.5.3 Chest X-ray (Part B only)

A chest X-ray must be performed in Part B only at the time points specified in the Flow Chart.

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

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

5.2.6.1.2 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: AEs which possibly lead to disability will be handled as “deemed serious for any other reason” and be reported as SAEs.

Patients may be hospitalized for administrative reasons during the trial, including hospitalization for respite care. These as well as hospitalizations/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 hospitalization/surgical procedure has not changed/worsened after signing informed consent)

5.2.6.1.3 AEs considered "Always Serious"

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

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

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

5.2.6.1.4 Adverse events of special interest (AESIs)

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

In this trial, DLTs, the following events are defined 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 4.1.7.

BI 754091 infusion related reactions (Part B only)
Infusion-related reactions CTCAE Version 5.0 Grade ≥2 are defined as AESIs.

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

- Allergic reaction
- Anaphylaxis
- CRS
- Serum sickness
- Infusion reactions

- Infusion-like reactions

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

In the event of an infusion-related reaction ≤ Grade 2, the infusion rate of BI 754091 may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. In patients experiencing infusion-related reactions ≤ Grade 2, subsequent infusions may be administered at 50% of the initial rate.

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

As with any mAb, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and trial personnel must be trained to recognise and treat anaphylaxis. All trial sites will have emergency resuscitation services and access to intensive care available.

Cytokine release syndrome

Events of Grade ≥2 CRS are defined as AESIs. Patients will be closely monitored for CRS and, in case of suspected or confirmed CRS, appropriate treated according to best medical judgement based on institutional standards and/or publications (e.g., Lee at al. 2016 [R16-2323]). For the treatment of CRS, supportive therapy including steroids and / or interleukin 6 receptor (IL6R) antagonists (R15-0031) may be used as clinically indicated.

Patients will remain hospitalised for at least three days after the first administration of BI 891065. On day four or later, the investigator will then evaluate whether it is appropriate to discharge the patient based on the patient's condition. Thereafter, patients will be monitored with regular safety visits. All trial sites will have emergency resuscitation services and access to intensive care available. Hospitalisations for routine monitoring is not considered as an SAE.

Monitoring will include measurement of body temperature, heart rate, and blood pressure at regular intervals as presented in the Flow Chart. Patients will be assessed for signs or symptoms of CRS (e.g., hypotension, hypoxia, tachycardia, fever, nausea, fatigue, headache, myalgias, and malaise).

Patients will be informed about possible signs and symptoms of CRS, and the need to immediately contact or present to the investigational site if symptoms occur after discharge.

The following recommendations for the management of CRS regarding administration of BI 754091 and BI 891065 should be considered by the Investigator as guidance:

- In case of Grade 2 CRS, the intake of BI 891065 and infusion of BI 754091 should be temporarily interrupted. BI 891065 maybe resumed as soon as symptoms of CRS have completely resolved to baseline for at least 48 hours.

  In case less than 50% of a BI 754091 dose was administered due to CRS, a dose of 50% of the intended dose may be administered on the day when BI 891065 is re-started to ensure the patient receives an adequate dose of BI 754091. Please see section 3.3.4.1 regarding replacement of patients.
- In case of Grade 2 CRS, patients should be under close surveillance during the first 2 re-exposure administrations of BI 891065 and (if the CRS occurred during the or shortly after the infusion of BI 754091) during the first re-exposure administration of BI 754091 to ensure appropriate surveillance.

In the case of Grade 3 or 4 CRS, the study treatment should be permanently discontinued (section 4.1.6).

Immune-related adverse event (irAE) (Part B only)

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

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

Hepatic injury and potential drug-induced liver injury (DILI)

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

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

A potential hepatic injury is defined by the following alterations of hepatic laboratory parameters in patients with abnormal aminotransferase levels of >ULN and ≤3 fold ULN at baseline:

- an elevation of AST and/or ALT ≥3 fold the baseline value combined with an elevation of bilirubin ≥2 fold the baseline value measured in the same blood draw sample, or
- aminotransferase (ALT, and/or AST) elevations ≥5 fold the baseline value.

A potential hepatic injury is defined by the following alterations of hepatic laboratory parameters in patients with abnormal aminotransferase levels of >3 fold and ≤5 fold ULN at baseline (patients with liver metastases only):

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

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be reported according to Figure 5.2.6.1.4: 1, and be followed up according to the "potential DILI checklist" provided in the eDC system.

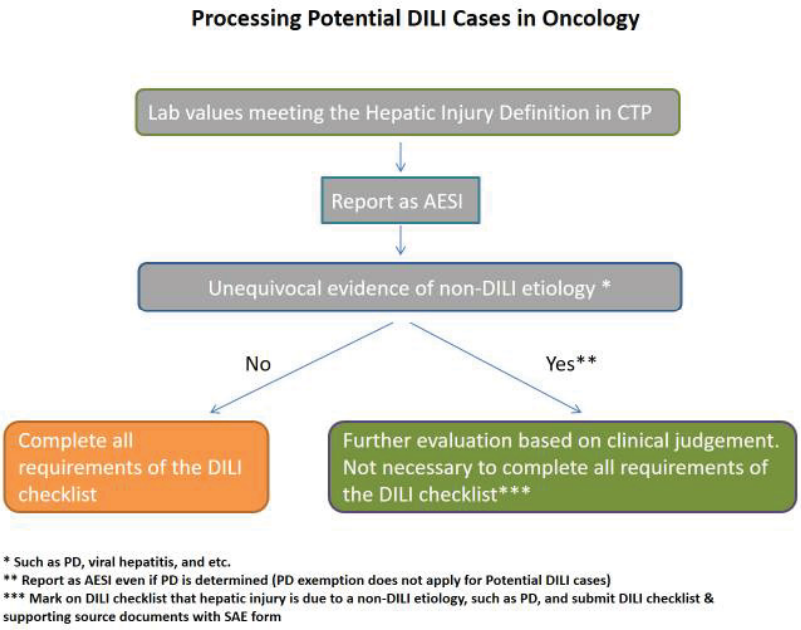


Figure 5.2.6.1.4: 1 Processing potential DILI cases

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the potential DILI checklist should be followed

The observation of the critical importance of altered liver function has been referred to informally as Hy's Law, and is described in the FDA's guidance on drug induced liver injury. Hy's Law cases have the following 3 components:

- The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST
- Among trial subjects showing such aminotransferase elevations, often with elevations much greater than 3 times ULN, one or more also show elevation of serum total bilirubin to >2 times ULN, without initial findings of cholestasis (elevated serum ALP)
- No other reason can be found to explain the combination of increased aminotransferase and total bilirubin, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.

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 Common Terminology Criteria for Adverse Events (CTCAE) version 5 (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 30-day follow-up-visit: all AEs (non-serious and serious) and all AESIs.
- After the 30-day follow-up-visit until the individual patient's end of trial: all related SAEs and all 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 new occurrence of cancer of new histology and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see section 5.2.6.2.2), but not on the CRF.

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

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. Reporting and consenting must be in line with local regulations. The ISF will contain the trial specific information and consent for the pregnant partner.

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

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

5.2.6.2.4 Exemptions to SAE reporting

Collection and reporting of PD
The outcome "disease progression" / "progressive disease (PD)" is used to assess trial endpoints for the analysis of efficacy and as such is exempted from AE/SAE reporting. "Disease progression" / "progressive disease (PD)", and signs/symptoms thereof which can exclusively be determined to be due to the progression of the underlying malignancy and meet the expected pattern of disease progression for the disease under study will be recorded on the appropriate pages of the eCRF as part of efficacy data collection only. It will not be recorded on the AE page in the eCRF and will not be reported on the SAE Form even when it meets standard seriousness criteria.

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

Exempted events are monitored at appropriate intervals.

Lab values meeting the hepatic injury definition as defined in section 5.2.6.1.4 will need to be reported as AESI. PD reporting exemption does not apply to hepatic injury. Please follow Figure 5.2.6.1.4: 1 for reporting hepatic injury / potential DILI cases.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Blood and urine samples will be collected for the purpose of PK analysis. Further information about sampling is provided in section 5.3.2.

Date and clock times of PK sampling will be recorded in the CRFs, and the following information should be collected in the eCRF for the last 4 administrations prior to PK sampling and on the day of PK sampling for BI 891065:

1. Date and clock times of drug administration
2. Information with respect to food intake (date and time) in case the patient takes the drug after meals
3. If vomiting or diarrhoea occurs within 3 hours after drug administration, the time of the onset of the episode(s)

The potential of BI 891065 to inhibit OATP1B1/B3 will be assessed by using an exploratory plasma biomarker: Coproporphyrin. Plasma samples are taken from patients in Part A at time points given in Table 10.3: 1. Assays are under development. Measurement will be done when feasible assays have been developed and validated.

5.3.2 Methods of sample collection

The planned PK analyses will require blood and urine sampling at the time points indicated in the Flow Chart. Correct, complete and legible documentation of drug administrations and blood sampling times, as well as adequate handling and identification of PK samples, are mandatory to obtain data of adequate quality for the PK analysis.

Details on sample characteristics, collection, processing, handling, and shipment are provided in the Laboratory Manual.

5.3.2.1 Plasma sampling for [redacted] pharmacokinetics and [redacted]

[redacted], blood will be taken from an antecubital or forearm vein at the time points listed in the flow charts and specified in PK time schedules in section 10.3. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture.

After completion of the trial, the plasma samples may be used for further methodological investigations, e.g., for stability testing, assessment of metabolites. However, only data related to the analyte and/or its metabolites 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 following signature of the final trial report.

5.3.2.2 Plasma sampling for [redacted] pharmacokinetics

[redacted], samples will be drawn at the time points listed in the flow charts and specified in PK time schedules in section 10.3.

For Part B, if collected from an arm, it is essential to collect blood from the arm that is opposite to the arm used for infusion in order to avoid artificially high or low drug concentration determinations.

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

5.3.2.3 Urine sampling and analysis for pharmacokinetics of [redacted]

A background urine sample will be collected before administration of trial medication (within 2 hours before drug dosing) and aliquots will be retained to check for analytical interference. All urine voided during the sampling intervals is indicated in section 10.3: An aliquot will be collected and stored. Patients will be told to empty their bladders at the end of each sampling interval.

In order to facilitate urine sampling, patients will be advised to drink at least 100 mL water before the end of each urine sampling interval. Details on urine sample characteristics, processing, handling, and shipment are provided in the Laboratory Manual.

After completion of the trial, the urine samples may be used for further methodological investigations, e.g., for stability testing, 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 upon the final trial report has been signed.

[redacted]

[redacted]

5.4 ASSESSMENT OF BIOMARKER(S)

SMAC mimetics induce rapid degradation of cIAP1 (by activating the auto ubiquitin ligase activity and targeting the protein to proteasome degradation). The degradation of cIAP1 leads, amongst others, to the activation of the alternative NF-Kb pathway, and activation of subsets of immune cells and secretion of cytokines. Cytokine secretion will be monitored, therefore, also in the combination with the PD-1 checkpoint inhibitor. These include mechanism-related cytokines (e.g., IL-2, IL-6, IL-10, IFN-γ, and TNFα), as well as exploratory immune-related cytokines.

The biomarkers in this clinical trial are exploratory. Most of these assessments are hypothesis generating and will be used to expand our understanding of the disease and trial drugs.
As medical knowledge in this field is constantly evolving, other tissue/blood biomarkers that may become relevant as predictive markers of treatment response may also be explored via available blood or acquisition of additional tumour tissues/blood. The list of biomarkers planned to be studied during the trial may change based on new information in the literature or early analyses.

5.4.1 Methods of sample collection

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

[redacted]

5.4.3 Storage period of samples

Remaining blood samples from the biomarker analysis will be destroyed no later than 3 years after the finalisation of the CTR.

5.4.4 Pharmacogenomic biomarkers

Pharmacogenetics (PGx) investigates genetic variations in patients to explain and to predict their individual response to drugs.

To perform the pharmacogenetic analysis, all patients will provide a blood sample for DNA isolation at Visit 1 of Cycle 1 (C1V1) or at a later visit during treatment. DNA will be extracted from the blood sample to explore the relationship of potential bilirubin increase and OATP 1B1, 1B3 and UGT1A polymorphism.

The results of pharmacogenetic tests will not be disclosed to patients because they are exploratory analyses. All data and samples that had already been collected up to the time of withdrawal of consent will still be used. The pharmacogenetic samples will not be stored upon completion of the genotype analysis and will be destroyed before the end of the clinical trial.

Detailed instructions for handling, storage, and shipment of the biomarker samples will be provided in the laboratory manual included in the ISF.

As of November 2020, the sponsor came to the conclusion that the genotyping analysis would not result in gaining additional supportive information and the analysis was cancelled.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

5.6.1 Immunogenicity testing

All patients in Part B: for anti-drug antibodies (ADA) assessment, blood samples will be drawn at the time points listed in the Flow Chart and section 10.3. Details on sample collection, characteristics, processing, handling, and shipment are provided in the Laboratory Manual.

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

The presence of ADA in relation to BI 754091 will be assessed using a validated immunoassay in a tiered approach (screening, confirmatory, and titration analysis as appropriate).

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

Patients meeting the inclusion and exclusion criteria for the part they are participating in and who have signed a written ICF, are eligible for participation in the trial. Patients will visit the clinical site at the time points specified in the Flow Chart. The allowed windows for each visit are also specified in the Flow Chart. Additional flexibility (e.g., to allow for public holidays and patient unavailability) may be allowed if agreed between the investigator and the sponsor. If a patient misses a scheduled visit, and reports to the Investigator between the missed visit and the next scheduled visit, the assessments for the missed visit must be done with the actual date and the reason must be given for the delayed visit. The next visit should still take place at the time it was originally scheduled in this treatment cycle. In case the day of treatment administration (visit 1 of a cycle) is delayed, all subsequent visits of a cycle will be recalculated based on the actual date of treatment of the delayed cycle.

Once the decision for any reason is made for a patient to stop the treatment with BI 891065 or the combination of BI 891065 plus BI 754091, an EOT visit must occur as soon as possible (preferably within 7 days and no later than 14 days after the decision to discontinue the treatment). After the EOT visit, the patient must undergo a follow-up safety evaluation 30 (+7) days after the last administration of trial therapy.

Additional follow-up visits for PD after the 30-day safety follow-up visit will only be performed for patients who did not progress on treatment (see section 6.2.3.3). The follow-up visits for PD will be performed once every 12 weeks at least (in person or by telephone) until PD, introduction of a new anti-cancer treatment, death, loss to follow-up, withdrawal of consent, or end of the whole trial.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

The investigations as outlined in the Flow Chart will be performed at the respective visits. Specific details to conduct of physical examination, collection of vital signs (including blood pressure measurement), laboratory investigations, assessment of ECG, and other safety parameters can be found in the subsections of Section 5.2.

Procedure for collection of blood samples for PK, ADA and biomarkers are given in sections 5.3, 5.6.1, and 5.4, and detailed sampling time point information is given in section 10.3.

6.2.1 Screening

At enrolment, each potential patient will provide written informed consent prior to starting any trial specific procedures. Upon signature of the informed consent, patients will be assigned a unique patient number as enrolment (screening) occurs.

6.2.1.1 Screening Period

Screening (Visit 1) will take place 1 to 14 days prior to first administration of trial medication (except for tumour assessment, for which scans up to 28 days prior to the first administration is accepted).

If an extension of screening period is required, this should be discussed and agreed with the sponsor. A repeat testing during the screening period for items not meeting the eligibility criteria is basically not allowed. The exemption to this should be discussed and agreed with the sponsor.

6.2.1.2 Baseline Conditions

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

6.2.1.3 Medical History

6.2.1.3.1 Medical history of cancer

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

Previously administered anti-cancer therapies will be reported, including start and end dates (month and year may be sufficient), as well as whether therapy was given as neoadjuvant, adjuvant, or palliative therapy. The date of tumour progression after previous lines of treatment will be recorded, if known.

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

6.2.1.3.2 Other medical history

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

6.2.1.4 Concomitant medications

Past medications relevant to patient's safety during the trial as judged by the Investigator will be recorded in eCRF. From the date of signature of the ICF, all concomitant medications will be recorded. Post-trial therapy for advanced or metastatic disease will also be documented.

6.2.2 Treatment period(s)

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

6.2.3 Follow-up period and trial completion

6.2.3.1 End-of-treatment (EOT) visit

The EOT visit will be performed after permanent discontinuation of trial treatment for any reason, preferably within 7 days but no later than 14 days after Investigator has decided to discontinue the trial medication or became aware that the trial medication had been terminated.

The assessments of the EOT visit will then be performed instead of at the next planned visit. If the patient finishes active treatment without having PD, tumour assessment/imaging must be performed at the time of treatment discontinuation, unless it has been done within the past 4 weeks.

6.2.3.2 30-day safety follow-up visit (end of residual-effect period)

The Residual Effect Period (REP) of BI 891065 monotherapy and combination therapy of BI 891065 and BI 754091 are defined as 30 days. The safety follow-up visit is performed 30 (+7) days after permanent discontinuation of the trial medication. The information collected at this visit must include all new AEs that occurred after the EOT visit, and a follow-up of AEs ongoing at EOT.

6.2.3.3 Follow-up visits for PD (extended follow-up period)

Additional follow-up visits for progression after the 30-day safety follow-up visit will only be performed for patients who did not progress on treatment. These will be performed once every 12 weeks at least (preferably in person, but if the patient cannot visit the study sites, collecting information by telephone is accepted).

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

- Disease progression
- Start of a new anti–cancer therapy

- Death
- Withdrawal of consent
- Lost to follow-up
- 6 months after the last patient completed the 30-day safety follow-up visit
- 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.

- Date of contact
- For each reportable serious adverse event / AESI, the investigator should provide the information with regard to concomitant medication and the medication administered to treat the adverse events on the appropriate CRF pages and the SAE form including trade name, indication and dates of administration
- Treatment and date with any subsequent anti-cancer therapy (including surgery and radiotherapy) 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 PD the actual date of PD shall be recorded)

6.2.3.4 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

6.2.3.5 Study procedures modification after implementation of protocol version 5

After implementation of protocol version 05, the patient will have assessments as medically indicated to monitor the safety at the discretion of the investigator.

These assessments may include: ECG, safety lab, and vital signs at a frequency decided by the investigator.

The study treatment is administered as continuous daily dosing and the administration information will be documented in the eCRF. Tumour assessment will be performed according to standard of care based on medical opinion of the investigator. The results of any assessments will be documented in the source data, but will not be collected in the eCRF. The blood sampling for cytokine at the EOT visit is not required. Findings which qualify as an (S)AE will be reported in the eCRF and in case of an SAE, on the SAE form (timelines and distribution requirements for SAEs apply).

The data collection is required only for the following items:

- Adverse events

- Concomitant medications that are used to treat adverse events
- Drug dispensing
- Dose changes
- At each cycle visit: visit date and medication compliance to BI 891065
- At EOT visit: visit date, end of treatment – BI 891065, and subject retention
- At safety follow-up visit: visit date and end of study page
- Death details (if applicable)

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

7.1.1 Part A

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 above 0.33 (EWOC criterion). The dose-finding of Part A will be guided by a Bayesian 2-parameter logistic regression model with overdose control (R13-4806; R13-4803).

The model is given as follows:
$\text{logit}(\pi_d) = \log(\alpha) + \beta * \log(d/d^*)$,
where $\text{logit}(\pi) = \log(\pi/(1-\pi))$.
π_d represents the probability of having a DLT in the MTD evaluation period at dose d, d^* = 200 mg is the reference dose, allowing for the interpretation of α as the odds of a DLT at dose d^*, and $\theta = (\log(\alpha), \log(\beta))$ with $\alpha, \beta > 0$ is the parameter vector of the model.

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

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 100 %.

The MTD may be considered reached if one of the following criteria is fulfilled:
- The posterior probability of the true DLT rate in the target interval [0.16 – 0.33) of the MTD is above 0.5, OR
- At least 12 patients have been treated in the dose escalation phase of the trial, of which at least 6 at the MTD.

The SMC may decide 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.

The BLRM is set up for a fixed dosing schedule of once daily (q.d.) across dose levels of BI 891065. For the purpose of dose-toxicity modelling, a b.i.d. regimen will be converted in

the BLRM to an equivalent q.d. regimen that has a similar C_{max} at steady state, based on the assumption that safety events are triggered by C_{max} at steady state. For example, the 200 mg b.i.d. regimen will be modelled as equivalent to a 300 mg q.d regimen in reference to the simulation results from trial 1379-0001. For any other b.i.d. doses considered, their conversions will be specified in the TSAP. If multiple b.i.d. doses are tested, appropriate modifications to the BLRM to account for the heterogeneity of different dosing schedules might be considered. Details will be specified in the TSAP if needed.

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

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

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

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

Prior derivation:
To determine the prior distribution for θ, a meta-analytic predictive (MAP) approach will be used. Toxicity information on BI 891065 from the 1379-0001 Phase I study will be incorporated. Exact details on the derivation of the prior distributions and on the evaluation of the model using hypothetical data scenarios and operating characteristics are provided in Appendix 10.4.1, a brief description is given here.

The historical data for BI 891065 can be found in Table 7.1.1: 1.

Table 7.1.1: 1 Historical data for BI 891065

Trial	Dose	N of patients with DLTs during MTD evaluation period / N of patients
1379-0001	5 mg q.d.	0/2
	15 mg q.d.	0/1
	25 mg q.d.	0/2
	50 mg q.d.	0/4
	100 mg q.d.	0/3
	200 mg q.d.	0/3
	400 mg q.d.	0/6

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

- The MAP prior was derived using the information in Table 7.1.1: 1 allowing for moderate to substantial between-trial heterogeneity. This mixture component was assigned 90% mixture weight.
- A second, weakly informative component was added with 10% mixture weight.

The prior distributions are given in Table 7.1.1: 2. The corresponding prior probabilities of a DLT at different doses and the corresponding probability of undertoxicity, targeted toxicity, and overtoxicity are shown in Table 7.1.1: 3. As can be seen from Table 7.1.1: 3, all dose levels of BI 891065 have prior probability of overtoxicity below 25%. Therefore, they fulfil the overdose criterion and are suitable starting dose levels.

Table 7.1.1: 2 Prior distribution

Parameter	Means, standard deviations, correlation	Mixture weight
θ: component 1	(-3.66, -0.28), (1.20, 0.83), -0.10	0.9
θ: component 2	(-3, 0), (2, 1), 0	0.1

Table 7.1.1: 3 Prior probabilities of DLTs

Dose	Probability of true DLT rate in					Quantiles		
	[0,0.16)	[0.16,0.33)	[0.33,1]	Mean	StD	2.5%	50%	97.5%
50 mg q.d.	0.981	0.014	0.005	0.022	0.050	0.000	0.007	0.137
100 mg q.d.	0.968	0.024	0.008	0.032	0.062	0.000	0.013	0.186
200 mg q.d.	0.932	0.050	0.018	0.053	0.085	0.002	0.026	0.282
200 mg b.i.d*	0.873	0.086	0.041	0.08	0.12	0.003	0.039	0.436
400 mg q.d.	0.813	0.115	0.072	0.107	0.155	0.004	0.051	0.606

*: The 200 mg b.i.d. dose is modelled as equivalent to a 300 mg q.d. dose in terms of dose-toxicity relationship in the BLRM.

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

7.1.2 Part B

Part B of the trial will be performed as an open-label single-arm trial. The primary objective of this part is to determine the MTD of BI 891065 in combination with BI 754091 at fixed dose of 240 mg. To determine the MTD, patients are entered sequentially into escalating dose cohorts. The dose escalation will be guided by a Bayesian 5-parameter logistic regression model with overdose control (R15-4233).

This logistic regression model is defined as follows. Let $\pi_{1,d1}$ be the probability of having a DLT when giving dose d_1 of BI 891065 as monotherapy, and $\pi_{2,d2}$ the probability of having a DLT when giving dose d_2 of the combination partner BI 754091 as monotherapy, respectively. A logistic regression is used to model the dose-toxicity relationship for each of these drugs individually:

BI 891065: $\text{logit}(\pi_{1,d1}) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$
BI 754091: $\text{logit}(\pi_{2,d2}) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*)$
Here, the doses $d_1^* = 200$ mg and $d_2^* = 240$ mg represent the reference doses for BI 891065 and BI 754091, respectively.

Assuming no toxicity interaction between the two compounds, the probability of a DLT when giving the combination dose d_1, d_2 is obtained as
$\pi^0_{12,d1,d2} = \pi_{1,d1} + \pi_{2,d2} - \pi_{1,d1}\pi_{2,d2}$
with corresponding odds
$\text{odds}(\pi^0_{12,d1,d2}) = \pi^0_{12,d1,d2} / (1 - \pi^0_{12,d1,d2})$
In order to account for a potential positive (higher toxicity than expected under independence) or negative (lower toxicity than expected under independence) interaction between BI 891065 and BI 754091, a dose-dependent interaction term $-\infty<\eta<\infty$ is introduced in the model by the following definition:

$odds(\pi_{12,d1,d2}) = odds(\pi^0_{12,d1,d2}) \exp(\eta\ d_1/d_1^*\ d_2/d_2^*)$
and $\pi_{12,d1,d2}$ is used in the likelihood
$r_{d1,d2} \sim Binomial(n_{d1,d2},\pi_{12,d1,d2})$
where $r_{d1,d2}$ denotes the random variable describing the observed number of DLTs in $n_{d1,d2}$ patients at the dose combination d_1, d_2.

Since a Bayesian approach is applied, prior distributions f for each of the parameter vectors $\theta_1=(\log(\alpha_1),\log(\beta_1))$, $\theta_2=(\log(\alpha_2),\log(\beta_2))$ and for the interaction term η need to be specified.

The prior distributions for θ_k will be specified as a mixture of two bivariate normal distributions,
$f(\theta_k) = a_{1,k}\ f_1(\theta_k) + a_{2,k}\ f_2(\theta_k)$
with
$a_{1,k}$, $a_{2,k}$ the prior mixture weights ($a_{1,k} + a_{2,k} = 1$), k = 1,2 and
$f_i(\theta_k) = MVN(\mu_{ik}, \sum_{ik})$ a bivariate normal distribution with mean vector μ_{ik} and covariance matrix $\sum_{ik}$ where

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

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

A weakly informative normal prior distribution will be used for η.

The estimated probability of DLT $\pi_{12,d1,d2}$ at each dose combination d_1, d_2 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 the starting dose of Part B is the combination with the highest posterior probability of the DLT rate falling in the target interval [0.16, 0.33) among the dose combinations fulfilling the EWOC principle. Per EWOC it should be unlikely (<25% posterior probability) that the DLT rate at the dose combination will exceed 0.33. However, the maximum allowable dose increment for the subsequent cohort will be no more than 100% for each drug.

The MTD may be considered reached if one of the following criteria is fulfilled:
- The posterior probability of the true DLT rate in the target interval [0.16 – 0.33) of the MTD is above 0.50, OR
- At least 9 patients have been treated in the dose escalation phase of the trial, of which at least 6 at the MTD

The BLRM is set up for a fixed dosing schedule of once daily (q.d.) across dose levels of BI 891065. For the purpose of dose-toxicity modelling, a b.i.d. regimen will be converted in the BLRM to an equivalent q.d. regimen that has a similar C_{max} at steady state, based on the

assumption that safety events are triggered by C_{max} at steady state. For example, the 200 mg b.i.d. regimen will be modelled as equivalent to a 300 mg q.d regimen in reference to the simulation results from trial 1379-0001. For any other b.i.d. doses considered, their conversions will be specified in the TSAP. If multiple b.i.d. doses are tested, appropriate modifications to the BLRM to account for the heterogeneity of different dosing schedules might be considered. Details will be specified in the TSAP if needed.

Prior derivation:
To determine the prior distributions for θ_1 and θ_2, a MAP approach will be used. Toxicity information on BI 891065 from Part A of this trial, Part A and Part B from trial 1379-0001, and toxicity information on BI 754091 from trials 1381-0001, 1381-0004 will be incorporated. Exact details on the evaluation of model using hypothetical data scenarios and operating characteristics are provided in the statistical Appendix 10.4.2; a brief description is given here.

The historical data for BI 891065 can be found in Table 7.1.2: 1. For BI 754091, the historical data can be found in Table 7.1.2: 2. The historical data for the combination of BI 891065 and BI 754091 can be found in Table 7.1.2: 3.

Table 7.1.2: 1 Historical data for BI 891065 monotherapy (status as of 14 Feb 2020)

Trial	Dose	N of patients with DLTs during MTD evaluation period / N of patients
1379-0001 Part A	5 mg q.d.	0 / 2
	15 mg q.d.	0 / 1
	25 mg q.d.	0 / 2
	50 mg q.d.	0 / 4
	100 mg q.d.	0 / 3
	200 mg q.d.	0 / 3
	400 mg q.d.	0 / 6
1379-0006 Part A	100 mg q.d.	1 / 3

Table 7.1.2: 2 Historical data for BI 754091 monotherapy (status as of 04 Feb 2020)

Trial	Dose (mg)	N of patients with DLTs / N of patients
1381-0001	80	0 / 3
	240	0 / 86
	400	0 / 3
1381-0004	240	0 / 6

Table 7.1.2: 3 Historical data for dose combination of BI 891065 and BI 754091 from BI trial 1379-0001 (status as of 13 Nov 2019)

Dose BI 891065	Dose BI 754091	N of patients with DLTs during MTD evaluation period / N of evaluable patients
50 mg q.d.	240 mg	0/6
200 mg q.d.	240 mg	0/8
400 mg q.d.	240 mg	1/5

The following steps were used to derive the prior distributions for all parameters:

- θ_1:
  - The meta-analytic-predictive prior was derived using the information in Table 7.1.2: 1, allowing for moderate to substantial between-trial heterogeneity. This mixture component was assigned 90% mixture weight.
  - A second, weakly-informative component was added with 10% mixture weight.
- θ_2:
  - The meta-analytic-predictive prior was derived using the information in Table 7.1.2: 2, allowing for moderate to substantial between-trial heterogeneity. This mixture component was assigned 90% mixture weight.
  - A second, weakly-informative component was added with 10% mixture weight.
- η: based on the a priori assumption of no interaction between the two compounds, a normal distribution with mean 0 and standard deviation 0.56 was chosen. At the starting dose combination, the corresponding 95% prior interval covers an up to 1.4 fold increase (or decrease) in the odds of a DLT over no interaction.

The prior distributions are given in Table 7.1.2: 4. The corresponding prior probabilities of a DLT at different dose combinations and the corresponding probabilities of under toxicity, targeted toxicity and over toxicity are shown in Table 7.1.2: 5. As can be seen from Table 7.1.2: 5, the dose combinations 25 mg q.d. BI 891065 and 240 mg BI 754091, 50 mg q.d. BI 891065 and 240 mg BI 754091, 100 q.d. mg BI 891065 and 240 mg BI 754091, and 200 mg q.d. BI 890165 and 240 mg BI 754091 have prior probabilities of over toxicity below 25% in both scenarios. They all fulfil the overdose criterion and are therefore suitable starting dose combinations.

Table 7.1.2: 4 Prior distributions

Parameter	means, standard deviations, correlation	mixture weight
$\log(\alpha_1)$, $\log(\beta_1)$: component 1	(-1.847, -0.404), (0.568, 0.689), 0.071	0.9
$\log(\alpha_1)$, $\log(\beta_1)$: component 2	(-1.847, -0.404), (2, 1), 0	0.1
$\log(\alpha_2)$, $\log(\beta_2)$: component 1	(-2.932, -0.177), (0.568, 0.883), -0.017	0.9
$\log(\alpha_2)$, $\log(\beta_2)$: component 2	(-2.932, -0.177), (2, 1), 0	0.1
η	0, 0.56	N/A

Table 7.1.2: 5 Prior probabilities of DLTs

Dose BI 891065	**Dose BI 754091**	**Probability of true DLT rate in**					**Quantiles**		
		[0,0.16)	**[0.16,0.33)**	**[0.33,1]**	**Mean**	**StD**	**2.5%**	**50%**	**97.5%**
25 mg q.d.	**240 mg**	0.84	0.131	0.029	0.114	0.096	0.027	0.093	0.357
50 mg q.d.	**240 mg**	0.759	0.205	0.036	0.133	0.103	0.034	0.111	0.397
100 mg q.d.	**240 mg**	0.603	0.338	0.059	0.165	0.114	0.044	0.14	0.475
200 mg q.d.	**240 mg**	0.387	0.427	0.186	0.227	0.147	0.048	0.193	0.616
200 mg b.i.d*	**240 mg**	0.315	0.352	0.333	0.284	0.195	0.038	0.237	0.771
400 mg q.d.	**240 mg**	0.296	0.282	0.422	0.332	0.239	0.028	0.275	0.881

*: The 200 mg b.i.d. dose is modelled as equivalent to a 300 mg q.d. dose in terms of dose-toxicity relationship in the BLRM.

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

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

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.

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

7.3.1 General considerations

7.3.1.1 Patient analysis sets

Treated set (TS):
This patient set includes all patients who were documented to have received at least one dose of any trial medication. The TS is used for safety analyses and in efficacy analyses.

MTD evaluation set:
This patient set includes all patients who were documented to have received at least one dose of any trial medication and were considered evaluable for DLT assessment (see section 3.3.4.1). The MTD evaluation set will be used for the primary analyses of DLTs and MTD determination.

Rules for replacement of patients are defined in the section 3.3.4.1. The list of replaced patients will be stored in the trial master file.

Pharmacokinetic parameter analysis set (PKS):
This set includes all patients in the treated set (TS) who provide at least one PK endpoint that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a patients will be included in the PKS, even if he/she contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.

ECG Set:
This set includes all patients in the treated set who do not have an artificial pacemaker and have at least one on-treatment value for at least one ECG variable.

ECG Pharmacokinetic Concentration Set (ECGPCS):
This set includes all patients from the ECG Set who provide at least one time-matched pair of valid BI 891065 plasma concentration and corresponding ECG variable to be used in the exposure-response analysis.
The decision about concentration value validity needs to be made within the Clinical Pharmacology group.

The analysis of ECG data will be based on the ECG Set, except those analyses concerning the relationship between plasma concentrations and ECG variables which will be based on the ECGPCS. Listings for patients with artificial pacemakers will be based on the TS.

Adherence to the protocol will be assessed by the trial team. Important protocol deviations (IPD) categories will be specified in the IQRMP, IPDs will be identified no later than in the

Report Planning Meeting, and the IPD categories will be updated as needed.

7.3.1.2 Pharmacokinetics

The pharmacokinetic parameters listed in section 2.1 and 2.2 for BI 891065 and BI 754091 will be calculated according to the relevant Standard Operating Procedure (SOP) of the Sponsor (001-MCS-36-472). Pharmacokinetic 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. A reference to the software used, e.g., name, will be indicated in the CTR.

Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of pharmacokinetic parameters. Concentrations used in the pharmacokinetic calculations will be in the same format as in the bioanalytical report (that is to the same number of decimal places provided in the bioanalytical report).

7.3.2 Primary endpoint analyses

7.3.2.1 Part A

In order to identify the MTD and/or RD of BI 891065, the number of evaluable patients with DLTs during the MTD evaluation period at each dose level must be presented.

For the analysis of tolerability and safety, please refer to section 7.3.5.

7.3.2.2 Part B

In order to identify the MTD and/or RD of the combination therapy of BI 891065 and BI 754091, the number of evaluable patients with DLTs during the MTD evaluation period at each dose level must be presented.

For the analysis of tolerability and safety, please refer to section 7.3.5.

7.3.3 Secondary endpoint analyses

The secondary endpoints (refer to Section 2.1.3) will be analysed descriptively.

[redacted]

7.3.5 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the REP, a period of 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. 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 Medical Dictionary for Drug Regulatory Activities (MedDRA) at database lock.

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

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

7.3.6 Interim Analyses

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.

No formal interim analysis of efficacy data is foreseen, although efficacy data when available may be considered as part of the safety evaluations.

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

For pharmacokinetics, no interim analysis is planned. Exploratory pharmacokinetic evaluations can be done during the trial on an ad-hoc basis.

7.4 HANDLING OF MISSING DATA

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

Handling of missing PK data will be performed according to the relevant Corporate Procedure (001-MCS-36-472).

PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.

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 this trial. Approximately 12 patients are expected for Part A, and approximately 9 patients expected for Part B. Fewer or more patients might be needed based on the recommendation of the SMC and the criteria specified. 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 10.4.

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. In exceptional cases, data may be published before the clinical trial report as long as this is discussed and agreed to by the investigators and the sponsor.

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective 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 [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

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

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

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial patient 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 4.1.11.

8.3.1 Source documents

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

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

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

Copies of source documents necessary for tumour assessment will be provided to an authorised vendor. Before sending or uploading those copies, the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents.

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

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

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

Exemptions from expedited reporting are described in section 5.2.6.2.4.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

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

- The facilities storing biological samples from clinical trial participants are qualified for the storage of biological samples collected in clinical trials
- A fit for purpose documentation (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/PK data

8.6 TRIAL MILESTONES

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

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (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 clinical trial portal (Clinergize) to facilitate document exchange and maintain electronic ISF.

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

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

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

Data management will be done by BI or a vendor according to BI SOPs. Statistical evaluation will be done by BI according to BI SOPs.

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

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

9. REFERENCES

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10. APPENDICES

10.1 IMMUNE-RELATED ADVERSE EVENTS OF SPECIAL INTEREST

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

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

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

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

Endocrine (report as AESI for any grade)
• Type 1 diabetes mellitus (if new onset)
Hematologic (report as AESI if an irAE is ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)
• Autoimmune haemolytic anaemia • Aplastic anaemia • Thrombotic thrombocytopenic purpura • Idiopathic (or immune) thrombocytopenia purpura • Disseminated intravascular coagulation • Haemolytic-uraemic syndrome • Any Grade 4 anaemia regardless of underlying mechanism
Hepatic (report as AESI if an irAE is ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat the AE**)**
• Hepatitis • Autoimmune hepatitis • Transaminase elevations (ALT and/or AST)
Infusion Reactions (report as AESI for any grade)
• Allergic reaction • Anaphylaxis • Cytokine release syndrome • Serum sickness • Infusion reactions • Infusion-like reactions
Neurologic (report as AESI for any grade)
• Autoimmune neuropathy • Guillain-Barre syndrome • Demyelinating polyneuropathy • Myasthenic syndrome

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

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

10.2 MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS

Regarding diagnosis, grading and therapeutic management of immune-related adverse events, grading and treatment, up-to-date published guidelines should be considered (e.g. P19-00269). Only limited guidance on management of specific irAEs can be given here.

Please refer to published guidelines (e.g. ASCO guideline, Brahmer [P19-00269]) for details.

In general,

- BI 754091 should be continued with close monitoring in case of grade 1 irAEs, with the exception of irAEs that may rapidly evolve into severe or fatal conditions (encephalitis of any grade, myocarditis of any grade, pneumonitis that is grade 1 but shows radiographic evidence of worsening – see detailed guidance below).
- For most Grade 2 irAEs, BI 754091 should be withheld and treatment with corticosteroids is commonly warranted, usually with an initial dose of 0.5 to 1 mg/kg prednisone / prednisone equivalent daily. Restart of therapy is commonly possible once symptoms and/or laboratory values have resolved to grade 1 or less, and on ≤10 mg prednisone / prednisone equivalent per day.
- For Grade 3 irAEs, BI 754091 has to be withheld, and treatment with high-dose corticosteroids (1-2mg/kg/day prednisone / prednisone equivalent) is usually warranted. Upon improvement, steroids should be tapered slowly over 4-6 weeks. Non-steroidal immunosuppressives (e.g. infliximab, mycophonlate mofetil) should be considered if no improvement or worsening occurs within the initial 48 to 72 hours. Upon recovery to grade 1 or less, and on ≤ 10 mg prednisone / prednisone equivalent per day, restarting BI 754091 may be considered for selected irAEs, but caution is advised, in particular in patients with early-onset irAEs. Expert consultancy and agreement with the sponsor is recommended prior to restart of therapy.
- Most Grade 4 irAEs warrant permanent discontinuation of BI 754091.
- Restart of therapy is commonly possible for endocrine irAEs regardless of grade once stable hormone replacement has been instituted and symptoms have recovered. In case of multiple hormone deficiencies, corticosteroid replacement has to precede thyroid hormone replacement therapy by several days in order to avoid adrenal crisis.

In case of prolonged steroid therapy or treatment with immunosuppressives consider the possibility of opportunistic infections and tuberculosis reactivation. Careful monitoring and consideration of administration of prophylactic antibiotics where appropriate are warranted.

Commonly, referral to experts in the management of organ-specific conditions is highly recommended, especially for irAEs grade 3 or grade 4, or irAEs where management is complex.

The list of irAEs for which BI 754091 should be permanently discontinued are summarised in section 4.1.6

- encephalitis, aseptic meningitis, transverse myelitis, or Guillain-Barre syndrome of any grade
- acquired thrombotic thrombocytopenic purpura of any grade

- myocarditis of any grade
- myasthenia gravis, peripheral neuropathy or autonomic neuropathy of grade ≥3
- myositis grade 2 with objective findings (see below), any myositis grade ≥3
- hepatitis grade ≥3 (transaminase >5 times ULN or total bilirubin >3 times ULN), recurrent hepatitis grade ≥2
- nephritis grade ≥3, persisting grade 2 nephritis unresponsive to initial steroid therapy or worsening, and recurrent nephritis grade ≥2
- pneumonitis grade ≥3,
- rash, bullous dermatoses, severe cutaneous adverse reaction, Stevens Johnson Syndrome, toxic epidermal necrolysis of grade 4, and recurrent rash grade ≥3
- colitis grade 4, and recurrent colitis of any grade
- uveitis, iritis, episcleritis of grade ≥3
- autoimmune-hemolytic anemia grade ≥2
- haemolytic uremic syndrome grade ≥3
- immune thrombocytopenia grade 4
- any recurrent irAE grade ≥3
- inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or
- persistent Grade 2-3 AEs that do not recover to Grade 1 or less within 12 weeks.

Dose adjustment of BI 754091 besides interrupting or permanently discontinuing BI 754091 are not allowed.

In rare situations when benefit and risk assessment is considered positive for a patient to continue BI 754091 treatment despite guidance to permanently discontinue (e.g. in case no alternative anti-cancer therapy is available), it should be discussed with the sponsor.

Pneumonitis:

- For Grade 1 pneumonitis with radiographic evidence of worsening, withhold BI 754091 until improvement or resolution; BI 754091 may be reintroduced upon radiographic improvement. In the absence of radiographic improvement within 3-4 weeks, follow guidance as for grade 2 event.
- For Grade 2 pneumonitis, hold BI 754091 until resolution to at least grade 1. If not already started, initiate therapy for the event as per available guidelines. Follow guidance as for grade 3 pneumonitis if no clinical improvement after 48 -72 hr of starting therapy.
- For Grade 3-4 pneumonitis, permanently discontinue BI 754091 and immediately initiate treatment according to available guidelines.

Diarrhoea/Colitis:

- For Grade 1 diarrhoea/colitis, consider interruption of BI 754091 therapy.
- For Grade 2 diarrhea/colitis, withhold BI 754091 until patient's symptoms recovered to grade 1 or less. Consider initiating treatment with steroids.
- For Grade 3 diarrhoea/colitis, withhold BI 754091 and immediately start treatment (steroids, non-steroidal immunosuppressents) as per available guidelines.
- For Grade 4 diarrhoea/colitis, permanently discontinue BI 754091 and immediately commence adequate therapy (e.g. i.v. corticosteroids).

- For Grade 1-3 colitis, restart of BI 754091 may be considered once symptoms improve to Grade 1 or less without need for continued steroids. After careful benefit risk assessment, BI 754091 may also be restarted after recovery to grade 1 or less, and on corticosteroid ≤ 10 mg per day
- BI 754091 should be permanently discontinued for recurrent diarrhoea/colitis of any grade.

Diabetes

- Consider withholding BI 754091 in case of grade 2 hyperglycemia. Check for ketonuria. In case of new onset of diabetes or unexpected worsening of pre-existing diabetes, check for new manifestation of type 1 diabetes.
- For new onset Type 1 diabetes mellitus, or Grade 3-4 hyperglycaemia associated with ketosis (ketonuria or metabolic acidosis)
  - Initiate insulin therapy
  - Evaluate subjects as appropriate per available guidelines regarding presence of type 1 diabetes
  - BI 754091 should be withheld until glucose level is controlled with insulin with no sign of ketoacidosis.
- BI 754091 may be restarted once insulin therapy has established stable glycemic control

Thyroid disorders:

For diagnosed thyroid disorders, thyroid hormone supplementation and monitoring should occur as per available guidelines

- Primary hypothyroidism:
  - For Grade 1 hypothyroidism, BI 754091 may be continued, with regular monitoring of thyroid values.
  - For Grade 2 hypothyroidism, consider withholding BI 754091
  - For Grade 3-4 hypothyroidism, withhold BI 754091, consider admission and IV therapy, especially in case of myxedema
  - BI 754091 may be restarted once symptoms resolve to baseline with appropriate thyroid hormone supplementation
- Primary hyperthyroidism
  - For Grade 1 hyperthyroidism, BI 754091 may be continued , with regular monitoring of thyroid values.
  - For Grade 2 hyperthyroidism, consider withholding BI 754091, initiate therapy as per available guidelines.
  - For Grade 3-4 hyperthyroidism, withhold BI 754091. Consider hospitalization, especially in case of thyreotoxicosis.
  - BI 754091 may be restarted once symptoms resolve to baseline.

Note: in case of concomitant adrenal dysfunction, this must be corrected first, prior to thyroid hormone replacement (reduced stress tolerance)

Adrenal insufficiency

- Interruption of BI 754091 therapy should be considered for adrenal insufficiency grade 1 or 2, and is warranted for grade 3 and grade 4 adrenal insufficiency, until patient is stabilized on hormone replacement therapy.

- Therapy with BI 754091 may be restarted once stable replacement therapy has been achieved.
- Note: in case of concomitant hypothyroidism, steroid replacement therapy should precede thyroid hormone substitution to avoid adrenal crisis.

Hypophysitis:
- Diagnostic workup for hypophysitis should be considered e.g. for patients with multiple endocrinopathies, unexplained fatigue, new severe headaches or vision changes.
- Patients should be appropriately advised regarding potentially reduced stress tolerance and increased substitution demands e.g. in case of infections, and to wear a medical alert bracelet to inform medical personnel about potentially increased hormone demands in situations of stress, in case of emergencies.
- Interruption of BI 754091 therapy should be considered for Grade 1 or 2 hypophysitis , and is warranted for Grade 3 and higher hypophysitis, until patient is stabilized on hormone replacement therapy.

Hepatitis:
- Work-up for other causes of elevated liver enzymes, see also section on potential DILI.
- For Grade 1 hepatitis (elevated AST/ALT < 3x ULN and/or total bilirubin <1.5x ULN), BI 754091 may be continued, close monitoring of liver values is warranted.
- For Grade 2 hepatitis (AST/ALT 3–5x ULN and/or total bilirubin >1.5 to ≤ 3x ULN), BI 754091 should be suspended. Monitoring of liver values every 3 days is recommended. Initiate treatment according to available guidelines. Restarting of BI 754091 may be considered upon recovery to grade 1 or less, and on corticosteroid ≤ 10 mg per day .
- For Grade 3 or higher hepatitis, BI 754091 has to be permanently discontinued.

Nephritis:
- For Grade 1 nephritis, consider temporarily withholding BI 754091.
- For Grade 2 nephritis, withhold BI 754091. Consult nephrology. Initiate treatment according to guidelines. In case of no improvement or worsening, permanently discontinue BI 754091.BI 754091 may only be re-started upon recovery to grade 1 or less , and on corticosteroid ≤ 10 mg per day.
- For Grade 3 or higher nephritis, permanently discontinue BI 754091. Consult nephrology. Treat with steroids 1-2 mg/kg prednisone or equivalent. If improved to grade 1 or less, taper corticosteroids over no less than 4-6 weeks.
- BI 754091 should also be permanently discontinued for recurrent nephritis grade 2 or higher.

Rash
- For Grade 1 rash, continue BI 754091. Initiate topical treatment.
- For Grade 2 rash, BI 754091 may be continued, in case of no improvement upon weekly monitoring, consider interruption of BI 754091 therapy. Treat topically, add systemic corticosteroid therapies as clinically appropriate.
- For Grade 3 rash, withhold BI 754091. Initiate topical and systemic therapy as per available guidelines. Upon improvement of event to grade 1 or less, and on corticosteroid

≤ 10 mg per day, consult with dermatology whether therapy with BI 754091 might be restarted, especially in case no alternative anti-neoplastic therapy is available.
- For Grade 4 rash, BI 754091 should be permanently discontinued.
- BI 754091 should also be discontinued for recurrent rash grade 3 or higher.

Bullous dermatosis
- For Grade 1 bullous dermatosis, use local wound care and observation. BI 754091 can be continued.
- For Grade 2 bullous dermatosis, withhold BI 754091. Administer topical therapy, add systemic therapy as clinically adequate.
- For Grade 3 bullous dermatosis, withhold BI 754091, initiate topical and systemic therapy as per available guidelines. Restarting of BI 754091 may be considered after dermatology consultation.
- For Grade 4 bullous dermatosis, permanently discontinue BI 754091.

Severe cutaneous adverse reaction (SCAR), Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN)
- For Grade 2 events, withhold BI 754091, initiate treatment as per available guidelines. Closely monitor for improvement or worsening.
- For Grade 3 events, withhold BI 754091. Initiate treatment as per available guidelines. In case mucous membranes are affected, involve appropriate disciplines in management to prevent sequelae from scarring (e.g. ophthalmology).
- For Grade 4 events, permanently discontinue BI 754091, immediately administer adequate therapy. Immediate admission to burn center or intensive care with dermatology and wound care is recommended, involve appropriate other disciplines as needed in management of mucosal involvement.

In case of Grade 2 or Grade 3 events, BI 754091 may only be re-started upon event recovered to Grade 1 or less, on corticosteroid ≤ 10 mg per day, and after consultation with dermatology.

Encephalitis/Aseptic meningitis
- BI 754091 should be permanently discontinued for any grade.

Myasthenia gravis
- For Grade 2 myasthenia gravis, withhold BI 754091,
- For Grade 3 or 4 myasthernia gravis, permanently discontinue BI 754091

Guillain Barré Syndrome (GBS)
- Discontinue BI 754091 permanently for any grade GBS.

Transverse Myelitis
- Discontinue BI 754091 permanently for any grade transverse myelitis.

Peripheral neuropathy, autonomic neuropathy
- For Grade 1 events, may continue BI 754091, but with low threshold to discontinue while monitoring closely for worsening.

- For Grade 2 events, withhold BI 754091 until resolution to grade 1 or less, and on corticosteroid ≤ 10 mg per day. Initiate therapy as appropriate per available guidelines.
- For Grade 3 or grade 4 events, permanently discontinue BI 754091.

Inflammatory Arthritis
- For Grade 1 arthritis, BI 754091 can be continued. Administer analgetic treatment (acetaminophen, nonsteroidal anti-inflammatory drug [NSAID]).
- For Grade 2-4 arthritis, withhold BI 754091. Initiate treatment as per available guidelines, cave regarding reactivation of tuberculosis/opportunistic infections in case of prolonged immunosuppressive/DMARD therapy.

BI 754091 may be restarted after consultancy with rheumatology once recovery to grade 1 or less, and on corticosteroid ≤ 10 mg per day.

Myositis

Diagnostic workup should consider the need to also evaluate myocardial involvement.
- For Grade 1 myositis, BI 754091 may be continued. Initiate adequate therapy as clinically warranted. In case of elevated CK or muscle weakness, treat as grade 2.
- For Grade 2 myositis, withhold BI 754091, discontinue permanently in patients with objective findings (elevated enzymes, abnormal EMG, abnormal muscle MRI or biopsy). Initiate therapy as per available guidelines. Resuming BI 754091 may be considered in patients without objective findings, symptoms have resolved to grade 1 or less without any immunosuppressive therapy, and after consultation with rheumatology/neurology.
- For Grade 3 or 4 myositis, permanently discontinue BI 754091.
- BI 754091 should be permanently discontinued if there is any evidence of myocardial involvement.

Polymyalgia-like syndrome
- For Grade 1 event, BI 754091 can be continued.
- For Grade 2 event, withhold BI 754091 and promptly initiate adequate therapy. If no improvement, treat as grade 3.
- For Grade 3 or G4 event, withhold BI 754091, promptly initiate adequate therapy Rheumatology consultancy is highly recommended.

BI 754091 may be resumed after careful assessment of risks and benefits, rheumatology consultancy highly recommended prior to reinitiation. BI 754091 may only be re-started upon recovery to grade 1 or less and on corticosteroid ≤ 10 mg per day.

Myocarditis
- Discontinue BI 754091 permanently for any grade of myocarditis.

Uveitis/Iritis, Episcleritis
- For Grade 1 events, treatment with BI 754091 can continue. Treat topically as needed.
- For Gade 2 events, withhold therapy with BI 754091, urgent ophthalomology referral is recommended. Initiate topical treatment, consider systemic therapy if needed. Restart of BI 754091 is permitted once resolved to grade 1 or less, and off systemic steroids (for the ocular condition, if steroids needed for other irAEs, up to 10 mg prednisone or equivalent

are permitted). Continuation of topical/ocular steroids is permitted and does not prohibit resuming BI 754091 therapy.
- For Grade 3 or 4 events, permanently discontinue BI 754091 therapy. Seek emergent ophthalmology consultation.. Initiate adequate local and systemic treatment.

Autoimmune-hemolytic anemia (AIHA)
- For Grade 1 AIHA, continue treatment with BI 754091. Close follow-up of anemia and other lab values.
- For Grade 2-4 AIHA, discontinue BI 754091 permanently. Initiate systemic therapy as per guideline. Consult Hermatology.

Acquired thrombotic thrombocytopenic purpura (TTP), haemolytic uremic syndrome.
Timely recognition upon suggestive findings is essential, timely/immediate involvement of hematology consultancy may be beneficial.
- For any grade TTP, permanently discontinue BI 754091.
- For HUS (TTP excluded), withhold BI 754091 for grade 1 and grade 2, provide supportive care. Upon full recovery, BI 754091 may be restarted after carefuly weighing of risks and benefits.
- For Grade 3 or Grade 4 HUS, discontinue BI 754091 permanently.

Immune thrombocytopenia (ITP)
- In case of Grade 1 ITP, BI 754091 can be continued.
- For Grade 2 or Grade 3 ITP, withhold BI 754091 and initiate systemic therapy. BI 754091 may be restarted upon resolution to at least grade 1.
- For Grade 4 ITP, permanently discontinue BI 754091.

10.3 TIME SCHEDULE FOR ECG, BLOOD AND URINE SAMPLING FOR PK, AND BLOOD SAMPLING FOR BIOMARKER

Table 10.3: 1 Time schedule for ECG, blood and urine sampling for PK, and blood sampling for biomarker in Part A

Cycle	Visit	Day	CRF Time/ PTM	Time point [hh:min]/event	Triplicate ECGs*	PK plasma for [redacted]	Plasma for [redacted]	Cytokines	PK urine for [redacted]
1	1a	1	-1:00	-1:00	X				
			-0:30	-0:30	X				
			-0:15	-0:15	X				
			-0:05	Just before BI 891065 admin		X	X	X	X
			0:00	BI 891065 admin					↕
			0:30	0:30		X	X		
			1:00	1:00	X	X	X	X	
			2:00	2:00	X	X	X		
			3:00	3:00	X	X	X	X	↕
			5:00	5:00		X	X		
			6:00	6:00		X	X		
			7:00	7:00		X	X		
			8:00	8:00		X	X	X	↕
			10:00	10:00		X	X		↕
	1b	2	24:00	No drug admin	X	X	X	X	↕
			36:00	36:00		X	X		
	1c	3	47:55	Just before BI 891065 admin		X	X		
			48:00	BI 891065 admin					
	2	8	167:55	Just before BI 891065 admin		X		X	
			168:00	BI 891065 admin					
	3	12	263:55	Just before BI 891065 admin		X			
			264:00	BI 891065 admin					

Table 10.3: 1 Time schedule for ECG, blood and urine sampling for PK, and blood sampling for biomarker in Part A (continued)

Cycle	Visit	Day	CRF Time/ PTM	Time point [hh:min]/event	Triplicate ECGs*	PK plasma	P [redacted] r	Cytokines	PK [redacted]
1	4	15	335:55	Just before BI 891065 admin	X	X	X	X	
			336:00	BI 891065 admin					↑
			336:30	0:30		X	X		↕
			337:00	1:00	X	X	X		↕
			338:00	2:00	X	X	X		↕
			339:00	3:00	X	X	X		↑
			341:00	5:00		X	X		↕
			342:00	6:00		X	X		↕
			343:00	7:00		X	X		↕
			344:00	8:00		X	X		↕
			346:00	10:00		X	X		↕
	5	16	359:55	Just before drug admin	X	X	X		
			360:00	BI 891065 admin					
2	1	1	-0:05	Just before BI 891065 admin		X		X	
			0:00	BI 891065 admin					
EOT[b]								X	

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

a Urine will be collected only for q.d. dosing group. A spot urine sample (x) is to be obtained prior to administration of trial medication. Other urine samples are to be collected over the post-dose intervals indicated between the arrows 0-3, 3-8, 8-10, 10-24 (Cycle 1 Days 1 and 15) and 24-48 h (Cycle 1 Day 1 only) and detailed in Section 5.3.2.3.

b Blood sampling for cytokine at the EOT visit is no longer required.

Table 10.3: 2 Time schedule for ECG and blood sampling for PK, biomarker, and ADA in Part B

Cycle	Visit	Day	CRF Time/ PTM	Time point [hh:min]/event	Triplicate ECGs*	PK plasma for [redacted]	PK plasma for [redacted]	Plasma for [redacted]	Cytokines	ADA
1	1a	1	-1:00	-1:00	X					
			-0:30	-0:30	X					
			-0:05	Just before BI 754091 admin	X		X		X	X
			0:00	BI 754091 admin						
			1:00	Just before infusion end			X			
			1:25	1:25		X		X		
			1:30	BI 891065 admin						
			2:00	2:00		X		X		
			2:30	2:30	X	X		X	X	
			3:30	3:30	X	X		X		
			4:30	4:30	X	X		X	X	
			6:30	6:30		X		X		
			7:30	7:30		X		X		
			8:30	8:30		X		X		
			9:30	9:30		X		X	X	
			11:30	11:30		X		X		
	1b	2	25:25	Just before BI 891065 admin	X	X	X	X	X	
			25:30	BI 891065 admin						
	2	8	167:55	Just before BI 891065 admin		X	X		X	
			168:00	BI 891065 admin						
	3	12	263:55	Just before BI 891065 admin		X	X			
			264:00	BI 891065 admin						

Table 10.3: 2 Time schedule for ECG and blood sampling for PK, biomarker, and ADA in Part B (continued)

Cycle	Visit	Day	CRF Time/ PTM	Time point [hh:min]/event	Triplicate ECGs*	PK plasma [redacted]	PK plasma [redacted]	[redacted]	Cytokines	ADA
1	4	15	335:55	Just before BI 891065 admin	X	X	X	X	X	X
			336:00	BI 891065 admin						
			336:30	0:30		X		X		
			337:00	1:00	X	X		X		
			338:00	2:00	X	X		X		
			339:00	3:00	X	X		X		
			341:00	5:00		X		X		
			342:00	6:00		X		X		
			343:00	7:00		X		X		
			344:00	8:00		X		X		
			346:00	10:00		X		X		
	5	16	359:55	Just before BI 891065 admin	X	X		X		
			360:00	BI 891065 admin						
2	1	1	-0:05	Just before BI 754091 admin		X	X	X	X	
			0:00	BI 754091 admin						
3, 4, 8, 12, 16	1	1	-0:05	Just before BI 754091 admin			X			X
			0:00	BI 754091 admin						
EOT							X		X	X
30-Day FU							X			X

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

10.4 STATISTICAL APPENDICES

A Bayesian logistic regression model with overdose control will be used to guide dose escalation in this part of the 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 10.4.1: 3 and Table 10.4.2: 3 for Part A and Part B respectively. 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 10.4.1: 1 for Part A and Table 10.4.2: 1 for Part B). For simplicity reasons, a cohort size of 3 patients who are all evaluable is assumed.

10.4.1 Part A

Hypothetical data scenarios:
Hypothetical data scenarios are shown in Table 10.4.1: 1. These scenarios reflect potential on-study data constellations and related escalation as allowed by the model and the 100% escalation limit. 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 100 mg. In this case, the next optimal dose, i.e. the dose with the highest probability of being in the target interval, is 400 mg. Since the escalation is restricted to a maximum of 100 % from the previous dose per protocol, the next dose to be tested in the trial would be 200 mg. Similarly, scenario 4 represents the case that 3 patients have been treated at 100 mg and 3 at 200 mg, none of them with a DLT. In this case, the model requires to escalate to 400 mg.

Scenario 3 shows the case that 2 DLTs are observed in the first three patients at the starting dose of 100 mg. The model then allows the next dose to be de-escalated to 50 mg.

Finally, scenario 8, 9 and 10 illustrate a case where escalation has proceeded up to the highest dose of 400 mg, where the MTD could be declared at 400 mg.

Table 10.4.1: 1 Hypothetical data scenarios

Scenario	Dose (q.d. mg)	# Patients	# DLT	Current Dose: P (OD)	Next recommended dose	Next dose:		
						P (UD)	P (TD)	P (OD)
1	100	3	0	0.001	400*[200]	0.834	0.106	0.060
2	100	3	1	0.041	400*[200]	0.564	0.253	0.184
3	100	3	2	0.316	50	0.533	0.262	0.205
4	100 200	3 3	0 0	0.002	400	0.871	0.091	0.039
5	100 200	3 3	0 1	0.030	400	0.596	0.237	0.167
6	100 200	3 3	0 2	0.193	200	0.479	0.327	0.193
7	100 200	3 3	1 1	0.140	200	0.520	0.340	0.140
8	100 200 400	3 3 6	0 0 0	0.001	400	0.970	0.029	0.001
9	100 200 400	3 3 6	0 0 1	0.023	400	0.814	0.163	0.023
10	100 200 400	3 3 6	0 0 2	0.134	400	0.496	0.371	0.134
11	100 200 400	3 3 6	0 0 3	0.413	200	0.824	0.164	0.013
12	100 200 400	3 3 6	0 0 4	0.745	200	0.763	0.198	0.039

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 10.4.1: 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: super high-toxicity scenario

Table 10.4.1: 2 Assumed true dose-toxicity scenarios

Scenario		Dose (mg q.d.)					
		40*	50	100	200	400	600*
1: Prior	P(DLT)	NA	0.022	0.032	0.053	0.107	0.181
2: High Tox		NA	0.194	0.253	0.425	0.527	NA
3: Low Tox		NA	0.008	0.028	0.054	0.143	0.181
4: Non-Logistic		NA	0.032	0.098	0.268	0.467	NA
5: Low-High		NA	0.008	0.052	0.241	0.335	NA
6: Super High Tox		0.260	0.450	0.578	0.660	0.737	NA

* To allow the model to implement the above scenarios and to evaluate the operating characteristics, 40 mg and 600 mg doses were included even if they will not be tested in the trial.

For each of these scenarios, 1000 trials were simulated. Each cohort consisted of 3 patients and dose escalation complied with the following rules:

- Escalate to the dose which maximises the probability of the targeted toxicity region and satisfies the overdose criterion if it is ≤ 100% increase from the current dose.
- If the recommended dose satisfying the overdose criterion is > 100% increase in dose, then escalate to the highest dose level which is ≤ 100% increase from the current dose.

The MTD was considered reached if at least 6 patients have been evaluated at a dose level which is the model's recommendation for the next dose cohort and for which the posterior probability of targeted toxicity was at least 50%.
It was then assessed how often a dose was declared as MTD with true DLT rate in the under-, targeted or over-dose range.
Furthermore, the average, minimum and maximum number of patients per trial and the average number of DLTs per trial are reported. Results are shown in Table 10.4.1: 3.

Table 10.4.1: 3 Simulated operating characteristics

	% of trials declaring a MTD with true DLT rate in				# Patients	# DLTs
	underdose	target dose	overdose	Stopped	Mean (Min-Max)	Mean (Min-Max)
1	17.7	82.3	0	0	16.5 (12-42)	1.9 (1-7)
2	0	45.4	37.8	16.8	12.9 (3-30)	4.5 (1-11)
3	22.2	77.6	0	0.2	16.4 (12-42)	1.9 (0-6)
4	18.8	52.8	27.1	1.3	13.7 (6-33)	3.7 (1-9)
5	7.4	42.8	49.5	0.3	13.4 (6-27)	3.0 (1-8)
6	0	0.1	11.6	88.3	8.1 (3-27)	4.5 (2-12)

In Scenario 1, which reflects the case that the true dose-toxicity is aligned with prior means, 82.3% of the simulated trials declared a dose 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, 45.4% of the simulated trials declared a dose as MTD with true DLT rate in the targeted dose range. 16.8% 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, 77.6% of the simulated trials declared a dose as MTD with true DLT rate in the target dose range.

Scenario 4 represents a case where the assumed true dose-toxicity curve does not follow a logistic shape. In this scenario, 52.8% of trials declared MTDs with true DLT rate in the target interval.

Scenario 5 shows that when the true DLT rate is low-high, 42.8% of the simulated trials declared a dose as MTD with true DLT rate in the targeted dose range. 428 trials declared 200 mg as the MTD, and 495 trials declared 400 mg as the MTD.

Scenario 6 shows that when the true DLT rate is super high, most 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 8.1 patients (Scenario 6) to 16.5 patients (Scenario 1) 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 10.4.1: 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 most 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 was used for data scenarios and simulations.

10.4.2 Part B

Hypothetical data scenarios:
Hypothetical data scenarios are shown in Table 10.4.2: 1. These scenarios reflect potential on-study data constellations and related escalation as allowed by the model and the 100% escalation limit. 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 combination of 200 / 240. In this case, the next optimal dose combination is 400 / 240.

Scenario 2 shows the case that one patient out of the 3 treated patients at 200 / 240 experiences a DLT, then the model would still recommend to treat the next patient with the same dose combination of 200 / 240.

Scenario 3 shows the case that 2 DLTs are observed in the first three patients at the starting dose combination of 200 / 240. The model then allows the next dose combination to be de-escalated to 100 / 240.

Finally, scenario 4, 5 and 9 illustrate a case where escalation has proceeded up to the highest dose combination of 400 / 240, where the MTD could be declared at that dose combination.

Table 10.4.2: 1 Hypothetical data scenarios

Scenario	Dose combination (mg)	# Patients	# DLT	Current Dose: P (OD)	Next recommended dose combination	Next dose:		
						P (UD)	P (TD)	P (OD)
1	200 / 240	3	0	0.024	400 / 240	0.572	0.251	0.178
2	200 / 240	3	1	0.110	200 / 240	0.501	0.389	0.110
3	200 / 240	3	2	0.350	100 / 240	0.485	0.369	0.147
4	200 / 240 400 / 240	3 6	0 0	0.015	400 / 240	0.857	0.128	0.015
5	200 / 240 400 / 240	3 6	0 1	0.085	400 / 240	0.567	0.348	0.085
6	200 / 240 400 / 240	3 6	0 2	0.282	200 / 240	0.632	0.350	0.018
7	200 / 240 400 / 240	3 6	0 3	0.567	200 / 240	0.420	0.523	0.057
8	200 / 240 400 / 240	3 6	0 4	0.813	200 / 240	0.268	0.594	0.138
9	200 / 240 400 / 240	3 6	1 1	0.173	400 / 240	0.392	0.436	0.173
10	200 / 240 400 / 240	3 6	1 2	0.422	200 / 240	0.406	0.526	0.068

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 10.4.2: 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: super high-toxicity scenario

Table 10.4.2: 2 Assumed true dose-toxicity scenarios

Scenario		Dose combination (mg)				
		25 / 240	50 / 240	100 / 240	200 / 240	400 / 240
1: Prior	P(DLT)	0.081	0.093	0.114	0.159	0.257
2: High Tox		0.161	0.194	0.253	0.398	0.607
3: Low Tox		0.068	0.095	0.101	0.124	0.251
4: Non-Logistic		0.023	0.032	0.150	0.168	0.467
5: Low-High		0.011	0.028	0.072	0.170	0.535
6: Super High Tox		0.260	0.450	0.578	0.660	0.737

For each of these scenarios, 1000 trials were simulated. Each cohort consisted of 3 patients and dose escalation complied with the following rules:

- Escalate to the dose combination which maximises the probability of the targeted toxicity region and satisfies the overdose criterion if it is ≤ 100% increase from the current dose.
- If the recommended dose combination satisfying the overdose criterion is > 100% increase in dose, then escalate to the highest dose level which is ≤ 100% increase from the current dose.

The MTD was considered reached if at least 6 patients have been evaluated at a dose level which is the model's recommendation for the next dose cohort and for which the posterior probability of targeted toxicity was at least 50%.

It was then assessed how often a dose combination was declared as MTD with true DLT rate in the under-, targeted or over-dose range.

Furthermore, the average, minimum and maximum number of patients per trial and the average number of DLTs per trial are reported. Results are shown in Table 10.4.2: 3.

Table 10.4.2: 3 Simulated operating characteristics

	% of trials declaring a MTD with true DLT rate in				# Patients	# DLTs
	underdose	target dose	overdose	Stopped	Mean (Min-Max)	Mean (Min-Max)
1	55.1	43.6	0.0	1.3	11.5 (3-42)	2.2 (0-7)
2	0.0	29.8	48.5	21.7	10.3 (3-30)	3.9 (1-11)
3	47.7	51.5	0.0	0.8	11.8 (3-42)	2.1 (0-6)
4	3.9	79.6	14.7	1.8	11.1 (3-30)	2.9 (1-8)
5	2.7	88.6	7.7	1	11.1 (3-24)	3.0 (1-7)
6	0	7.8	27.6	64.6	11.0 (3-30)	5.2 (2-13)

In Scenario 1, which reflects the case that the true dose-toxicity is aligned with prior means, 43.6% of the simulated trials declared the dose combination 400 / 240 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, only 29.8% of the simulated trials declared a dose combination as MTD with true DLT rate in the targeted dose range, and 48.5% in the overdose interval. 21.7% 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, 51.5% of the simulated trials declared the dose combination 400 / 240 mg as MTD with true DLT rate under the targeted dose range, and 47.7% 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, 79.6% 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, 88.6% 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, 64.6% of simulated trials stopped, since none of the doses is considered tolerable anymore. This is an expected situation for a super high-toxicity scenario.

The mean patient numbers range from 10.3 patients (Scenario 2) to 11.8 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.

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

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 was used for data scenarios and simulations.

10.5 IRECIST RESPONSE ASSESSMENT

Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. Therefore, overall response in this study will also be assessed using iRECIST (R17-0923) in addition to RECIST 1.1. The criteria of iRECIST are identical to those of RECIST 1.1 in many respects, but have been adapted to account for instances where an increase in tumour burden, or the appearance of new lesions, does not reflect true tumour progression.

Key differences are described in this section. All responses defined using iRECIST criteria are designated with a prefix.

10.5.1 Confirming progression

Unlike RECIST 1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after iUPD.

iCPD is confirmed if further increase in tumour burden, compared to the last assessment, is seen as evidenced by one or more of the following:

- Continued increase in tumour burden (from iUPD) where RECIST 1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions
    1. Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum
    2. Continued unequivocal progression in non-target disease with an increase in tumour burden
    3. Increase in size of previously identified new lesion(s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.
- RECIST 1.1 criteria are met in lesions types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR or iCR if those criteria are met compared to baseline). As can be seen in Table 10.5.2: 1 and Table 10.5.2: 2, respectively, the prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response (BOR) providing that iCPD is not documented at the next assessment after iUPD.

10.5.2 New lesions

New lesions should be assessed and measured as they appear using RECIST 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis (or 15 mm in short axis for nodal lesions), and recorded as New Lesions-Target (NLT) and New

Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of new target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the case report form.

PD is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions.

Table 10.5.2: 1 Time point iResponse

Target Lesions*	Non-Target Lesions*	New Lesions*	Time Point iResponse	
			No prior iUPD**	Prior iUPD**; ***
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non-iUPD	No	iPR	iPR
iPR	Non-iCR/Non-iUPD	No	iPR	iPR
iSD	Non-iCR/Non-iUPD	No	iSD	iSD
iUPD with no change OR decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	NLs confirms iCPD if NLs were previously identified and increase in size (≥5 mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD
iSD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD)
iUPD	Non-iCR/Non-iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on: o further increase in SOM of at least 5 mm, otherwise remains iUPD
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: • previously identified T lesion iUPD SOM ≥5 mm and / or • NT lesion iUPD (prior assessment - need not be unequivocal PD)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: • previously identified T lesion iUPD ≥5 mm and / or • previously identified NT lesion iUPD (need not be unequivocal) and/or • size or number of new lesions previously identified
Non-iUPD/PD	Non-iUPD/PD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on • increase in size or number of new lesions previously identified
* Using RECIST 1.1 principles. If no PSPD occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD would be the same. ** in any lesion category. *** previously identified in assessment immediately prior to this TP.				
iCPD = confirmed immune progression; iCR = immune complete response; iPR = immune partial response; iSD = immune stable disease; iUPD = unconfirmed immune progression; NL = new lesion; NLT = new lesion - target; NLNT = new lesion - non-target; PD = progressive disease; SOM = sum of measures; TP = time-point				

Table 10.5.2: 2 iRECIST Best Overall Response

TPR1	TPR2	TPR3	TPR4	TPR5	iBOR
iCR	iCR, iPR, iUPD, NE	iCR, iPR, iUPD, NE	iUPD	iCPD	iCR
iUPD	iPR, iSD, NE	iCR	iCR, iPR, iSD, iUPD, NE	iCR, iPR, iSD, iUPD, iCPD, NE	iCR
iUPD	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, NE, iCPD	iPR, iSD, iUPD, NE, iCPD	iPR
iUPD	iSD, NE	PR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, iCPD, NE	iPR
iUPD	iSD	iSD, iUPD, NE	iSD, iUPD, iCPD, NE	iSD, iUPD, iCPD, NE	iSD
iUPD	iCPD	Anything	Anything	Anything	iCPD
iUPD	iUPD	iCPD	Anything	Anything	iCPD
iUPD	NE	NE	NE	NE	iUPD

- Table assumes a randomised study where confirmation of CR or PR is not required.
- NE = not evaluable that cycle.
- Designation "I" for BOR can be used to indicate prior iUPD to aid in data interpretation.
- For patients with non-target disease only at baseline, only CR or non-CR/non-PD can be assigned at each TPR but is not shown in the table for ease of presentation

TPR: Time point response
iBOR: iRECIST best overall response

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		28 Aug 2019
EudraCT number **EU number**		Not applicable
BI Trial number		1379-0006
BI Investigational Medicinal Product(s)		BI 891065 BI 754091
Title of protocol		An open label, Phase I study of BI 891065 monotherapy and combination therapy of BI 891065 and BI 754091 in Asian patients with advanced solid tumours
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		Flow Chart
Description of change		f Pregnancy tests are mandatory for women with child-bearing potential. A serum **(or plasma)** beta human chorionic gonadotropin (β-HCG) pregnancy test must be done at screening. Thereafter, either a serum **(or plasma)** or urine pregnancy test will be done on Day 1 of each cycle, at the EOT visit, and at the 30-day safety FU visit.
Rationale for change		Clarification
Section to be changed		Flow Chart 3.3.3 Exclusion criteria 5.2.3.6 Virology
Description of change		The following flow chart footnote was modified: g HBV, HCV, and HIV testing should be performed at screening ~~unless~~ **(see section 5.2.3.6 for HBV and HBV test requirements). In Part A, these tests are exempted if** test results obtained in routine clinical practice within 6 months before the informed consent date are available. **In part B, HBV and HCV tests are mandatory but HIV testing is not mandatory if test results obtained in routine clinical practice within 6 months before the informed consent date are available.** Section 3.3.3 criteria 13 was modified: Any of the following laboratory evidence of hepatitis virus infection. ➢ Positive results of hepatitis B surface (HBs) antigen ➢ Presence of hepatitis B core (HBc) antibody together with hepatitis virus B (HBV) Deoxyribonucleic acid (DNA) ➢ Presence of hepatitis virus C (HCV) antibody together with HCV Ribonucleic acid (RNA) **In Part A, t**~~T~~est results obtained in routine clinical

		practice are acceptable if done within 6 months before the informed consent date. Section 5.2.3.6 was modified: HBV, HCV, and HIV testing should be performed at screening ~~unless~~**. In Part A these tests are exempted if** test results obtained in routine clinical practice within 6 months before the informed consent date are available. **In part B, HBV and HCV tests are mandatory but HIV testing is not mandatory if test results obtained in routine clinical practice within 6 months before the informed consent date are available.** **The required test items are as follows:** **For HBV: HBs antigen and HBc antibody tests are performed.** HBV-DNA test is required only for patients with HBc antibody positive results. ~~Similarly~~ **For HCV: HCV antibody test is performed.** HCV-RNA test is required only for patients with HCV antibody positive results.
Rationale for change		As there is a theoretical possibility of hepatitis virus reactivation with anti-PD-1 treatments, the HBV and HCV tests in screening are mandated even if test results obtained routine clinical practice within 6 months are available. Test items required for hepatitis virus tests are clarified.
Section to be changed		Flow Chart 1.4.2 Risks 5.2.6.1.4 Adverse events of special interest (AESIs)
Description of change		A footnote was added in Flow Chart: **r Patients will remain hospitalised for at least three days after the first administration of BI 891065. 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 adverse events and if necessary haematology and clinical chemistry examination.** The mitigation strategy for Cytokine release syndrome in Table 1.4.2: 1 was modified: To keep patients ~~under close surveillance at study sites for 10 hours~~ **hospitalised for 3 days** after the first administration of BI 891065. Provide recommendation for the management of CRS in the clinical trial protocol. Cytokine levels are measured. A part of the description of Cytokine release syndrome in section 5.2.6.1.4 was modified: Patients will remain ~~under surveillance for 10 hours after the first administration of BI 891065 (i.e., until the blood sampling for PK on day 1 is completed). Although patients will not be required to stay overnight on the first day of monotherapy or combination therapy treatments, they should be advised to remain close to the study site where medical coverage will be ready to support them, if required~~

		hospitalised for at least three days after the first administration of BI 891065. On day four or later, the investigator will then evaluate whether it is appropriate to discharge the patient based on the patient's condition. Thereafter, patients will be monitored with regular safety visits.
Rationale for change		Based on a feedback from a regulatory authority, a requirement of hospitalisation following the first administration was added, together with the assessment/examination to be performed before discharging patients.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		3.3 Selection of trial population
Description of change		Approximately 21 patients (12 in Part A, 9 in Part B) are planned to be included. This trial will be conducted in Japan and Taiwan. Japanese patients will be recruited in all treatment cohorts, and Taiwanese patients will be recruited in the highest planned dose ~~of each part~~ **in Part A and all cohorts in Part B** (for details, please refer to section 4.1.3).
Rationale for change		Clarification
Section to be changed		4.1.7 Dose limiting toxicities
Description of change		• Neutropenia **≥** Grade 3 with documented infection (inequality symbol "≥" was added)
Rationale for change		Clarification based on a feedback from a regulatory authority
Section to be changed		4.1.7 Dose limiting toxicities
Description of change		• Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with bleeding ~~or a requirement for platelet transfusions~~
Rationale for change		The condition of platelet transfusion is already covered in another bullet point "Thrombocytopenia of any Grade which requires platelet transfusions ".
Section to be changed		4.1.7 Dose limiting toxicities
Description of change		• AST or ALT >3 times ULN and concurrent total bilirubin >2 times ULN without initial findings of

		cholestasis (e.g., findings consistent with Hy's law or the FDA definition of potential DILI**, see section 5.2.6.1.4**)
Rationale for change		Clarification
Section to be changed		4.2.1.2 Caution for concomitant medication and/or food
Description of change		The section was added with following information: **BI 891065 is a substrate of CYP3A4. In ongoing overseas trial of 1379-0001, the exposure (C_{max}, AUC) tended to increase in two patients who took moderate CYP3A4 inhibitor from 25 patients at 5 to 400 mg dose cohort. Caution is necessary for the intake of CYP3A4 inhibitor (ex. clarithromycin, erythromycin, fluconazole, itraconazole, verapamil, ketoconazole, and diltiazem) or grapefruits and their juices, because the possibility cannot be excluded for the increase of plasma concentration.**
Rationale for change		Caution for the concomitant use of CYP3A4 inhibitors was added as the possibility of increases in the blood concentration of BI 891065 when CYP3A4 inhibitors are concomitantly used cannot be excluded.
Section to be changed		5.2.6.1.4 Adverse events of special interest (AESIs)
Description of change		Immune-related adverse event (irAE) (Part B only) Immune-related AEs are AEs associated with immunotherapy treatments that appear to be associated with the immune therapy's mechanism of action. These adverse reactions, which can be severe, may involve the gastrointestinal, skin, liver, endocrine, respiratory, renal, or other organ systems. The Sponsor has defined a list of potential irAEs which need to be reported as ~~irAEs~~ **AESI** in section 10.1.
Rationale for change		Correction of an error
Section to be changed		5.2.6.1.4 Adverse events of special interest (AESIs)
Description of change		Added: **The observation of the critical importance of altered liver function has been referred to informally as Hy's Law, and is described in the FDA's guidance on drug induced liver injury. Hy's Law cases have the following 3 components:** • **The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST** • **Among trial subjects showing such aminotransferase elevations, often with elevations much greater than 3 times ULN, one or more also show elevation of serum total bilirubin to >2 times ULN, without initial findings of cholestasis (elevated serum ALP)** • **No other reason can be found to explain the combination of increased aminotransferase and total bilirubin, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.**
Rationale for change		Clarification

Section to be changed		5.6.1 Immunogenicity testing
Description of change		~~After completion of the trial, p~~**P**lasma samples may be used for further methodological investigations, **(**e.g., stability testing~~.~~**),** ~~H~~**h**owever, only data related to the ADAs will be generated by these additional investigations.
Rationale for change		The description was updated as methodological investigations using plasma samples may be performed before the completion of the trial.
Section to be changed		10.1 Immune-related adverse event of special interest
Description of change		Renal (report as AESI if an irAE is ≥ Grade 2) • Nephritis • Nephritis autoimmune • Renal failure • Renal failure acute • Creatinine elevations (report as an ~~irAEs~~ **AESI** if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)
Rationale for change		Correction of an error

11.2 GLOBAL AMENDMENT 2

Date of amendment		09 Oct 2019
EudraCT number **EU number**		Not applicable
BI Trial number		1379-0006
BI Investigational Medicinal Product(s)		BI 891065 BI 754091
Title of protocol		An open label, Phase I study of BI 891065 monotherapy and combination therapy of BI 891065 and BI 754091 in Asian patients with advanced solid tumours
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		4.1.1 Identity of the Investigational Medicinal Products
Description of change		Table 4.1.1: 1 BI 891065 Unit strength: 5 mg, 20 mg, 50 mg, **100 mg** tablets
Rationale for change		A new formulation, 100 mg tablets, became available.
Section to be changed		3.1 Overall trial design and plan
Description of change		*snip* At any time in the trial, it will not be permitted to escalate to a dose which does not fulfil the EWOC principle (refer to section ~~5~~ **7**).
Rationale for change		Correction of error

11.3 GLOBAL AMENDMENT 3

Date of amendment		23 Mar 2020
EudraCT number **EU number**		Not applicable
BI Trial number		1379-0006
BI Investigational Medicinal Product(s)		BI 891065 BI 754091
Title of protocol		An open label, Phase I study of BI 891065 monotherapy and combination therapy of BI 891065 and BI 754091 in Asian patients with advanced solid tumours
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		General
Description of change		The originally planned dosing schedule of "once daily" was removed, and replaced with appropriate word depending on the context e.g., 400 mg per day ~~once daily~~.
Rationale for change		BI decided to investigate b.i.d. dosing schedules that may potentially associated with better tolerability.
Section to be changed		Flow Chart
Description of change		Tumour biopsy was added in the flow chart table. Following footnote was added: **n The following tumour biopsies will be mandatory for all patients in Part B of the trial:** - **One fine needle biopsy must be freshly taken between screening and first trial drug treatment.** - **One fine needle biopsy from the same lesion on treatment as soon as possible after the 21-day observation period is completed and the patient has been on the uninterrupted and unchanged dose of BI 891065 for at least two continuous weeks. Biopsy collection should be delayed until these conditions are met. If it is absolutely impossible to obtain a biopsy from the same lesion, another lesion may be chosen.**
Rationale for change		BI decided to test the cIAP1 degradation in tumour tissue in this trial, to reinforce the data obtained in preceding trial 1379-0001.
Section to be changed		Flow Chart
Description of change		**The text in the flow chart table at "BI 891065 intake" was updated as follows:** **~~Continuous daily dosing except for C1D2 in Part A~~** **Continuous dosing of once or twice daily, with exceptions for PK assessment** **Following footnote was added:** **BI 891065 is taken either once daily (q.d.) or twice daily (b.i.d.), depending on the assigned treatment regimen. BI 891065 doses should be taken orally at approximately the same time each morning (and evening for patients with b.i.d. dosing). There are exceptions depending on the part (Part A or Part B) and dosing regimen (q.d. or b.i.d.):**

<table>
<tr><td></td><td></td><td>- Part A q.d. dosing: a dose will be skipped on cycle 1 day 2
- Part A b.i.d. dosing: following doses will be skipped in cycle 1 – day 1 evening, day 2 morning and evening, and day 15 evening
- Part B q.d. dosing: no exceptions
- Part B b.i.d. dosing: following doses will be skipped in cycle 1 – day 1 evening and day 15 evening</td></tr>
<tr><td>Rationale for change</td><td></td><td>Q.d. and b.i.d. dosing schedules may be investigated. Exceptions of dosing schedule for PK are clarified per part per dosing schedule.</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Section to be changed</td><td></td><td>Flow Chart</td></tr>
<tr><td>Description of change</td><td></td><td>Foot note h was updated:
[…] Urine samples are taken in Part A in once daily (q.d.) dosing schedule cohorts only.</td></tr>
<tr><td>Rationale for change</td><td></td><td>It is clarified that the urine PK is not required in b.i.d. dosing schedule cohorts.</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Section to be changed</td><td></td><td>1.4.2 Risks</td></tr>
<tr><td>Description of change</td><td></td><td>Table 1.4.2: 1 Potential risks, their rationale, and mitigation strategy
<table>
<tr><td>Potential risks of clinical relevance for this trial</td><td>Summary of data, rationale for the risk</td><td>Mitigation strategy</td></tr>
<tr><td colspan="3">[…]</td></tr>
<tr><td colspan="3">Investigational Medicinal Product BI 754091</td></tr>
<tr><td colspan="3">[…]</td></tr>
<tr><td>Infusion related reactions</td><td>As with any mAb, hypersensitivity reactions to study medication administration are possible and they are potentially severe.</td><td>Patients with history of severe hypersensitivity reactions to other mAbs are excluded. Recommendations for the management of infusion related reactions are given in ~~this~~ section 5.2.6.1.4.</td></tr>
<tr><td colspan="3">[…]</td></tr>
<tr><td colspan="3">Trial procedures</td></tr>
<tr><td colspan="3">~~No trial specific risks are expected in relation to the trial procedures, as blood samplings and imaging examinations are routinely performed in this patient population. Frequency of blood sampling or radiation exposure from tumour imaging are considered to be slightly higher than that of routine clinical practice, but are kept as necessary minimum to ensure patients' safety and appropriate assessment of efficacy.~~</td></tr>
<tr><td>Tumour biopsy related AEs (Part B only)</td><td>Tumour biopsies are mandatory in Part B. There are known risks associated with biopsies such as pain or bleeding.</td><td>The risks are clearly explained in the informed consent document.</td></tr>
</table></td></tr>
</table>

		[…]
Rationale for change		An error in the cross-reference in the mitigation strategy for infusion related reaction was corrected. Risks associated with biopsy were added with the mitigation strategy.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		3.1 Overall trial design and plan
Description of change		~~After the completion of dose escalation in Part A (i.e., the MTD is reached or the safety in the highest dose is confirmed), Part B will commence and~~ **In Part B,** successive cohorts of patients will receive escalating **daily** dose of BI 891065 in combination with a fixed dose of BI 754091 at 240 mg once every 3 weeks. The planned starting dose of BI 891065 in Part B is 200 mg, **and this cohort will commence after the safety of the same dose level in Part A is confirmed.** ~~but o~~**O**ther doses may be investigated depending on the safety data obtained from Part A and from the preceding first-in-human trial (1379-0001).
Rationale for change		The completion of Part A is no longer a prerequisite to commence Part B.
Section to be changed		3.3.2 Inclusion criteria
Description of change		Added: **8. For Part B: Patients must have at least 1 tumour lesion amenable to biopsy, and must be willing to undergo a biopsy prior to first treatment and after 3 weeks while on therapy.** **9. For Part B: Patients with following cancer types: bladder, colon, breast, NSCLC, ovarian, pancreatic, renal, esophagogastric, sarcoma, prostate, and melanoma.**
Rationale for change		BI decided to test the cIAP1 degradation in tumour tissue in this trial, to reinforce the data obtained in preceding trial 1379-0001. The inclusion had to be limited to the cancer types specified in here, as the immunohistochemistry test for cIAP1 degradation is only validated in these cancer types.
Section to be changed		3.3.3 Exclusion criteria
Description of change		10. Any of the following cardiac criteria […]

		➢ Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years-of-age, or any concomitant medication **with** known **or possible risk of** ~~to prolong the~~ QT interval **prolongation**
Rationale for change		The cardiac risk exclusion criteria has been clarified.
Section to be changed		3.3.4.1 Discontinuation of trial treatment
Description of change		Following criteria for patient replacement was added: • **Patients who have reduced BI 891065 dose level during the first treatment cycle, unless they develop a DLT** • **(Part B only) Patients who have received less than 50% of the BI 754091 initial dose, unless they develop a DLT** Following criterion for patient replacement was modified: • Patient who misses ~~≥7~~ **>5** doses of BI 891065 during the first treatment cycle for reasons other than treatment-related AEs and who does not experience DLTs
Rationale for change		To align the condition with the preceding trial 1379-0001.
Section to be changed		4.1.2.1 Starting dose of BI 891065
Description of change		It was clarified that twice daily dosing will be investigated in Part A and Part B. The following sentence was added: **Twice daily dosing will be explored, aiming to reduce peak plasma concentrations compared to single dosing of the same daily dose, which may reduce occurrences of bilirubin increase, and may allow for better tolerability of similar total daily doses compared to once daily dosing, and potentially higher daily doses.**
Rationale for change		The reason for investigating the twice daily dosing was provided.
Section to be changed		4.1.3 Dose-finding scheme
Description of change		Table 4.1.3: 1 Example of dose escalation in Part A

Dose level	Proposed daily dose of BI 891065~~*~~	Participating countries
1	100 mg	Japan
2	200 mg~~**~~	Japan
3	400 mg~~**~~	Japan and Taiwan

***The total daily dose will be given in q.d. or b.i.d. dosing schedule.**
Actual dose **level and dosing schedule ~~assignment~~ for a cohort will be communicated separately as determined by the SMC. Intermediate or lower dose level(s) may be investigated depending on the latest DLT rate estimate.

Table 4.1.3: 2 Example of dose escalation in Part B

Dose level	Proposed daily dose of BI 891065~~*~~	Proposed dose of BI 754091 (every three weeks)	Participating countries

		<table><tr><td>1</td><td>200 mg~~**~~</td><td>240 mg</td><td>Japan and Taiwan</td></tr><tr><td>2</td><td>400 mg~~**~~</td><td>240 mg</td><td>Japan and Taiwan</td></tr></table> ***The total daily dose will be given in q.d. or b.i.d. dosing schedule.** **Actual dose **level and dosing schedule** ~~assignment~~ for a cohort will be communicated separately as determined by the SMC. Intermediate or lower dose level(s) may be investigated depending on the latest DLT rate estimate.
Rationale for change		q.d. and b.i.d. dosing schedules may be investigated. The dosing schedule will be determined by SMC and be communicated to the investigators.
Section to be changed		4.1.5.1 Administration of BI 891065
Description of change		[…] ~~BI 891065 doses should be taken orally at approximately the same time each morning. The exception to this is Part A Cycle 1 Day 2 where study drug is not taken.~~ **BI 891065 is taken either q.d. or b.i.d., depending on the assigned treatment regimen. Refer to Flow Chart for exceptions of dosing schedule where study drug is skipped.** Patients will be asked to fast overnight (minimum of 10 hours) prior to the **morning dose on** the following intensive PK days:
Rationale for change		q.d. and b.i.d. dosing schedules may be investigated. Exceptions of dosing schedule for PK are clarified per part per dosing schedule in the Flow Chart.
Section to be changed		4.1.6 Dose modifications (pause, delay, dose reduction, and discontinuation)
Description of change		The description was updated as follows: ~~As a general rule, related AEs of ≥ Grade 2 deemed intolerable by the patient or the treating physician and not responding to appropriate medical management and any AEs of ≥ Grade 3 will result in a pause of treatment with BI 891065 (in Part A) and with BI 891065 and BI 754091 (Part B) until resolution to baseline or Grade 1. When the administration of BI 754091 is delayed in Part B, the start of the cycle is also delayed and the date of BI 754091 administration is always considered Day 1/Visit 1 of the cycle.~~ ~~If the treatment pause is ≤12 weeks, the patient can be re-exposed to BI 891065 at one dose level lower than the dose administered before the pause (except for patients who are receiving the lowest dose allowed) according to Table 4.1.6: 1 and Table 4.1.6: 2, and the same fixed dose of BI 754091 as long as the re-exposure is considered clinically indicated by the Investigator.~~ ~~In case the treatment has been paused for reasons other than related AEs, the dose of BI 891065 at the re-exposure should be the same as before.~~ **AEs that are immune related should be managed according to the Guidelines for irAE management (as outlined in Appendix 10.2).** **For Grade 4 AE/SAEs that are not immune related, study drug should be withdrawn. However, if it can be excluded with high certainty that the event was related to study medication, study drug should be paused, and resumption of study drug may be allowed after discussion with the Sponsor.**

For Grade 3 AE/SAEs that are not immune related, study drug should be paused.

For Grade 2 AEs/SAEs that are not immune related but are deemed intolerable by the patient or the treating physician and not responding to appropriate medical management, the physician should decide if a pause of treatment is warranted considering relevant variables such as perceived relatedness to study drug.

If, after a treatment pause of ≤12 weeks, the non-immune related SAE/AE resolves to baseline or Grade 1 and the physician thinks it is clinically appropriate to restart study drug, then the physician may choose to restart BI 891065 at one dose lower than the dose administered before the pause (except for patients who are receiving the lowest dose allowed) according to Table 4.1.6: 1 and Table 4.1.6: 2, and BI 754091 at the same fixed dose of BI 754091. Up to two dose reductions of BI 891065 are allowed per patient. If the AE/SAE prompting interruption has unequivocally been excluded to be drug related, reintroduction of BI 891065 at the same dose as prior to the pause may be considered.

There will be no dose reductions or escalations of BI 754091 in any one patient. However, in the event of an infusion-related reaction ≤ Grade 2, the infusion rate of BI 754091 may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. In patients experiencing infusion-related reactions ≤ Grade 2, subsequent infusions may be administered at 50% of the initial rate. If an infusion-related reaction is Grade 3 or higher in severity at any point during the study, treatment with BI 891065 and BI 754091 will be permanently discontinued.

As a general rule for Part B, both drugs (BI 891065 and BI 754091) will be stopped, paused, or re-exposed together. Exemptions have to be justified and aligned with the Sponsor in writing.

Table 4.1.6: 1 Dose reduction recommendations for BI 891065 in ~~Part A~~ **q.d. dosing (up to two dose reductions are allowed per patient)**

BI 891065 dose before the pause	BI 891065 dose at restart
400 mg	200 mg
200 mg	100 mg
100 mg	50 mg (lowest dose allowed)

Table 4.1.6: 2 Dose reduction recommendations for BI 891065 in ~~Part B~~ **b.i.d. dosing**

BI 891065 dose before the pause	BI 891065 dose at restart
~~400 mg~~	~~200 mg~~
200 mg **x 2**	100 mg **x 2**
100 mg **x 2**	50 mg **x 2 (lowest dose allowed)**

		~~50 mg~~ | ~~25 mg (lowest dose allowed)~~ **Grade ≥3 infusion related reactions** was added in the list of AEs that need permanent discontinuation of the study treatment.
Rationale for change		Dose reductions and dose delay text was clarified and aligned with the other edits made to the trial protocol.
Section to be changed		4.1.7 Dose limiting toxicities
Description of change		A criterion of non-haematological toxicities was updated • Any AEs that require dose reduction or ~~treatment discontinuation according to section 4.1.6~~ **will be assessed by SMC and may be considered as DLTs unless the SMC considers the dose reduction as not strictly medically warranted** • **Permanent treatment discontinuation according to section 4.1.6**
Rationale for change		To align the condition with the preceding trial 1379-0001.
Section to be changed		5.2.2 Vital signs
Description of change		Vital signs will be evaluated at the time points specified in the flowchart, prior to blood sampling**, or after a sufficient period of rest (usually 5 minutes is sufficient, but a longer rest may be required if there are any problems at the blood sampling)**.
Rationale for change		Conditions to assess vital signs were clarified.
Section to be changed		5.2.3.2 Biochemistry
Description of change		The standard biochemistry panel will consist of glucose (serum or plasma), sodium, potassium, chloride, calcium, phosphate, ~~urea,~~ serum creatinine (measured by enzymatic assay, Isotope dilution mass spectroscopy [IDMS] standardised Jaffe assay, or non-IDMS Jaffe assay), AST, ALT, alkaline phosphatase, lactate dehydrogenase, **gamma glutamyl transferase,** bilirubin (total, direct, and indirect bilirubin), haptoglobin, total protein, albumin, **urea or** urea nitrogen, uric acid and creatine kinase (CK). If CK is elevated, then CK-MB [cardiac], Troponin (either I or T), and myoglobin should be reactively tested.
Rationale for change		Gamma glutamyl transferase was added to investigate the mechanism of bilirubin elevation. It is clarified that urea and urea nitrogen are interchangeable and testing either one of them based on the availability at the local lab is sufficient.
Section to be changed		5.2.6.2.3 Pregnancy
Description of change		The following paragraph was added: **Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires a written consent of the pregnant partner. Reporting and consenting must be in line with local regulations. The ISF will contain the trial specific information and consent for the pregnant partner.**
Rationale for change		To update information on pregnant partner with current template.
Section to be changed		5.3.1 Assessment of pharmacokinetics
Description of change		Date and clock times of PK sampling will be recorded in the CRFs, and the following information should be collected in the eCRF for the last 4 ~~days~~ **administrations** prior to PK sampling and on the day of PK sampling for BI 891065:

		1. Date and clock times of drug administration 2. Information with respect to food intake (date and time) in case the patient takes the drug after ~~breakfast~~ **meals** 3. If vomiting or diarrhoea occurs within 3 hours after drug administration, the time of the onset of the episode(s)
Rationale for change		Requirements were adjusted to allow the PK assessment in both q.d. and b.i.d. dosing schedule.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		7.1 STATISTICAL DESIGN – MODEL
Description of change		Descriptions of BI 891065 doses in section 7.1 tables were updated to clarify whether they are q.d. or b.i.d.
Rationale for change		Clarification
Section to be changed		7.1.1 Part A
Description of change		Added: **The BLRM is set up for a fixed dosing schedule of once daily (q.d.) across dose levels of BI 891065. For the purpose of dose-toxicity modelling, a b.i.d. regimen will be converted in the BLRM to an equivalent q.d. regimen that has a similar Cmax at steady state, based on the assumption that safety events are triggered by Cmax at steady state. For example, the 200 mg b.i.d. regimen will be modelled as equivalent to a 300 mg q.d regimen in reference to the simulation results from trial 1379-0001. For any other b.i.d. doses considered, their conversions will be specified in the TSAP. If multiple b.i.d. doses are tested, appropriate modifications to the BLRM to account for the heterogeneity of different dosing schedules might be considered. Details will be specified in the TSAP if needed.**
Rationale for change		Methods of using BLRM in b.i.d. dosing were clarified.
Section to be changed		7.1.2 Part B
Description of change		**The BLRM is set up for a fixed dosing schedule of once daily (q.d.) across dose levels of BI 891065. For the purpose of dose-toxicity modelling, a b.i.d. regimen will be converted in the BLRM to an equivalent q.d. regimen that has a similar Cmax at steady state, based on the assumption that safety events are triggered by Cmax at steady state. For example, the 200 mg b.i.d. regimen will be modelled as equivalent to a 300 mg q.d regimen in reference to the simulation results from trial 1379-0001. For any other b.i.d. doses considered, their conversions will be specified in the TSAP. If multiple b.i.d. doses are tested, appropriate modifications to the BLRM to account for the heterogeneity of different dosing schedules might be considered. Details will be specified in the TSAP if needed.**

Rationale for change		Methods of using BLRM in b.i.d. dosing were clarified.

11.4 GLOBAL AMENDMENT 4

Date of amendment		30 Apr 2021
EudraCT number **EU number**		Not applicable
BI Trial number		1379-0006
BI Investigational Medicinal Product(s)		BI 891065 BI 754091
Title of protocol		An open label, Phase I study of BI 891065 monotherapy and combination therapy of BI 891065 and BI 754091 in Asian patients with advanced solid tumours
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		Flowchart footnote and sections 6.2.3.5 and 10.3.
Description of change		Descriptions to reduce the required study procedures and data collections were added.
Rationale for change		The assessments of primary and secondary endpoints have been completed, and sufficient data have been collected for further endpoint by an interim DBL on 29 Mar 2021. The CTR will be prepared based on the data locked at this interim DBL. As of April 2021, one patient is still receiving the study treatment as per the protocol, but further data collection is no longer needed for the analysis. Therefore, the data to be collected will be reduced to a necessary minimum. The assessments will be performed as medically indicated to monitor the safety at the discretion of the investigator, and the results will be documented in the source data but will not be collected in the eCRF except for AE/SAE and the information about the treatment continuation and study termination.
Section to be changed		Section 5.4.4
Description of change		A statement was added that the genotyping analysis was cancelled.
Rationale for change		Based on the clinical outcome, the sponsor concluded that the genotyping analysis would not result in gaining additional supportive information.

APPROVAL / SIGNATURE PAGE

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Document Name: clinical-trial-protocol-version-05

Title: An open label, Phase I study of BI 891065 monotherapy and combination therapy of BI 891065 and BI 754091 in Asian patients with advanced solid tumours

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	07 May 2021 03:51 CEST
Author-Trial Clinical Pharmacokineticist		07 May 2021 07:01 CEST
Approval-Team Member Medicine		07 May 2021 08:31 CEST
Approval-Therapeutic Area [redacted]		07 May 2021 14:27 CEST
Author-Trial Statistician		10 May 2021 03:32 CEST
Verification-Paper Signature Completion		10 May 2021 06:02 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed