Clinical Trial Protocol

	Document Number:	**c11957282-07**
EudraCT No.: **EU Trial No:**	2017-000465-74	
BI Trial No.:	1379-0001	
BI Investigational Product(s):	BI 891065 + BI 754091	
Title:	An open-label Phase I dose finding trial with BI 891065 alone and in combination with BI 754091 to characterise safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy in patients with advanced and/or metastatic malignancies	
Lay Title:	A trial to find the safe dose for BI 891065 alone and in combination with BI 754091 in patients with incurable tumours or tumours that have spread	
Clinical Phase:	I	
[redacted] **Physician [redacted] / Coordinating Principal Investigator**	[redacted]	
Trial Clinical Monitor:	[redacted] Phone: [redacted] Fax: [redacted]	
Status:	Final protocol (Revised Protocol [based on global amendment 6])	
Version and Date:	**Version: 7.0**	**Date: 12 February 2020**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Finished product name	Not applicable
Active ingredient name:	BI 891065 + BI 754091
Protocol date	04 May 2017
Revision date	12 February 2020
Trial number	1379-0001
Title of trial:	An open-label Phase I dose finding trial with BI 891065 alone and in combination with BI 754091 to characterise safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy in patients with advanced and/or metastatic malignancies
Trial sites:	Multi-centre trial
Clinical phase:	I
Objectives:	To investigate the maximum tolerated dose (MTD)/recommended dose for further development based on dose limiting toxicities (DLT), safety and tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of BI 891065 alone and in combination with BI 754091 in patients with advanced and/or metastatic malignancies
Methodology:	Open-label dose escalation followed by expansion cohorts
Number of patients entered:	Approximately 104
Number of patients on each treatment:	Part A (dose escalation BI 891065 monotherapy): approximately 30 patients Part B (dose escalation BI 891065 in combination with BI 754091): approximately 31-37 patients Part C (expansion cohort with the combination treatment): approximately 44 patients in a pre-treated non-small cell lung cancer (NSCLC) cohort.
Diagnosis:	Parts A: Patients with a confirmed diagnosis of an advanced and/or metastatic solid tumour Part B: Patients with a confirmed diagnosis of advanced, unresectable and/or metastatic cancers who have failed standard treatment, or for whom no therapy of proven efficacy exists, or who are not amenable

	to standard therapies. Eligibility is limited to patients with the following cancer types: bladder, colon, breast, NSCLC, ovarian, pancreatic, renal, esophagogastric, sarcoma, prostate, and melanoma. Part C: Patients with metastatic NSCLC who developed disease progression (per RECIST v1.1) after the first scan (where SD, PR, or CR was demonstrated at the first scan), and require new anti-cancer therapy after first line treatment with an anti PD-1/anti PD-L1 mAb (given either as single agent therapy or in combination with a platinum-based chemotherapy regimen).
Main in- and exclusion criteria	Main inclusion criteria - Parts A and B: Adult patients with a 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. Eligibility is limited to the following tumour subtypes in Part B: bladder, colon, breast, NSCLC, ovarian, pancreatic, renal, esophagogastric, sarcoma, prostate, and melanoma. - Part C: Adult patients with metastatic NSCLC who developed disease progression (per RECIST v1.1) after the first scan (where SD, PR, or CR was demonstrated at the first scan), and require new anti-cancer therapy after first line treatment with an anti PD-1/anti PD-L1 mAb (given either as single agent therapy or in combination with a platinum-based chemotherapy regimen) - Life expectancy of at least 12 weeks after start of treatment according to Investigator's judgement - Parts B and C: Patients must have at least one tumour lesion amenable to biopsy, and must be willing to undergo biopsy prior to first treatment and, unless clinically contraindicated, during therapy. Main exclusion criteria - Treatment with another anticancer drug within 4 weeks or within 5 half-life periods (whichever is earlier) prior to first administration of BI 891065 - Known presence of central nervous system (CNS) metastases unless asymptomatic and off corticosteroids and/or anti-convulsant therapy for at least 2 weeks prior to start of treatment - Persistent toxicity from previous treatments that has not resolved to ≤ Grade 1 with the exception of alopecia - Systemic immunosuppressive medication (steroids of max. 10 mg prednisone equivalent per day are allowed, topical [e.g., inhaled] steroids are not considered as immunosuppressive) within 1 week of beginning the study

	- 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 drugs.
Test products:	BI 891065 + BI 754091
dose:	Part A BI 891065 Monotherapy: Dose tiers will start at 5 mg per day Dose-escalation steps as determined by the Safety Review Committee (SRC) Part B BI 891065 plus BI 754091: BI 891065 starting dose will be determined by the SRC based on data of Part A. Dose-escalation steps will be determined by the SRC. BI 754091: a fixed dose once every 3 weeks; anticipated starting dose of 240 mg (i.e., the dose currently selected in the Phase I Trial 1381.1 of BI 754091 monotherapy for expansion cohort patients and 1381.2). Based on further data for BI 754091, the starting dose may be adapted by the SRC. Part C: Dose of combination BI 754091 (fixed dose as determined in Part B) + BI 891065 as determined based on safety and PK data as well as target engagement in tumour tissue from Parts A and B.
mode of administration:	BI 891065: orally (*per os* [p.o.]) BI 754091: intravenous (i.v.)
Duration of treatment:	Reiterated treatment cycles of 3 weeks as long as the patient has clinical benefit or until undue drug toxicity (both according to the Investigator's judgment) or withdrawal of consent, whichever occurs first
Endpoints	<u>Primary Endpoints</u> Part A: The MTD of BI 891065 monotherapy and the number of patients with DLTs during the first treatment cycle. Part B: The MTD of BI 891065 in combination with BI 754091 and the number of patients with DLTs during the first treatment cycle. Part C: Objective response (OR) by the Investigator's assessment based on RECIST v1.1. <u>Secondary Endpoints</u> Part A: • The number of patients with DLTs observed during the entire treatment period. • $C_{max,ss}$, $AUC_{\tau,ss}$, and AUC_{0-tz} of BI 891065 • OR by Investigator's assessment based on RECIST v1.1. Part B: • The number of patients with DLTs observed during the entire treatment period.

	• $C_{max,ss}$, $AUC_{\tau,ss}$, and AUC_{0-tz} of BI 891065; C_{max} and AUC_{0-tz} of BI 754091 • OR by the Investigator's assessment based on RECIST v1.1. Part C: • Duration of OR based on RECIST v1.1.
Safety criteria:	Safety and tolerability of BI891065 as monotherapy and in combination with BI 754091 by evaluation of the incidence and severity of adverse events according to Common Terminology Criteria for Adverse Events (CTCAE) (Version 5.0), QTcF evaluation
Statistical methods:	Descriptive analysis (summary statistics) will be used to describe the safety and efficacy endpoints. 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.

FLOW CHART: BI 1379.1 (REFMAL 505) PART A TRIAL ASSESSMENTS

Part A Flow Chart **Trial period**	**Screening**	**Part A Dose Escalation BI 891065 Monotherapy Treatment Period**									**EOT[n]**	**30-Day Safety FU[o]**	**FU for PD[p]**
Cycle[a]		**C1**							**C2**	**C3+**			**Every 6 or 9 weeks**
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10+**			
Treatment day	**Up to 28 days[b]**	**1**	**2**	**3**	**8**	**12**	**15**	**16**	**1 (±2)**	**1 (±2)**		**+1 week**	**±5 days**
Informed consent	X												
Inclusion / exclusion criteria	X	X											
Medical history and demographics[c]	X												
Report planned hospitalisations	X												
Physical examination, height (screening only), and weight[c,d]	X	X					X		X	X	X	X	X
ECOG Performance score[c,d]	X	X							X	X	X	X	X
12-Lead Electrocardiograms (single/triplicate)[c,e]	X	X	X				X	X	X	X	X		
Cardiac testing (only if cardiac disease suspected)[f]	X												
Vital signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	
Serum pregnancy test[c,g]	X	X							X	X	X	X	
Safety laboratory (haematology, biochemistry)[c]	X	X			X	X	X		X	X	X		
Safety laboratory (amylase and lipase if symptoms of pancreatitis)		X							X	X	X		
Safety laboratory (coagulation)[c]	X	X							X	X	X		
Alpha-1 acid glycoprotein (AGP)		X							X				
Virology testing (≤28 days of treatment)	X												
Safety laboratory (urine)[c]	X	X			X	X	X		X	X	X		
Tumour assessment[h]	X	Every 6 weeks (then every 9 weeks after 6 months of treatment)									X		X

Part A Flow Chart **Trial period**	**Screening**	**Part A Dose Escalation BI 891065 Monotherapy Treatment Period**									**EOT[n]**	**30-Day Safety FU[o]**	**FU for PD[p]**
Cycle[a]		**C1**							**C2**	**C3+**			**Every 6 or 9 weeks**
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10+**			
Treatment day	**Up to 28 days[b]**	**1**	**2**	**3**	**8**	**12**	**15**	**16**	**1 (±2)**	**1 (±2)**		**+1 week**	**±5 days**
Blood, urine sampling for pharmacokinetics[i,j]		X	X	X	X	X	X[j]	X[j]	X				
[redacted]													
BI 891065 intake (daily except for C1D2)[l]		X		X	X	X	X	X	X	X			
Concomitant therapy	X	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	
Dose-limiting toxicity (DLT) assessment[m]		X	X	X	X	X	X	X	X	X	X		
SAEs/AESIs considered drug-related													X
Patient status												X	X
Review Patient Diary	X	X	X	X	X	X	X	X	X	X	X		

Part A BI 891065 Monotherapy Flow Chart Footnotes

a Treatment cycles (C) are 21 days (3 weeks). Patients may continue treatment with BI 891065 as long as they are deriving clinical benefit according to the Investigator's judgment. All circumstances for withdrawal of trial treatment are presented in Section 3.3.4.1.

b Screening should take place within 28 days of start of study treatment, however, may be extended as outlined in Section 6.2.1.1.

c Safety laboratory assessments including haematology, serum biochemistry, coagulation, serum pregnancy test, and urinalysis will be performed locally. The following screening parameters should be done ≤14 days prior to initiation of treatment: medical history and demographics, physical examination (including height and weight), Eastern Cooperative Oncology Group (ECOG) performance status, vital signs, electrocardiogram (ECG), haematology (per Section 5.2.3), clinical chemistry (sodium, potassium, phosphate, chloride, creatinine, calcium, venous bicarbonate HCO_3, albumin, total protein, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, total, direct and indirect bilirubin, lactate dehydrogenase, serum glucose, creatinine kinase [CK: if CK is elevated, then CK-MB, Troponin I, and myoglobin should be reactively tested, with further follow-up as clinically warranted], serum urea nitrogen, and serum uric acid), urinalysis, and screening pregnancy test. If these assessments are performed within 72 hours of initiation of treatment, they do not need to be repeated on Cycle 1 Day 1 with the exception of the ECOG performance status, an abbreviated physical examination, vital signs, and single/triplicate ECGs required as outlined in Section 5.2.4 and Table 10.3: 1. Tumour assessments (scans) should be performed ≤28 days prior to initiation of treatment. Refer to Section 5.2.3 for additional details. Vital signs (blood pressure, body temperature, and pulse rate) are checked at every visit prior to blood work and trial treatment and at the discretion of the Investigator (see Section 5.2.2).

d Physical examinations including the measurements of height (screening only) and weight will be done at screening, on Day 1 of each treatment cycle, at the end-of-treatment (EOT) visit, at the 30-day safety follow-up (FU) visit, and at the FU visits for PD. However, patients will have an additional abbreviated physical examination (focused on the specific disease, at the Investigator's discretion) on Cycle 1 Day 15. ECOG performance status will be done at screening, on Day 1 of Cycles 1 and 2, on Day 1 of every other cycle beginning with Cycle 3, at the EOT visit, at the 30-day FU visit, and at FU visits for PD (see Section 5.2.1).

e Triplicate or single 12-lead electrocardiograms (ECGs) will be done at the time points as outlined in Section 5.2.4 and Table 10.3: 1 and whenever the Investigator deems it necessary (see Section 5.2.4 and Appendix 10.3). ECG machines will be provided for Part A to facilitate central readings. While all triplicate ECGs will be transmitted to the central vendor, only the baseline, 6-hour, 8-hour, and 24-hour readings will be reviewed directly. The other triplicate ECG readings will be analyzed only after the PK analysis points to a t_{max}.

f Refer to Section 3.3.3 for details on which patients require cardiac testing (e.g., echocardiogram (ECHO)/multi-gated acquisition (MUGA) scan.

g Pregnancy tests are mandatory for women with child-bearing potential. A serum beta human chorionic gonadotropin (β-HCG) pregnancy test must be done with serum at screening. Thereafter, this test can be done in either serum or urine on Day 1 of each cycle, at the EOT visit, and at the 30-day FU visit (see Section 5.2.3).

h Tumour assessments should be done according to RECIST v1.1 and iRECIST and should include computed tomography (CT) scans of the chest and abdomen and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g., pelvis, brain) using an appropriate method (CT scan or magnetic resonance imaging [MRI]). 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 (see Section 5.1 for more detail). Assessments will be performed by the Investigator at screening and every 2 cycles (6 weeks -5 days) for the first 6 months of treatment, once every 3 cycles (9 weeks ±5 days) thereafter,

at the EOT visit (if not performed within the previous 4 weeks), and at the discretion of the Investigator. Baseline tumour assessments must be performed within 28 days before first drug intake.

i Pharmacokinetic (PK) sampling (blood and urine) will be done during Cycles 1 and 2. The visit days and sampling time points as outlined in the Appendix 10.3 tables are to be followed. The permitted visit windows noted in the table footnotes should only be used if medically indicated.

j Serum aliquot B samples for PK might be used for identification of metabolites at Days 1 (prior to treatment), 15, and 16 at the same time points as the PK samples. Details can be found in Section 5.3.2.3.

[redacted]

l Dosing of BI 891065 will be determined by the Safety Review Committee and communicated separately as each new cohort opens for recruitment. Patients will be observed after their first 3 doses of BI 891065 as outlined in Section 5.2.6.4.3. Patients will fast a minimum of 10 hours prior to select visits as outlined in Section 4.1.5.1. Patients should not take BI 891065 prior to certain visits that require pre-dose blood sampling as detailed in Table 10.3: 1.

m Dose-limiting toxicities (DLTs) will be collected throughout the trial and will be assessed for dose-escalation decisions following the first cycle of BI 891065 monotherapy (see Section 0).

n An EOT visit should be performed for all patients who permanently discontinue trial medication. If the decision to permanently discontinue treatment is taken at a scheduled visit, the EOT visit should be performed instead of the scheduled visit (preferably within 7 days and no later than 14 days after the last treatment). Please note that a patient with an initial radiologic PD does not have to be automatically withdrawn from treatment (see Section 3.3.4.1).

o The residual effect period (REP) starts after last dose of trial medication and ends 30 days later. A 30-day safety FU visit should take place before any other anti-cancer treatment starts.

p Follow-up for PD visits for tumour assessment by imaging (CT scan or MRI) for patients who discontinue trial treatment without having PD based on RECIST v1.1 and/or iRECIST should be performed every 6 weeks (±5 days) for the first 6 months of treatment and then every 9 weeks (±5 days) thereafter until PD or another withdrawal criterion is met (see Section 6.2.3.3). At these visits, serious adverse events (SAEs) and adverse events of special interest (AESIs) occurring during the trial that are considered to be related to trial treatment or procedures will be followed until resolution.

FLOW CHART: BI 1379.1 (REFMAL 505) PART B TRIAL ASSESSMENTS

Part B Flow Chart **Trial period**	**Screening**	**Part B Dose Escalation BI 891065 + BI 754091 Combination Treatment Period**									**EOT[p]**	**30-day Safety FU[q]**	**FU for PD[r]**
Cycle[a]		**C1**							**C2**	**C3+**			**Every 6 or 9 weeks**
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10+**			
Treatment day	**Up to 28 days[b]**	**1**	**2**	**8**	**12**	**15**	**16**	**17**	**1 (±2)**	**1 (±2)**		**+1 week**	**±5 days**
Informed consent	X												
Inclusion / exclusion criteria	X	X											
Medical history and demographics[c]	X												
Report planned hospitalisations	X												
Physical examination, height (screening only), and weight[c,d]	X	X				X			X	X	X	X	X
Vital signs[c,e]	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance score[c,d]	X	X							X	X	X	X	X
Electrocardiograms (single/triplicate)[c,e]	X	X	X			X	X		X	X	X		
Cardiac testing (only if cardiac disease suspected)[f]	X												
Serum pregnancy test[c,g]	X	X							X	X	X	X	
Safety laboratory (haematology, biochemistry)[c]	X	X			X	X			X	X	X		
Safety laboratory (amylase and lipase if symptoms of pancreatitis)		X							X	X	X		
Safety laboratory (coagulation)[c]	X	X							X	X	X		
Alpha-1 acid glycoprotein (AGP)		X							X				
Virology testing (≤28 days of treatment)	X												
Safety laboratory (urine)[c]	X	X			X	X			X	X	X		
Tumour assessment[c,h]	X	Every 6 weeks (then every 9 weeks after 6 months of treatment)									X		X
Blood sampling for BI 891065 pharmacokinetics[i]		X	X	X	X	X[j]	X[j]	X[j]	X				
Blood sampling for BI 754091 pharmacokinetics[i]		X	X	X	X	X	X	X	X	X	X	X	
Food administration for Food Interaction Assessment[j]							X						

Part B Flow Chart **Trial period**	**Screening**	**Part B Dose Escalation BI 891065 + BI 754091 Combination Treatment Period**									**EOT[p]**	**30-day Safety FU[q]**	**FU for PD[r]**
Cycle[a]		**C1**							**C2**	**C3+**			**Every 6 or 9 weeks**
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10+**			
Treatment day	**Up to 28 days[b]**	**1**	**2**	**8**	**12**	**15**	**16**	**17**	**1 (±2)**	**1 (±2)**		**+1 week**	**±5 days**
[redacted]													
Tumour biopsy (cIAP degradation)[m]	X								X				
BI 891065 intake[n]		X	X	X	X	X	X	X	X	X			
BI 754091 administration[n]		X							X	X			
Concomitant therapy	X	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	
Dose-limiting toxicity (DLT) assessment[o]		X	X	X	X	X	X	X	X	X	X		
SAEs/AESIs considered drug-related													X
Patient status												X	X
Review Patient Diary	X	X	X	X	X	X	X	X	X	X	X		

Part B Dose Escalation BI 891065 + BI 754091 Flow Chart Footnotes

a Treatment cycles (C) are 21 days (3 weeks). Patients may continue treatment with BI 891065 and BI 754091 as long as they are deriving benefit according to the Investigator's judgment. All circumstances for withdrawal of trial treatment are presented in Section 3.3.4.1.

b Screening should take place within 28 days of start of study treatment, however, may be extended as outlined in Section 6.2.1.1.

c Safety laboratory assessments including haematology, serum biochemistry, coagulation, serum pregnancy test, and urinalysis will be performed locally. The following screening parameters should be done ≤14 days prior to initiation of treatment: medical history and demographics, physical examination (including height and weight), Eastern Cooperative Oncology Group (ECOG) performance status, vital signs, electrocardiogram (ECG), haematology (per Section 5.2.3), clinical chemistry (sodium, potassium, phosphate, chloride, creatinine, calcium, venous bicarbonate HCO_3, albumin, total protein, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, total, direct and indirect bilirubin, lactate dehydrogenase, serum glucose, creatinine kinase [CK: if CK is elevated, then CK-MB, Troponin I/Troponin T, and myoglobin should be reactively tested, with further follow-up as clinically warranted], serum urea nitrogen, serum uric acid, and thyroid panel [TSH, free T4, and free T3]), urinalysis, and screening pregnancy test. If these assessments are performed within 72 hours of initiation of treatment, they do not need to be repeated on Cycle 1 Day 1 with the exception of the ECOG performance status, an abbreviated physical examination, vital signs, and single/triplicate ECGs as outlined in Section 5.2.4 and Table 10.3: 2 required prior to first administrations of trial treatments. Tumour assessments (scans) should be performed ≤28 days prior to initiation of treatment. Refer to Section 5.2.3 for additional details. Vital signs (blood pressure, body temperature, and pulse rate) are checked at every visit prior to blood work and trial treatment and at the discretion of the Investigator (see Section 5.2.2).

d Physical examinations including the measurements of height (screening only) and weight will be done at screening, on Day 1 of each treatment cycle, at the end-of-treatment (EOT) visit, at the 30-day safety follow-up (FU) visit, and at the FU visits for PD. However, patients will have an additional abbreviated physical examination (focused on the specific disease, at the Investigator's discretion) on Cycle 1 Day 15. ECOG performance status will be done at screening, on Day 1 of Cycles 1 and 2, on Day 1 of every other cycle beginning with Cycle 3, at the EOT visit, at the 30-day FU visit, and at FU visits for PD (see Section 5.2.1).

e Triplicate or single 12-lead electrocardiograms (ECGs) will be done at time points as outlined in Section 5.2.4 and Table 10.3: 2 and whenever the Investigator deems it necessary (see Section 5.2.4 and Table 10.3: 2). ECG machines will be provided for Part B to facilitate central readings. While all ECGs will be transmitted to the central vendor, only the baseline, 6-hour, 8-hour, and 24-hour (post BI 891065 dose) readings will be reviewed directly. The other readings will be analysed only after the PK analysis points to a t_{max}.

f Refer to Section 3.3.3 for details on which patients require cardiac testing (e.g., echocardiogram (ECHO)/multi-gated acquisition (MUGA) scan.

g Pregnancy tests are mandatory for women with child-bearing potential. A serum beta human chorionic gonadotropin (β-HCG) pregnancy test must be done with serum screening. Thereafter, this test can be done in either serum or urine on Day 1 of each cycle, at the EOT visit, and at the 30-day FU visit (see Section 5.2.3).

h Tumour assessments should be done according to RECIST v1.1 and iRECIST and should include computed tomography (CT) scans of the chest and abdomen and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g., pelvis, brain) using an appropriate method (CT scan or magnetic resonance imaging [MRI]). 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 (see Section 5.1 for more detail). Assessments will be performed by the Investigator at screening and every 2 cycles (6 weeks ±5 days) for the first 6 months of treatment, once every 3 cycles (9 weeks ±5 days) thereafter,

at the EOT visit (if not performed within the previous 4 weeks), and at the discretion of the Investigator. Baseline tumour assessments must be performed within 28 days before first drug intake.

i Pharmacokinetic (PK) blood sampling will be done during select treatment cycles. Please follow the visit days and sampling time points as outlined in the tables in Appendix 10.3. The permitted visit windows noted in the table footnotes should only be used if medically indicated. Please note that there are separate assays for determination of BI 891065 and BI 754091. Therefore, 2 tubes must be drawn at each time point, when appropriate.

j The effect of food will be tested in this part of the study until sufficient data is obtained. Only q.d. patients enrolled in Part B will participate in the food effect study. Please see Section 6.2.2.1 for details.

[redacted]

m The following tumour biopsies will be mandatory for all patients in the Part B dose-escalation portion 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.

n Dosing amounts, dosing frequency (e.g. b.i.d or q.d.) and escalations of the combination of BI 891065 + BI 754091 will be determined by the Safety Review Committee and communicated separately as each new cohort opens for recruitment. On BI 754091 infusion days, BI 891065 will be administered approximately 30 minutes after the end of the BI 754091 infusion. Patients will be observed after their dose of BI 891065 and BI 754091 given at Cycle 1 Day 1 (for 8 hours) and Cycle 2 Day 1 (for 6 hours) as outlined in Section 5.2.6.4.3. Patients will fast a minimum of 10 hours prior to select visits as outlined in Section 4.1.5.1. Patients should not take BI 891065 prior to certain visits that require pre-dose blood sampling as detailed in Table 10.3: 2 and Table 10.3: 3. For patients taking b.i.d. dosing, the evening dose should be skipped (Day 1 and Day 15 of Cycle 1). For all patients, the morning dose on Day 2 and Day 16 should be taken in the clinic (after pre-dose blood sampling is taken).

o Dose-limiting toxicities (DLTs) will be collected throughout the trial and will be assessed for dose-escalation decisions following the first cycle of BI 891065 plus BI 754091 combination therapy (see Section 0).

p An EOT visit should be performed for all patients who permanently discontinue trial medication. If the decision to permanently discontinue treatment is taken at a scheduled visit, the EOT visit should be performed instead of the scheduled visit (preferably within 7 days and no later than 14 days after the last treatment). Please note that a patient with an initial radiologic PD does not have to be automatically withdrawn from treatment (see Section 3.3.4.1).

q The residual effect period (REP) starts after last dose of trial medication and ends 30 days later. A 30-day safety FU visit should take place before any other anti-cancer treatment starts.

r Follow-up for PD visits for tumour assessment by imaging (CT or MRI) for patients who discontinue trial treatment without having PD based on RECIST v1.1 and/or iRECIST should be performed every 6 weeks (±5 days) for the first 6 months of treatment and then every 9 weeks (±5 days) thereafter until PD or another withdrawal criterion is met. At these visits, serious adverse events (SAEs) and adverse events of special interest (AESIs) occurring during the trial that are considered to be related to trial treatment or procedures will be followed until resolution.

FLOW CHART: BI 1379.1 (REFMAL 505) PART C (NSCLC) TRIAL ASSESSMENTS

Part C Lung Flow Chart **Trial period**	**Screening**	**Part C Dose Expansion in Patients with NSCLC BI 891065 + BI 754091 Combination Treatment**						**EOT[n]**	**30-day Safety FU[o]**	**FU for PD[p]**
Cycle[a]		**C1**					**C2+**			**Every 6 or 9 weeks**
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7+**			
Treatment day	**Up to 28 days[b]**	**1**	**2**	**8**	**15**	**16**	**1 (±2)**		**+1 week**	**±5 days**
Informed consent	X									
Inclusion / exclusion criteria	X	X								
Medical history and demographics	X									
Report planned hospitalisations	X									
Physical examination, height (screening only) and weight[c,d]	X	X			X		X	X	X	X
ECOG Performance score[c,d]	X	X					X	X	X	X
Vital signs[c]	X	X	X	X	X	X	X	X	X	
Electrocardiograms (single/triplicate)[c,e]	X (single)	X	X	X (single)	X	X	X (single)	X (single)		
Cardiac testing (only if cardiac disease suspected)[f]	X									
Serum pregnancy test[g]	X	X					X	X	X	
Safety laboratory (haematology, biochemistry)[c]	X	X					X	X		
Safety laboratory (amylase and lipase if symptoms of pancreatitis)		X					X	X	X	
Safety laboratory (coagulation)[c]	X	X					X	X		
Alpha-1 acid glycoprotein (AGP)		X					X (C2)			
Virology testing (≤28 days of treatment)	X									

Part C Lung Flow Chart **Trial period**	**Screening**	**Part C Dose Expansion in Patients with NSCLC BI 891065 + BI 754091 Combination Treatment**						**EOT[n]**	**30-day Safety FU[o]**	**FU for PD[p]**
Cycle[a]		**C1**					**C2+**			**Every 6 or 9 weeks**
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7+**			
Treatment day	**Up to 28 days[b]**	**1**	**2**	**8**	**15**	**16**	**1 (±2)**		**+1 week**	**±5 days**
Safety laboratory (urine)[c]	X	X					X	X		
Tumour assessment[c,h]	X	Every 6 weeks (then every 9 weeks after 6 months of treatment)						X		X
Blood sampling for BI 891065 pharmacokinetics[i]		X	X	X	X	X	X (C2 only)			
Blood sampling for BI 754091 pharmacokinetics[i]		X	X	X	X	X	X[i]	X	X	
[redacted]										
Tumour biopsy[l]	X						X (C3)	(X)		
BI 891065 intake [m]		X	X	X	X	X	X			
BI 754091 administration		X					X			
Concomitant therapy	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	
Dose-limiting toxicity (DLT) assessment		X		X	X		X	X		
SAEs/AESIs considered drug-related										X
Patient status									X	X
Review Patient Diary	X	X	X	X	X	X	X	X	X	X

Optional assessments are noted in parentheses. Please refer to the specific footnotes.

Part C Dose Expansion in Patients with NSCLC Flow Chart Footnotes

a Treatment cycles (C) are 21 days (3 weeks). Patients may continue treatment with BI 891065 and BI 754091 as long as they are deriving benefit according to the Investigator's judgment. All circumstances for withdrawal of trial treatment are presented in Section 3.3.4.1

b Screening should take place within 28 days of start of study treatment, however, may be extended as outlined in Section 6.2.1.1.

c Safety laboratory assessments including haematology, serum biochemistry, coagulation, serum pregnancy test, and urinalysis will be performed locally. The following screening parameters should be done ≤14 days prior to initiation of treatment: medical history and demographics, physical examination (including height and weight), Eastern Cooperative Oncology Group (ECOG) performance status, vital signs, electrocardiogram (ECG), haematology (per Section 5.2.3), clinical chemistry (sodium, potassium, phosphate, chloride, creatinine, calcium, venous bicarbonate HCO_3, albumin, total protein, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, total, direct and indirect bilirubin, lactate dehydrogenase, serum glucose, creatinine kinase [CK: if CK is elevated, then CK-MB, Troponin I/Troponin T, and myoglobin should be reactively tested, with further follow-up as clinically warranted], serum urea nitrogen, serum uric acid, and thyroid panel [TSH, free T4, and free T3]), urinalysis, and screening pregnancy test. If these assessments are performed within 72 hours of initiation of treatment, they do not need to be repeated on Cycle 1 Day 1 with the exception of the ECOG performance status, an abbreviated physical examination, vital signs, and single ECGs required prior to first administrations of trial treatments. Tumour assessments (scans) should be performed ≤28 days prior to initiation of treatment. Refer to Section 5.2.3 for additional details. Vital signs (blood pressure, body temperature, and pulse rate) are checked at every visit prior to blood work and trial treatment and at the discretion of the Investigator (see Section 5.2.2).

d Physical examinations including the measurements of height (screening only) and weight will be done at screening, on Day 1 of each treatment cycle, at the end-of-treatment (EOT) visit, at the 30-day safety follow-up (FU) visit, and at the FU visits for PD. However, patients will have an additional abbreviated physical examination (focused on the specific disease, at the Investigator's discretion) on Cycle 1 Day 15. ECOG performance status will be done at screening, on Day 1 of Cycles 1 and 2, on Day 1 of every other cycle beginning with Cycle 3, at the EOT visit, at the 30-day FU visit, and at FU visits for PD (see Section 5.2.1).

e Triplicate electrocardiograms (ECGs) are required in connection with pharmacokinetic sample collection as outlined in Table 10.3: 3. When triplicate ECGs are not done, single 12-lead ECGs will be done per the flow chart above for safety purposes at screening, on Cycle 1 Day 8, on Day 1 of each additional cycle, at the EOT visit, and whenever the Investigator deems it necessary (see Section 5.2.4).

f Refer to Section 3.3.3 for details on which patients require cardiac testing (e.g., echocardiogram (ECHO)/multi-gated acquisition (MUGA) scan.

g Pregnancy tests are mandatory for women with child-bearing potential. A serum beta human chorionic gonadotropin (β-HCG) pregnancy test must be done with serum at screening. Thereafter, this test can be done in either serum or urine on Day 1 of each cycle, at the EOT visit, and at the 30-day FU visit (see Section 5.2.3).

h Tumour assessments should be done according to RECIST v1.1 and iRECIST and should include computed tomography (CT) scans of the chest and abdomen and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g., pelvis, brain) using an appropriate method (CT scan or magnetic resonance imaging [MRI]). 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 (see Section 5.1 for more detail). Assessments will be performed by the Investigator at screening and every 2 cycles (6 weeks ±5 days) for the first 6 months of treatment, once every 3 cycles (9 weeks ±5 days) thereafter, at the EOT visit (if not performed within the previous 4 weeks), and at the discretion of the Investigator. Baseline tumour assessments must be performed within 28 days before first drug intake.

i Pharmacokinetic (PK) blood sampling will be done during select treatment cycles. Please follow the visit days and sampling time points as outlined in Table 10.3: 3. The permitted visit windows noted in the table footnotes should only be used if medically indicated. Please note that there are separate assays for determination of BI 891065 and BI 754091. Therefore, 2 tubes must be drawn at each time point.

[redacted]

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

- The equivalent of two 14-16G needle biopsies must be freshly taken between screening and the day before the first trial drug treatment. If archival formalin-fixed paraffin-embedded (FFPE) tumour material is available that is not older than 6 months, 26 4-5µm sections would be acceptable as well.
- The equivalent of two 14-16G needle biopsies on treatment at the beginning of Cycle 3 (i.e., after 6 weeks of treatment). If possible the biopsy should be collected from the same lesion as the pre-treatment biopsies. In case study drug was interrupted for 3 weeks or longer, consult with the Sponsor regarding whether or not to delay the biopsy.
- Another biopsy (optional) should be taken upon PD (according to RECIST v1.1 and iRECIST), if possible (see Section 5.4.2.3).

m Patients should not take BI 891065 prior to certain visits that require pre-dose blood sampling as detailed in Table 10.3: 4. Patients could be assigned q.d. or b.i.d. dosing. For patients taking b.i.d. dosing, the evening dose on infusion days should be skipped (Day 1 and Day 15 of Cycle 1). For all patients, the morning dose on Day 2 and Day 16 should be taken in the clinic (after pre-dose blood sampling is taken). On BI 754091 infusion days, BI 891065 will be administered approximately 30 minutes after the end of the BI 754091 infusion.. Patients will be observed after their first dose of BI 891065 on Cycle 1 Day 1 and Cycle 2 Day 2 for 4 hours as outlined in Section 5.2.6.4.3.

n An EOT visit should be performed for all patients who permanently discontinue trial medication. If the decision to permanently discontinue treatment is taken at a scheduled visit, the EOT visit should be performed instead of the scheduled visit (preferably within 7 days and no later than 14 days after the last treatment). Please note that a patient with an initial radiologic PD does not have to be automatically withdrawn from treatment (see Section 3.3.4.1).

o The residual effect period starts after last dose of trial medication and ends 30 days later. A 30-day safety FU visit should take place before any other anti-cancer treatment starts.

p Follow-up for PD visits for tumour assessment by imaging (CT or MRI) for patients who discontinue trial treatment without having PD based on RECIST v1.1 and/or iRECIST should be performed every 6 weeks (±5 days) for the first 6 months of treatment and then every 9 weeks (±5 days) thereafter until PD or another withdrawal criterion is met At these visits, serious adverse events (SAEs) and adverse events of special interest (AESIs) occurring during the trial that are considered to be related to trial treatment or procedures will be followed until resolution.

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ABBREVIATIONS

ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
AGP	Alpha-1 acid glycoprotein
ALT	Alanine transaminase
AST	Aspartate aminotransferase
AUC	Area under the curve
β-HCG	Beta human chorionic gonadotropin
BI	Boehringer Ingelheim
b.i.d.	Twice a day
BLRM	Bayesian Logistic Regression Model
cIAP	Cellular inhibitor of apoptosis
CK	Creatinine kinase
CK-MB	Creatinine kinase - cardiac muscle subunit
C_{max}	Maximum measured plasma concentration
CNS	Central nervous system
C_{pre}	Pre-dose plasma concentration
CR	Complete response
CRF	Case report form
CRS	Cytokine release syndrome
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical trial protocol
CYP	Cytochrome P450
DILI	Drug-induced-liver-injury
DLT	Dose-limiting toxicities
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOT	End of treatment
EudraCT	European Clinical Trials Database
EWOC	Escalation with overdose control
FACS	Fluorescence activated cell sorting
FDA	Food and Drug Administration
FLC	Serum free light chain
FU	Follow up
G	Gauge
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIV	Human immunodeficiency virus
IAP	Inhibitor of apoptosis
ICH	International Conference of Harmonization
i.e.	*Id est*

IMiD	Immunomodulator
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
ISF	Investigator site file
i.v.	Intravenous
mAb	Monoclonal antibody
MDSC	Myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multi-gated acquisition scan
NIH	National Cancer Institute
NSCLC	Non-small cell lung cancer
OR	Objective response
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PDc	Pharmacodynamics
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PFS	Progression-free survival
PK	Pharmacokinetics
p.o.	*Per os* (oral)
PR	Partial response
q.d.	Once a day
RECIST	Response Evaluation Criteria in Solid Tumors
REP	Residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
ROS1	ROS Proto-Oncogene 1
SAE	Serious adverse event
sCR	Stringent complete response
[redacted]	
SRC	Safety Review Committee
TLS	Tumour lysis syndrome
TNFα	Tumour necrosis factor alpha
$t_{1/2}$	Terminal half-life
TSAP	Trial Statistical Analysis Plan
ULN	Upper limit of normal
US	United States
VGPR	Very good partial response
XIAP	X-linked inhibitor of apoptosis protein

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Despite the recent advancements in cancer treatment, cancer remains a leading cause of death globally. In the United States (US), approximately 1,685,210 new cancer cases were expected to be diagnosed in 2016. The American Cancer Society estimated that there would be approximately 595,000 deaths due to cancer in the US during 2016 (R16-4925). The type of cancer chosen for the expansion cohort in this trial is non-small-cell lung cancer (NSCLC).

Non small-cell lung cancer

Lung cancer remains the most common cancer in the world. In the US, the American Cancer Society estimated that approximately 224,390 new cases of lung cancer and 158,080 deaths from lung cancer were expected in 2016 (P16-11525). The most prevalent (80% to 85%) of all lung cancers is NSCLC. At initial diagnosis, 55% of patients have distant spread of disease (R16-4724). According to the US National Cancer Institute (NIH), the 5-year relative survival of distant stage disease is 4.9% (R16-4740). Real-world data (FRAME study [R16-3671]), has shown median overall survival (OS) in patients with advanced or metastatic NSCLC of 10.3 months. This is in the range (7.4 to 11.8 months) obtained from Phase III studies (R04-1314; R08-4164; R12-3987; R07-4508).

Treatment of advanced stage NSCLC is changing at the moment. Pembrolizumab was approved that year by the Food and Drug Administration (FDA) for 1st-line treatment of patients with metastatic NSCLC with high levels of programmed cell death protein ligand 1 (PD-L1) (tumour proportion score ≥50%) (R16-5013). First-line treatment of patients with advanced NSCLC who are not pembrolizumab candidates consists of 4 to 6 cycles of platinum-based chemotherapy. The 2nd line treatment of NSCLC has also been markedly transformed by the introduction of PD-1/PD-L1 immune checkpoint inhibitor monoclonal antibodies (mAbs) (nivolumab, durvalumab and atezolizumab in addition to pembrolizumab). Treatment of patients with advanced NSCLC with nivolumab, pembrolizumab, or atezolizumab monotherapy results in very durable responses in approximately 15% to 20% of patients (R15-3715; R15-6023; R16-0876).

[redacted]

[redacted]

1.2 DRUG PROFILES

1.2.1 BI 891065 [redacted]

[redacted]

[redacted]

1.2.2 BI 754091 [redacted]

[redacted]

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

[redacted]

[redacted]

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

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 patients with advanced or metastatic malignancies. 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 of BI generated evidence of a tumour regression effect of the combination of [redacted] BI 891065 and [redacted]

This trial is the first study with BI 891065 monotherapy as well as BI 891065 in combination with BI 754091 in humans and will consist of 3 parts:

- Part A: Dose escalation of BI 891065 as monotherapy, followed by
- Part B: Dose escalation of BI 891065 in combination with BI 754091, followed by
- Part C: An expansion phase of BI 891065 in combination with BI 754091 in the selected indication.

Parts A and B of the trial will be undertaken in patients with advanced/refractory solid tumours. Part A will determine the MTD and/or the recommended dose for Part B as well as investigate the safety, PK, and pharmacodynamics (PDc) of BI 891065 monotherapy. Target engagement will be determined in peripheral blood [redacted] Dose escalation in Part A will be guided by a BLRM with overdose control. The data obtained from the trial will determine the MTD estimate based on a BLRM employing an escalation with overdose control (EWOC) principle (R13-4803). The BLRM estimates the MTD by updating estimates of the probability of observing a DLT in the MTD evaluation period (first treatment cycle) 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 criterion (refer to Section 7).

In both Parts A and B, the Safety Review Committee (SRC) will recommend and decide on the size for the next dose escalation cohort. After all patients in a cohort in Part A and Part B

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.

Part C will be in the selected indication (NSCLC) in order to assess efficacy (objective response [OR]) and reconfirm safety and tolerability at the combination doses determined in Part B.

The therapeutic benefit or specific adverse events in patients cannot always be anticipated during the trial setup. Later on, there may be new scientific knowledge about biomarkers and other factors contributing to diseases or the action of a drug. In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking.

1.4 BENEFIT - RISK ASSESSMENT

BI 891065 and BI 754091 inhibit tumour growth and induce tumour regression in pre-clinical models. BI 891065 has not yet been studied in humans, and BI 754091 is currently being assessed in a first-in-human trial. 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 a clinical benefit in cancer patients.

Only a minimum number of patients should be exposed to doses of BI 891065 that are presumed to be below the threshold of activity. Therefore, a Bayesian Logistic Regression Model (BLRM) design will be used 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. For Part B, to ensure patient safety, the starting dose of BI 891065 when combined with BI 754091 will not be higher than 75% of the BI 891065 MTD/ recommended dose for further development defined in Part A. For more details of the selection of doses, please refer to Section 4.1.2.

Since this is the first-in-human trial for BI 891065, patients in Part A will remain under surveillance for 10 hours after first administrations of BI 891065 and for at least 8 hours after administration of the second and third administrations of BI 891065. For Part B, patients will remain under surveillance after the administration of BI 891065 in combination with BI 754091 for 8 hours after the first dose of BI 891065 in Cycle 1, and then for 6 hours after the first dose of BI 891065 in Cycle 2. For Part C, patients will remain under surveillance for 4 hours after the first dose of BI 891065 in both Cycle 1 and Cycle 2 (see Section 5.2.6.4.3). All trial sites will have emergency resuscitation services and access to intensive care available.

Specific attention will be given to symptoms of immune-mediated events (see Appendix 10.1), infusion-related reactions (see Section 5.2.6.4.2), and cytokine release syndrome (CRS; see Section 5.2.6.4.3). 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 (see Section 5.2.6.7). Safety data from trials

1381.1 and 1381.2 will also be integrated in the safety assessments for the combination of the compounds.

Previous anti-PD-l mAbs have been associated in the clinical setting with inflammatory adverse reactions resulting from increased or excessive immune activity (irAEs), likely to be related to the mechanism of action. These adverse reactions, which can be severe, may involve the gastrointestinal, skin, liver, endocrine, respiratory, renal, or other organ systems.

The assessment of biomarkers in tumour tissue in Part B and Part C is important for clinical development (see Section 5.4). Only patients with at least 1 tumour lesion amenable to biopsy will be enrolled in Part B and Part C (see Section 3.3.2).

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

A Safety Review Committee (SRC) will be responsible for the continuous assessment of the trial data to ensure overall safety of the patients treated. Based on the models and on additional information (patient profiles), the members of the SRC will reach a joint recommendation on the next dose level of BI 891065 and/or of the dose combination to be investigated and the size for the next dose-escalation cohort. They will also provide the Investigators and the Sponsor with advice about the conduct of the trial and the integrity of the data (see Section 8.7).

In summary, the present trial will implement a number of safety measures to mitigate possible risks. Therefore, a potential benefit is offered to patients with advanced and/or metastatic malignancies [redacted] Treatment with both compounds is expected 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 main objective of the dose-escalation parts of the trial is to determine the maximum tolerated dose (MTD), based on the frequency of patients experiencing dose-limiting toxicities (DLTs), and/or the recommended dose for further development of BI 891065 monotherapy as well as of BI 891065 in combination with BI 754091, and to evaluate its safety and tolerability by monitoring the occurrence and severity of adverse events (AEs).

Secondary objectives are the determination of the pharmacokinetic (PK) profile of BI 891065 monotherapy as well as of BI 891065 in combination with BI 754091, and the preliminary assessment of anti-tumour activity.

In the expansion cohort of the trial, the main objectives are to assess efficacy and to further assess the safety, PK, and PDc profiles at the investigated dose level.

2.1.2 Primary endpoints

2.1.2.1 Part A

The primary endpoints for Part A of the trial are the MTD of BI 891065 and the number of patients with DLTs during the first treatment cycle. The MTD is defined as the highest dose with less than 25% risk of the true DLT rate being equal to or above 33%.

The primary endpoints of this part will be evaluated based on a timeframe from first treatment administration until the end of the MTD evaluation period (the end of the first cycle).

For doses below 25 mg, single patient cohorts will be treated at 5 mg and 15 mg if not specified otherwise by the SRC. A BLRM employing the EWOC principle will be used during the escalation phase for selection of doses to investigate and for estimation of the MTD. Cohorts of patients will receive escalating doses of BI 891065 until the MTD is reached or the highest possible dose has been tested. Each cohort will consist of newly enrolled patients. Estimation of the MTD during the escalation phase of the trial will be based upon the estimation of the probability of a DLT in Cycle 1 in the set of evaluable patients (where evaluable patients refer to patients not fulfilling the criteria for replacement [Section 3.3.4.4]) for the MTD. The corresponding methodology is described in Section 7 and in the statistical appendix (see Appendix 10.5). The MTD estimate established during the dose escalation of Part A will be re-investigated at the end of Part A by re-running the BLRM using the DLT information from all treatment cycles to determine the recommended dose range for Part B.

2.1.2.2 Part B

The primary endpoints for Part B of the trial are the MTD of BI 891065 in combination with BI 754091 and the number of patients with DLTs during the first treatment cycle. Q.D. and b.i.d. dosing schedules may be explored in Part B. The MTD is defined as the highest dose combination with less than 25% risk of the true DLT rate being equal to or above 33%.

The primary endpoints of this part will be evaluated based on a timeframe from first treatment administration until the end of the MTD evaluation period (the end of the first cycle).

Another BLRM employing the EWOC principle will be used during the escalation phase for selection of dose combinations and for estimation of the MTD. It is planned that cohorts of patients will receive escalating doses of BI 891065 in combination with BI 754091 (at the dose pre-specified by the SRC) until the MTD is reached or the highest tolerated dose of BI 891065 determined in Part A has been tested. Each cohort will consist of newly enrolled patients. Estimation of the MTD during the combination escalation phase of the trial will be based upon the estimation of the probability of a DLT in Cycle 1 in the set of evaluable

patients for MTD. The corresponding methodology is described in Section 7 and in the statistical appendix (see Appendix 10.5). The MTD estimate established during the dose escalation of Part B will be re-investigated at the end of Part B by re-running the BLRM using the DLT information from all treatment cycles to determine the recommended dose combination for further development.

2.1.2.3 Part C (NSCLC)

The dose of each of the study drugs used for Part C will be determined from the data of Parts A and B.

The primary endpoint is OR by Investigator's assessments.

For patients with NSCLC, OR is defined as best overall response of CR or partial response (PR), where best overall response is determined according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 from the start of treatment until the earliest of PD, death or last evaluable tumour assessment before start of subsequent anti-cancer therapy.

Tumour imaging will be performed at baseline and then every 6 weeks for the first 6 months and then every 9 weeks thereafter as required by RECIST / iRECIST (R17-0923) until the earliest of PD, death or the last evaluable tumour assessment before start of subsequent anti-cancer therapy or until the end of the trial as defined in Section 8.6.

2.1.3 Secondary endpoints

The secondary endpoints in this trial are:

<u>For Part A</u>
- The number of patients with DLTs observed during the entire treatment period.
- $C_{max,ss}$, $AUC_{0\text{-}tz}$ and $AUC_{\tau,ss}$ of BI 891065 in the first treatment cycle.
- OR based on RECIST v1.1.

<u>For Part B</u>
- The number of patients with DLTs observed during the entire treatment period.
- $C_{max,ss}$, $AUC_{0\text{-}tz}$ and $AUC_{\tau,ss}$ of BI 891065; C_{max} and $AUC_{0\text{-}tz}$ of BI 754091 in the first treatment cycle.
- OR based on RECIST v1.1.

<u>For Part C</u>
- Duration of OR based on RECIST 1.1 defined as the time from first documented CR or PR until the earliest of PD or death among patients with OR.

For all three parts, the first treatment cycle, used as the analysis period for the PK endpoints, relates to the time frame from start of treatment until 3 weeks after start of treatment. All other secondary endpoints will be analysed based on the entire treatment period. This relates to the timeframe from start of treatment until 30 days after last trial medication.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is an open-label, first-in-human, Phase I dose-finding trial with BI 891065 as monotherapy and in combination with BI 754091 to characterise safety, tolerability, PK/PDc, and preliminary efficacy in patients with advanced and/or metastatic malignancies.

Part A of the trial will include patients with advanced/refractory solid tumours to determine the MTD and/or the recommended dose for Part B as well as to investigate the safety, PK, and PDc of BI 891065 monotherapy. Target engagement will be determined in peripheral blood (cIAP degradation in PBMCs). The data obtained from the trial will determine the

MTD estimate based on a BLRM employing the EWOC principle (R13-4803). The BLRM estimates the MTD by updating estimates of the probability of observing a DLT in the MTD evaluation period (first treatment cycle) 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 criterion (refer to Section 7). Dose-escalation will in addition be restricted to a maximum of 100% from the previous dose for any dose ≥15 mg BI 891065 (see Section 4.1.3). Successive cohorts of patients will receive increasing or decreasing doses of BI 891065 until the MTD is reached; the maximum dose level planned is 400 mg. For any dose-escalation cohort >15 mg BI 891065, at least 3 patients will be required (refer to Section 7). However, in the case that only 2 patients are evaluable for the MTD and neither has experienced a DLT within the MTD evaluation period, then dose-escalation can occur based on these 2 patients. Additional patients on the same dose level will not start treatment before the previous patient has received the first dose for 2 days.

Part B will be a dose escalation of BI 891065 in combination with a dose of 240 mg BI 754091 once every 3 weeks (the dose used for the expansion portion of Trial 1381.1). While it is planned that this dose will be stable, under exceptional circumstances changes may be made by the SRC. Should it be decided that a different starting dose of BI 754091 is warranted in the combination with BI 891065, this BI 754091 dose is not to exceed the highest dose assessed as safe for BI 754091 monotherapy, and in any case must not exceed 2000 mg for the single dose (technical limit). Patients with select advanced/refractory solid tumours without established treatment options will be entered in order to determine the MTD and/or recommended dose for the expansion cohort in Part C of BI 891065 in combination with BI 754091, to assess safety and tolerability, and to explore PK/PDc. Target engagement of BI 891065 in combination with BI 754091 will be investigated in tumours (cIAP degradation in tumour tissue).

The starting dose of BI 891065 for Part B will be defined based on the safety and PK/PDc observations in Part A. If an MTD is identified in Part A, the starting dose of BI 891065 for Part B will be ≤75% of the MTD. If no MTD is identified, but target engagement is confirmed by cIAP degradation in PBMCs, the starting dose of BI 891065 for Part B will be ≤75% of the highest tolerated dose of Part A. Dose escalation in Part B will be guided by a BLRM with overdose control. Escalation of BI 891065 will be restricted to a maximum of 100% from the previous dose. Successive cohorts of patients will receive increasing or decreasing doses of BI 891065 in combination with BI 754091 until the MTD of the combination is reached. The maximum dose level of BI 891065 in Part B is the highest tolerated dose from Part A. For any combination dose-escalation cohort, at least 3 patients will be required (refer to Section 7). However, in the case that only 2 patients are evaluable for the MTD and neither has experienced a DLT within the MTD evaluation period, then dose-escalation can occur based on these 2 patients. Based on the model and on additional information (patient profiles, cumulative safety outputs), the members of the SRC will reach a joint recommendation on the next dose level of BI 891065 and of the dose combination to be investigated and the size for the next dose-escalation cohort.

In both Parts A and B, the SRC will recommend and decide on the size for the next dose escalation cohort. After all patients in a cohort in Part A and Part B 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 (dose combinations in Part B) which fulfil the EWOC criterion and the additional maximum 100% escalation rule. Based on the model and on additional information (e.g., PK, PDc, patient profiles, cumulative safety outputs), the members of the SRC will reach a joint decision on the next dose level to be investigated.

For dose levels above 15 mg, if DLTs are observed in the first two consecutive patients of a previously untested dose level, subsequent enrolment to that cohort will be stopped. The BLRM will be re-run to confirm that the dose level still fulfils the EWOC principle. Based on this information, the SRC will evaluate whether the next patients will be enrolled at the same dose level, or if they will be enrolled at a lower dose level.

The SRC may recommend stopping the dose-finding phase after the criterion for MTD (see Section 7) is fulfilled. Further patients may be included to confirm this MTD estimate (i.e., to confirm that the EWOC criterion is still fulfilled). If no DLT is observed at a dose of which the efficacy is considered sufficient, the SRC may decide to include an additional number of patients at the same dose level and to declare this dose as the recommended dose for further development. The SRC can declare any dose fulfilling the EWOC criterion as recommended dose for further development, independent of the MTD estimate.

Once the combination dose is determined (to be confirmed by the Sponsor), the Part C expansion cohort will be initiated in patients with NSCLC who failed an anti-PD-1/anti-PD-L1 treatment as a first-line therapy, either by itself or in combination with platinum-based therapy (see Section 3.3.2). In Part C, the SRC will assess the safety data and trial conduct in regular intervals as described in the SRC documentation. In addition, Part C will further evaluate the efficacy of the combined compounds. The trial design is displayed in Figure 3.1: 1.

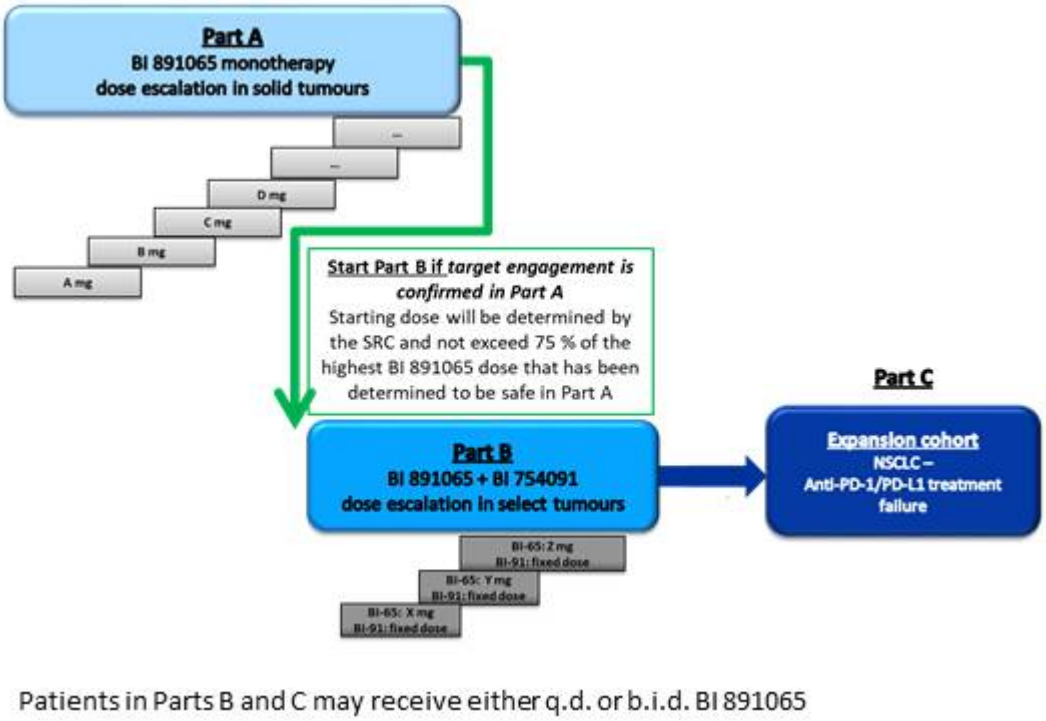


Figure 3.1: 1 Design of trial 1379.1 including 2 dose-escalation parts and 1 expansion cohort

Patients will continue treatment as long as they are deriving clinical benefit in the opinion of the Investigator, or until withdrawal of consent, occurrence of unacceptable toxicity, or for additional reasons detailed in Section 3.3.4.1.

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

The primary objective of this trial is to determine the MTD and/or the dose for later development of BI 891065 monotherapy as well as of BI 891065 in combination with BI 754091 and to confirm the selected combination dose for an expansion cohort. The open dose-escalation design will allow an assessment of the safety of BI 891065 monotherapy as well as in combination with BI 754091 in this first-in-human trial. Given the objectives of this trial, a placebo treatment group is not included.

Dose escalation and cohort size will be determined based on the recommendation of the SRC, guided by BLRMs with overdose control (one for monotherapy and one for combination therapy). An escalation with overdose control design will increase the chance of treating patients at efficacious doses while reducing the risk of overdosing. This design is based on practical experience and is an efficient method due to its ability to identify the dose with a desired toxicity rate and its allocation of a greater proportion of patients to doses at, or close to, that desired dose (R13-4802; R13-4804; R13-4805). The use of BLRMs for Phase I

studies has also been advocated by the EMA guideline on small populations (R07-4856) and by the FDA (R13-4881).

Part A will be focused on BI 891065 monotherapy to provide the first safety data that can be implemented in Part B of the trial where BI 891065 will be combined with BI 754091. Observations from Part A and Part B then can be integrated in Part C where patients in an expansion cohort will be treated with the combination of BI 891065 plus BI 754091. An SRC will also evaluate safety aspects in all expansion cohorts.

3.3 SELECTION OF TRIAL POPULATION

Approximately 60 patients (total) are planned to be included in the dose-escalation parts (Part A and Part B), and approximately 44 patients are planned in the dose-expansion cohort (Part C) of this international multi-centre trial.

A log of all patients enrolled into the trial (i.e., who have signed an informed consent form [ICF]) will be maintained in the Investigator site file (ISF) at the investigational site irrespective of whether or not they have been treated with investigational drug. Relevant data for all patients enrolled in the trial will be entered in the electronic Case Report Form (eCRF).

3.3.1 Main diagnosis for trial entry

Part A: 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.

Part B: Patients with a confirmed diagnosis of advanced, unresectable and/or metastatic cancers who have failed standard treatment, or for whom no therapy of proven efficacy exists, or who are not amenable to standard therapies. Eligibility is limited to patients with the following cancer types: bladder, colon, breast, NSCLC, ovarian, pancreatic, renal, esophagogastric, sarcoma, prostate, and melanoma.

Part C (NSCLC): Patients with metastatic NSCLC who developed disease progression (per RECIST v1.1) after the first scan (where SD, PR, or CR was demonstrated at the first scan), and require new anti-cancer therapy after first-line treatment with an anti PD-1/anti PD-L1 mAb (given either as single agent therapy or in combination with a platinum-based chemotherapy regimen).

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

3.3.2 Inclusion criteria

1. Provision of signed and dated, written ICF in accordance with ICH-GCP and local legislation prior to any trial-specific procedures, sampling, or analyses
2. Patients ≥18 years-of-age at the time of signature of the ICF

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 (that result in a low failure rate of less than 1% per year when used consistently and correctly) during trial participation and for at least 6 months after the last administration of trial medication. A list of contraception methods meeting these criteria is provided in the patient information.
4. Eastern Cooperative Oncology Group (ECOG) score: 0 or 1
5. Life expectancy of at least 12 weeks after the start of the treatment according to the Investigator's judgement
6. For Parts A and B: 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. Measurable lesions according to RECIST Version 1.1 must be present. Eligibility is limited to the following tumour subtypes in Part B: bladder, colon, breast, NSCLC, ovarian, pancreatic, renal, esophagogastric, sarcoma, prostate, and melanoma.
7. For Parts B and C: Patients must have measurable disease per RECIST v1.1, must have at least 1 tumour lesion amenable to biopsy, and must be willing to undergo a biopsy prior to first treatment and another biopsy while on therapy unless clinically contraindicated.
8. For Part C: Patients with metastatic NSCLC who developed disease progression (per RECIST v1.1) after the first scan (where SD, PR, or CR was demonstrated at the first scan), and require new anti-cancer therapy after first-line treatment with an anti PD-1/anti PD-L1 mAb (given either as single agent therapy or in combination with a platinum-based chemotherapy regimen).

3.3.3 Exclusion criteria

1. Major surgery (major according to the Investigator's and/or Medical Monitor's assessment) performed within 12 weeks prior to randomization or planned within 12 months after screening (e.g., hip replacement)
2. Presence of other active invasive cancers other than the one treated in this trial within 5 years prior to screening, except 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 (see Section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial
4. Previous administration of BI 891065 or BI 754091
5. Currently enrolled in another investigational device or drug trial, or less than 30 days since ending another investigational device or drug trial(s), or receiving other investigational treatments.

[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.

6. Patients who have been treated with any other anticancer drug within 4 weeks or within 5 half-life periods (whichever come earlier) prior to first administration of BI 891065. At least 7 days must have elapsed between the last dose of such agent and the first dose of study drug.
7. Persistent toxicity from previous treatments that has not resolved to ≤ Grade 1 (except for alopecia and Grade 2 neuropathy due to prior platinum-based therapy)
8. Active, known or suspected autoimmune disease except vitiligo or resolved asthma/atopy
9. Interstitial lung disease
10. Any of the following cardiac criteria:
    - Mean resting corrected QT interval (QTcF) >470 msec
    - Any clinically important abnormalities (as assessed by the investigator) in rhythm, conduction, or morphology of resting 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) <55% or the lower limit of normal of the institutional standard will be excluded. 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. Out of range laboratory values are defined as:
    - Alanine transaminase (ALT) and aspartate amino transferase (AST) >3 times the ULN if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases
    - 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
12. Human immunodeficiency virus (HIV) infection, acute or chronic viral hepatitis
13. Known hypersensitivity to the trial drugs or their excipients
14. 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 and/or Medical Monitor would make the patient inappropriate for entry into the trial.
15. Chronic alcohol or drug abuse or any condition that, in the Investigator’s and/or Medical Monitor’s opinion, makes them an unreliable trial patient or unlikely to complete the trial
16. Women who are pregnant, nursing, or who plan to become pregnant while in the trial and for at least 6 months after the last administration of trial medication.

17. Men who plan to father a child while in the trial and for at least 6 months after the last administration of trial medication.
18. Known presence of symptomatic central nervous system (CNS) metastases, unless asymptomatic and off corticosteroids and/or anti-convulsant therapy for at least 2 weeks prior start of treatment. Patients with asymptomatic CNS metastases may be enrolled following a 2-week washout period.
19. Patients receiving systemic treatment with any immunosuppressive medication within 1 week prior treatment start (steroids of max. 10 mg prednisolone equivalent per day are allowed, topical and inhaled steroids are not considered as immunosuppressive).
20. For Parts A and B: Patients with known epidermal growth factor receptor (EGFR), known anaplastic lymphoma kinase (ALK), or known ROS Proto-Oncogene 1 (ROS1) genomic tumour aberrations, unless disease has progressed following available EGFR or ALK targeted therapy (including osimertinib for EGFR T790M-mutated NSCLC)
21. Out of range lab values as defined:
    - Absolute neutrophil count (ANC) <1.5 x 10^9/L (<1500/mm^3)
    - Platelet (PLT) count <100 x 10^9/L
    - Haemoglobin <90 g/L (<9 g/dL)
    - Creatinine >1.5 times ULN (patients may enter if creatinine is >1.5 x ULN and estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m^2) (Chronic Kidney Disease Epidemiology [CKD-EPI] Collaboration equation); confirmation of eGFR is only required when creatinine is >1.5 X ULN.
22. For Part C: Patients with EGFR, ALK, or (if known) ROS1 genomic tumour aberrations
23. For Part C: Patients with any CTLA-4 therapy
24. For Part C: One or more lines of anti-cancer therapy between previous anti-PD-1/anti-PD-L1 mAb therapy and study entry.

3.3.4 Withdrawal of patients from therapy or assessments

Patients may potentially be withdrawn from trial treatment or from the trial as a whole ("withdrawal of consent") with very different ramifications. Please see Section 3.3.4.1 and Section 3.3.4.2, respectively.

Every effort should be made to keep the entered 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 entering the trial, as well as the explanation of the consequences of withdrawal. The decision to withdraw from trial treatment or from the whole trial as well as the reason must be documented in the patient files and CRF.

3.3.4.1 Withdrawal from trial treatment

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

- The patient wants to withdraw from trial treatment, without the need to justify the decision.
- The patient needs to take concomitant drugs that interfere with the investigational product or other trial medication.

- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy [see Section 5.2.6.8]).
- The patient has been non-compliant with important trial procedures and, in the opinion of both, the Investigator and Sponsor representative, is not willing or able to stick to the trial requirements in the future.
- Recurring radiologic progression. Note: In the case of initial radiological PD, patients will be allowed to stay on treatment if the following criteria are met:
  - The Investigator feels that it is in the patient's best interest
  - The patient signed an informed consent form specific for this circumstance after acknowledging that this practice is not considered standard in the treatment of cancer. The specific informed consent process for this circumstance includes discussion of alternative treatment options, including any available approved therapies (if applicable) and participation in alternative clinical trials.
  - Absence of clinical symptoms or signs indicating clinically significant PD
  - No decline in performance status
  - Absence of rapid PD or threat to vital organs or critical anatomical sites (e.g., central nervous system metastasis, respiratory failure due to tumour compression, spinal cord compression) requiring urgent alternative medical intervention
  - No significant, unacceptable, or irreversible toxicities related to study treatment.
- A pause of treatment or delayed start of treatment of more than 12 weeks due to SAEs/AEs
- The following adverse event(s) occur:
  - Cytokine release syndrome CTCAE Version 5.0 (R18-1357) Grade 3 or 4
  - Immune related AEs requiring permanent study drug discontinuation as described in Guidelines for Management of Immune-Related AEs (Appendix 10.2):
    - Grade 3 to 4 pneumonitis
    - Grade 3 to 4 adrenal insufficiency
    - Grade 4 diabetes mellitus
    - Any grade encephalitis
    - Grade 4 hypophysitis
    - Grade 4 rash
    - Grade 3 to 4 colitis or recurrent colitis of any grade
    - Any recurrent Grade 3 to 4 AE
    - Transaminase increases >5 times ULN or total bilirubin >3 times ULN
    - Inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks
    - SAEs/AEs of Grade ≥2 deemed intolerable by the patient or the treating physician and not responding to medical management and any SAEs/AEs of ≥Grade 3 that do not recover to Grade 1 or less within 12 weeks
    - Persistent Grade 2-3 AEs that do not recover to Grade 1 or less within 12 weeks
    - Grade 3 to 4 AEs that are classified as immune-related by the Investigator but are not listed in Appendix 10.1 if they do not resolve to Grade ≤ 1 or baseline with immunosuppressive therapy within 2 weeks.

- ≥Grade 4 drug-related AEs.

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and will be followed up as outlined in Part A Flow Chart, Part B Flow Chart, Part C Lung Flow Chart, and Section 6.2.3.1. For all patients the reason for withdrawal from trial treatment (e.g., adverse events) must be recorded in the CRF. These data will be included in the trial database and reported.

3.3.4.2 Withdrawal of consent for trial participation

Patients may withdraw their consent for trial participation at any time without the need to justify the decision. This will however mean that no further information may be collected for the purpose of the trial and negative implications for the scientific value may be the consequence. Furthermore it may mean that further patient follow up on safety cannot occur.

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

3.3.4.3 Discontinuation of the trial by the Sponsor

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

- Failure to meet expected enrolment goals overall or at a particular trial site
- Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial
- Violation of Good Clinical Practice (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).

3.3.4.4 Replacement of patients who have received at least one dose of BI 891065 or BI 754091

Replaced patients will not be evaluated for the MTD determination, and an additional patient will be entered at the same dose level. The following patients may be replaced:

- Patients who permanently discontinue treatment during treatment Cycle 1 of Part A or Part B for reasons other than a DLT, unless they develop a DLT.
- Patients who have missed more than 5 doses of BI 891065 in the first treatment cycle of Part A or Part B, unless they develop a DLT.
- Patients who have reduced BI 891065 dose level during treatment Cycle 1 Part A or Part B, unless they develop a DLT.
- Patients who have taken less than 80% of the BI 891065 overall dose during treatment Cycle 1 of Part B, unless they develop DLT.

- Patients who have received less than 50% of a BI 754091 initial dose of Part B, unless they develop a DLT.
- Patients who miss 2 or more partial or complete visits of the first cycle of Part A or Part B and (after discussion between the Sponsor and the Investigator) if the information needed to assess PK/PDc and safety parameters (including evaluation for DLTs), unless they develop a DLT.

Patients who permanently discontinue treatment because of a DLT will not be replaced.

Patients in the NSCLC expansion cohort (Part C) will not be replaced unless it becomes apparent that probably less than 40 patients will be evaluable for the assessment of the primary endpoint. In such a case, patients of the NSCLC expansion cohort concerned may be replaced only after confirmation of the Sponsor in writing.

3.3.4.5 Trial enrolment stopping rules in case of unacceptable toxicities

All AEs, including SAEs, AESIs, and deaths will be carefully analysed by the Sponsor. This data will also be taken into consideration by the SRC. Unacceptable toxicity will be defined as:

- Clinically relevant adverse events that are:
  - unexpected considering the mode of action, and are not manifestations of underlying disease or background events typical of the trial population
  - and/or are debilitating, non-reversible, not manageable
  - or lead to a fatal outcome
  - where evidence suggests that there was a reasonable possibility that the drug caused the adverse event.
- Higher than expected frequency of specific events (such as known consequences of the underlying disease or other events that commonly occur in the trial population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than would be expected in the trial population.

If one or both of the above criteria are met, the enrolment to the trial will be stopped to allow for in-depth analysis of the safety profile of BI 891065 (in combination with BI 754091). The risk-benefit profile of BI 891065 (in combination with BI 754091) will be re-assessed by the SRC. The outcome of the analysis and the recommendations will be shared with all involved regulatory health authorities prior to a possible re-start of enrolment. In case the benefit/risk assessment is no longer considered to be positive, the trial will be discontinued.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

Patients will receive either BI 891065 monotherapy or BI 891065 in combination with BI 754091 (see Table 4.1.1: 1 and Table 4.1.1: 2).

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
Route of administration:	Oral

Table 4.1.1: 2 BI 754091

Substance:	BI 754091
Pharmaceutical formulation:	Solution for infusion after dilution
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
Route of administration:	Intravenous infusion

4.1.2 Selection of doses in the trial

4.1.2.1 Starting dose of BI 891065

Based on the toxicities and exposures in the GLP-compliant dog study (the more sensitive species), a starting dose of 5 mg BI 891065 once daily has been chosen. To minimize the number of patients exposed to doses of BI 891065 presumed to be below the threshold of activity, an adapted dose-escalation approach (see Section 4.1.3) will be used for doses of BI 891065 below 25 mg. For details please refer to the Investigator's Brochure (c14463420-03).

4.1.2.2 Starting dose of BI 754091

A fixed dose of BI 754091 once every 3 weeks will be administered. The anticipated starting dose is 240 mg (i.e., the dose currently selected in the Phase I Trial 1381.1 of BI 754091 monotherapy for expansion cohort patients and 1381.2). Based on further data for BI 754091, the starting dose may be adapted by the SRC (informed by a BLRM with overdose control design).

4.1.3 Dose-escalation scheme

4.1.3.1 Cohorts at dose levels <25 mg BI 891065 daily

Enrolment into the first cohort at 5 mg BI 891065 daily will begin with 1 patient. If no drug-related AE ≥ Grade 2 (CTCAE Version 5.0) and no DLT is observed for the single patient (observation period is 3 weeks), a 15 mg daily single patient cohort will be initiated, unless the SRC recommends another dose or another cohort size for the second cohort. If no drug-related AE ≥ Grade 2 (CTCAE Version 5.0) and no DLT is observed for the single patient on 15 mg BI 891065 (observation period is 3 weeks), the 25-mg cohort will be initiated as described in Section 4.1.3.2, unless the SRC recommends another dose. Therefore, dose escalation to the second cohort will NOT be restricted to a maximum of 100% from the previous dose as in cohorts that follow the 15 mg cohort.

If drug-related AEs ≥ Grade 2 are observed in the above described single-patient cohorts (5 and 15 mg), the cohort and subsequent cohorts will be expanded to at least 3 patients.

The SRC will meet at the end of each of these treatment cohorts to decide on the next dose level based on available safety data and the BLRM recommendation.

4.1.3.2 Cohorts at dose levels ≥25 mg BI 891065 daily

The dose of BI 891065 is planned to be escalated in the Part A cohorts ≥25 mg daily at pre-defined provisional dose levels based on a maximum escalation of 100%. The provisional dose levels ≥25 mg daily to be assigned to separate cohorts of patients are listed in Table 4.1.3.2: 1. Intermediate or lower dose levels, depending on the number of DLTs observed in the trial may be investigated as long as they fulfil the EWOC criterion if agreed upon by the SRC.

Table 4.1.3.2: 1 Provisional dose levels for dose escalation of BI 891065 in Part A

Dose level	Proposed dose	Increase from previous dose
1	5 mg	Starting dose (fixed)
2	15 mg	300%
3	25 mg	67%
4	50 mg	100%
5	100 mg	100%
6	200 mg	100%
7	400 mg	100%

At the end of each treatment cohort, BI will convene a meeting with the SRC members. At the dose escalation meeting the clinical course (safety information including both DLTs and

all Common Terminology Criteria for Adverse Events [CTCAE; R18-1357] ≥ Grade 2 toxicity data during the MTD evaluation period and additional data if needed) for each patient in the current dose cohort will be described in detail. Updated safety data on other ongoing patients, including data in later cycles, as well as cIAP degradation in PBMCs (for dose cohorts ≥25 mg BI 891065), will be discussed as well. Based on that, a decision on the next dose level to be tested will be made.

For Part B (combination therapy), the dose of BI 891065 is planned to be escalated in cohorts at dose levels which will be determined based on the results of Part A. However, the starting dose of BI 891065 in Part B will be maximally 75% of the highest tolerated dose from Part A. Both q.d. and b.i.d. dose escalations may be performed in Part B. It is planned that a fixed dose of 240 mg BI 754091 will be used as determined in Trial 1381.1 (the dose chosen for the expansion cohorts). Based on emerging safety information in the 1381.1 and 1381.2 studies, the SRC may amend the dose of BI 754091 used in this trial. The SRC will determine the selected dose of BI 754091 for each combination cohort of this trial and communicate it to the investigators.

The dose and regimen of BI 891065 in combination with BI 754091 to be used in Part C will be determined based on the safety and PK/PDc data of Parts A and B, including data of target engagement in tumour tissue. The dose of BI 891065 might be changed during conduct of Part C, if needed.

4.1.4 Method of assigning patients to treatment groups

There will be no randomisation in this trial, as each part is single-arm and open-label. Patients will be assigned into escalating dose groups by order of admission into the trial. Recruitment into the trial will be conducted in a controlled manner. Patient numbers will be assigned as enrolment (screening) occurs. No patient will be enrolled without prior authorisation from [redacted] to ensure adherence with eligibility criteria, the escalation recruitment design and subsequent allocation to expansion cohorts. If a patient withdraws from the trial, then the enrolment code cannot be reused.

After assessment of all inclusion and exclusion criteria, each eligible patient entering Part A (monotherapy) will be assigned a dose of BI 891065 and each eligible patient entering Part B (combination therapy) will be assigned a q.d. or b.i.d. dose of BI 891065 and a dose of BI 754091, as determined by the SRC.

To determine the dose or doses for subsequent cohorts, the available safety data (including DLTs, AEs that are not DLTs, and AE information), target engagement, as well as the recommendations from the BLRM, will be evaluated by the SRC members at the dose-decision meeting.

The SRC must reach a consensus on whether to declare the MTD, escalate the dose any further, or de-escalate and/or expand recruitment into particular cohorts. Minutes from these meetings will be prepared and circulated to the trial team and each Investigator for comment prior to finalisation. Dose escalation will continue until at least one dose level higher than the estimated human therapeutic dose (maximum 400 mg daily dose of BI 891065) or until the trial is terminated for other reasons.

To further characterise the safety (e.g., specific suspected treatment-related AEs) or PK/PDc profiles of the BI 891065 plus BI 754091 combination, one or several doses may be expanded. Dose escalation may be terminated at any time based on emerging safety concerns without establishing the recommended expansion dose or the MTD.

In Part C (dose expansion), all patients will be treated with the doses determined by the assessment of DLTs, available PK, and available biomarker results from Parts A and B of the trial.

4.1.5 Administration of doses for each patient

4.1.5.1 Administration of BI 891065

BI 891065 may be taken in either a q.d. or b.i.d. dosing, depending on the assigned treatment regimen.

BI 891065 film-coated tablets were developed in four dosage strengths: 5, 20, 50, and 100 mg and will be provided in polypropylene bottles with screw-cap closures. The different tablet strengths should not be combined in the same bottle at any time. BI 891065 film-coated 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. For applicable cohorts, the fasting status and all meals on the PK days should be recorded in the patient diary.

Refer to Part A Flow Chart, Part B Flow Chart, Part C Lung Flow Chart, and Appendix 10.3 for information about sampling that is required prior to dose administration.

BI 891065 doses should be taken orally at approximately the same time each morning (and evening for patients with b.i.d. dosing). Exceptions are noted in the flowchart:

- Part A patients will skip a dose on Cycle 1 Day 2
- Part B patients assigned to a b.i.d. regimen will skip the evening dose on Cycle 1 Day 1 and Day 15 (in preparation for PK testing on Cycle 1 Day 2 and Day 16).

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

Part A: Cycle 1 Day 1, 15
Part B: Cycle 1 Day 1, 15, 16

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 (approximately 8 US ounces). Additional information about the food-interaction assessments in Part B are presented in Section 6.2.2.1.

Missed doses should not be made up if more than 6 hours have passed since scheduled dosing time. Missed doses must be recorded in the patient's 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 infusion according to the details in the Pharmacy Manual in the ISF.

4.1.6 Continuation of treatment

Patients may start the next cycle of therapy if criteria for continuation of therapy as outlined in Section 4.1.7 are met.

4.1.7 Dose reductions and dose delays

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 Medical Monitor and 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.

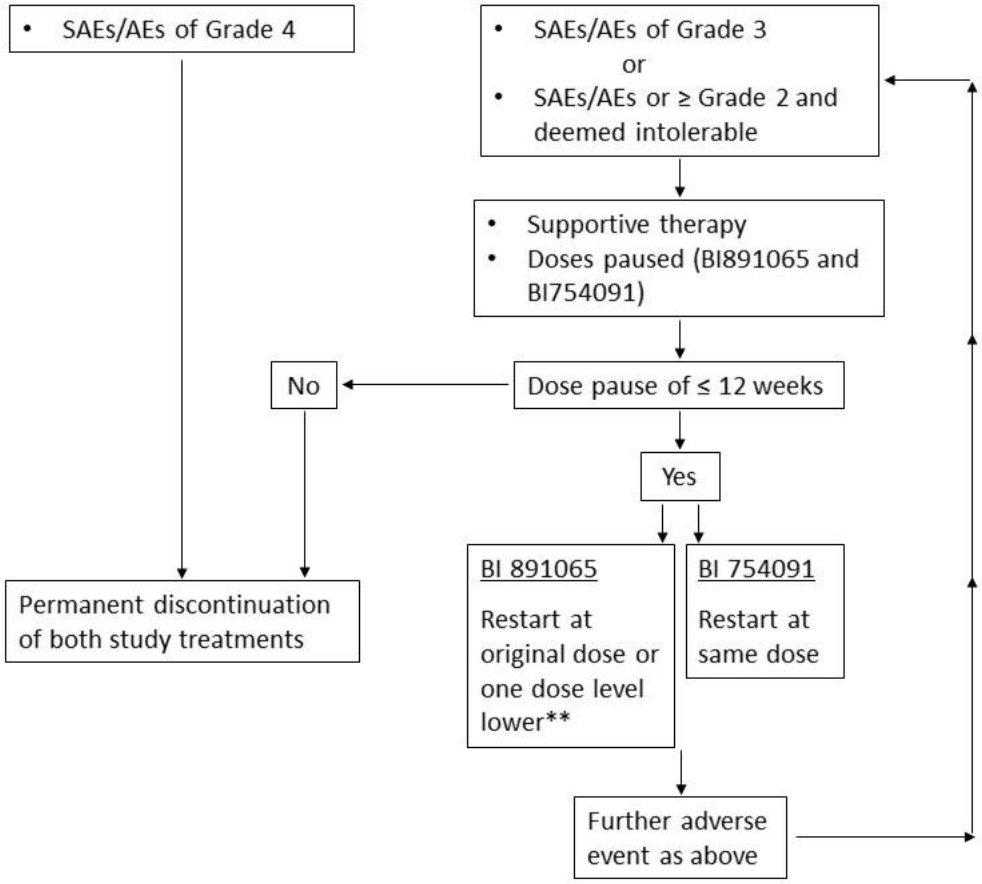
If, after a treatment pause of ≤12 weeks, the non-immune related SAE/AE resolves to baseline or Grade 1 and the physician thinks it is clinically appropriate to restart study drug, then the physician may choose to restart BI 891065 at one dose lower than the dose administered before the pause, and BI 754091 at the same fixed dose of BI 754091. 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 (see Section 5.2.6.4.2).

As a general rule for Part B and Part C, 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. Up to two dose reductions are allowed per patient. For q.d. dosing regimens, dose reductions of BI 891065 are allowed only to doses previously explored in earlier cohorts. If a patient on a b.i.d. dosing regimen has a dose reduction, the dose should be reduced as follows: 200 mg b.i.d reduced to 100 mg b.i.d; 100 mg b.i.d reduced to 50 mg b.i.d.

Criteria leading to permanent discontinuation of BI 891065 and BI 754091 are presented in Section 3.3.4.1.

A schematic of dose delays and reductions is presented in Figure 4.1.7: 1.



*See Appendix 10.2 for management of irAEs.

**The following caveat for restart of BI 891065:

- If at Cohort 1 dose, then restart at Cohort 1 dose
- Investigator to decide based on what is in the best interest of the patient. If dose is lowered, may escalate from lower dose to the maximum of the originally assigned dose when deemed clinically appropriate.
- If the AE/SAE prompting interruption is not drug related, BI 891065 may be re-introduced at the same dose level.

-

Figure 4.1.7: 1Schematic of dose delays and reductions for non-immune related AEs/SAEs*

4.1.8 Definition of dose-limiting toxicity

Dose-limiting toxicities (DLTs) will be recorded throughout the trial. Any DLT must be reported to the [redacted] Medical Monitor by the Investigator or designee within 24 hours of first knowledge, and to the [redacted] as an SAE when appropriate. All DLTs will be agreed upon between the Sponsor, the Study Chair, the [redacted] Medical Monitor, and the Investigators after review of the data from each cohort. Only DLTs starting in the first cycle of monotherapy during Part A or during the first cycle of BI 891065 in combination with BI 754091 during Part B are necessary for dose-escalation decisions made by the SRC. DLT information from later cycles will be taken into consideration if available.

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

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

Haematologic toxicities:

- For patients with solid tumours:
  - Any Grade 5 toxicity
  - Neutropenia ≥ Grade 4 lasting for >5 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 or a requirement for platelet transfusions
  - Grade 4 anaemia unexplained by underlying disease.

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)
- ≥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
- Any Grade 2 pneumonitis of any duration
- Any 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
- Any treatment-related ≥ Grade 2 toxicity that persists and results in an inability to administer BI 754091 on Cycle 2 Day 1.

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 immune-related DLTs are irAEs that meet the same grading criteria as DLT criteria but occur after the first cycle of BI 891065 in combination with BI 754091, but during the first 90-day assessment period. At the end of the escalation parts, the BLRM will be rerun using all DLTs.

4.1.9 Definition of maximum-tolerated dose

Please refer to Section 7.

4.1.10 Definition of evaluable patient

Patients that are evaluable for MTD are those who do not fulfil criteria for replacement as outlined in Section 3.3.4.4.

4.1.11 Blinding and procedures for unblinding

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

4.1.12 Packaging, labelling, and re-supply

The investigational products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Each site will be provided with an initial shipment of trial drug supply. Further medication will be automatically delivered depending on the recruitment on site using an Interactive Response Technology system.

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

4.1.13 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 [redacted] clinical monitor (as provided in the list of contacts) must be contacted immediately.

4.1.14 Drug accountability

The Investigator, or designee, will receive the investigational drugs delivered by the Sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol and informed consent form (ICF) by the Institutional Review Board (IRB) / ethics committee

- Availability of a signed and dated clinical trial contract between the Sponsor and the head of the investigational site
- Approval/notification of the regulatory authority (e.g., competent authority)
- Availability of the curriculum vitae of the Principal Investigator
- Availability of a signed and dated clinical trial protocol
- Availability of the proof of a medical license for the Principal Investigator
- Availability of FDA Form 1572.

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 alternative disposal of unused products.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational product and trial patients. The Investigator, or designee, will maintain records that document adequately that the patients were provided the doses specified by the clinical trial protocol (CTP) and reconcile all investigational products received from the Sponsor. Unused or partially used drug supplies will be destroyed on site at the end of the trial (after relevant reconciliations have been completed and records reviewed by the clinical monitor).

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 Appendix 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.

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.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Concomitant therapy, with reasons for the treatment, must be recorded in the case report form (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.

BI 891065 was found to be an inhibitor of various CYP450 enzymes *in vitro*, with Ki values in the range of 0.84 to 12 µM (see Section 1.2.1). 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). Table 4.2.2.1:1 provides a list of restricted and permitted medications. Alternatives with less potential for CYP450 based interactions should be considered, where available. Close monitoring for potential adverse reactions is warranted and patients should be informed about potential signs and symptoms of such adverse reactions (e.g., muscle pain). BI 891065 was also found to be an inhibitor of the drug transporters P-glycoprotein and BCRP *in vitro*, with IC_{50} values of 0.034 uM and 0.18-0.59 µM, respectively (see Section 1.2.1). Caution should be exercised when combining BI 891065 with P-gp and BCRP substrates. Table 4.2.2.1:1 provides a list of restricted and permitted medications.

Table 4.2.2.1:1 Restricted medication when coadministered with BI 891065

Sensitive CYP1A2, CYP2C8, CYP2C9 and CYP2C19, CYP2D6, CYP3A4 substrates with a high probability of exposure increase in combination with BI891065	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 BI891065	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 BI891065	Permitted if strictly indicated and with judicious dosing	Alfentanil, Amodiaquine, Felodipine, Loperamide, Maraviroc, Methadone, Montelukast, Nifedipine, Nimodipine, Pioglitazone , Repaglinide, Trazodone, Triazolam, Verapamil and Zolpidem.
Pgp substrates (partly with narrow therapeutic margin)	Not Permitted	Dabigatran etexilate Digoxin
Pgp substrates and in addition involvement of CYP3A4 with narrow therapeutic margin	Permitted if strictly indicated and with judicious dosing	Apixaban Rivaroxaban
Pgp and BCRP substrates with a probability of exposure increase in combination with BI891065	Permitted if strictly indicated and with judicious dosing	Fexofenadine, Verapamil and Rosuvastatin
Immunosuppressive medications* at doses exceeding 10 mg/day; TNFα blockers	Not Permitted*	Prednisone or equivalent, Methotrexate, Azathioprine
Live attenuated vaccines	Not Permitted during the trial through 30 days after the last dose of investigational product	
Herbal preparations/medications	Not Permitted from 7 days prior to first dose of study treatment	St. John’s wort, Kava, Ephedra (ma huang), Gingko biloba, Dehydroepiandrosterone (DHEA), Yohimbe, Saw palmetto, and Ginseng

*The following caveat applies for immunosuppressive medications:

- 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 upon discussion with the [redacted] Medical Monitor.
- For the treatment of CRS, supportive therapy including steroids and / or interleukin 6 receptor (IL6R) antagonists (R15-0031) may be used as clinically indicated.

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
- Part B patients will be asked to eat a specific meal per Section 6.2.2.1.

4.2.2.3 Contraception requirements

Women of childbearing potential and men able to father a child must use the contraception methods described in the patient information.

4.3 TREATMENT COMPLIANCE

The investigational products should only be used as directed in this protocol. For BI 754091 administration days, BI 891065 will be administered orally approximately 30 minutes after the end of the infusion of BI 754091, and only if considered safe by the Investigator.

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. Certificates of delivery and destruction should be signed.

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. Different tablet strengths need to be taken into consideration for computation.

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 dose, as determined from the previous monotherapy study (Trial BI 1381.1). 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 NSCLC tumour assessment and solid tumour assessment

Tumour response will be evaluated at the site according to RECIST Version 1.1 (R09-0262) and/or iRECIST (R17-0923 and Appendix 10.6). 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). Duplicates of the images will be collected and stored by a BI-appointed representative, and may be used for future independent central RECIST/iRECIST review, if deemed appropriate. In addition, 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).

The patients will be re-evaluated every 6 weeks for the first 6 months and then every 9 weeks thereafter until the earliest of PD, death, or last evaluable tumour assessment before start of subsequent anti-cancer therapy or until the end of the trial. The baseline scan(s) (CT scan and/or MRI according to Investigator's decision) from screening must have been performed within 4 weeks prior to treatment with the trial drug(s) and the Investigator will record the target (5 target lesions in total and maximum 2 per organ) and non-target lesions at baseline in the patient's medical records and in the CRF before the start of treatment. The same method of assessment and the same technique must be used to characterise each reported lesion at baseline and during treatment. Lesions in previously irradiated areas may not be considered measurable at baseline unless the lesions occurred after irradiation. Tumour assessment will be performed at screening (as close as possible to the treatment start and no

more than 28 days before the start of trial treatment), every 6 weeks for the first 6 months and every 9 weeks thereafter, and at the EOT visit (if not performed within the last 4 weeks).

If the patient stops with the trial medication for a reason other than progression, the tumour assessment according to RECIST v1.1 and iRECIST will be performed according to standard of care until the last follow-up needed according to the protocol (progression, death, lost to follow-up, end of the trial). Patients will be allowed to stay on treatment in the case of initial radiological PD, if the Investigator feels that it is in the patient's best interest, the patient signs an informed consent form specific for this circumstance, and the criteria listed in Section 3.3.4.1 are met.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified in Part A Flow Chart, Part B Flow Chart, and Part C Lung Flow Chart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin. Motoric functionally will be examined with an additional focus on the function of the cranial nerve VII. Any signs of facial nerve palsy have to be monitored closely until resolution.

Measurement of height and body weight will be performed at the time points specified in Part A Flow Chart, Part B Flow Chart, and Part C Lung Flow Chart.

During the physical examination, the patient should be assessed for possible adverse events. The results must be included in the source documents available at the site.

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in Part A Flow Chart, Part B Flow Chart, and Part C Lung Flow Chart prior to blood sampling and trial treatment administration. This includes body temperature, systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute). All except body temperature need to be taken in a seated position after 5 minutes of rest. Oxygen saturation will be measured, if needed.

Blood pressure and heart rate may also be measured after infusion of BI 754091 or at any time that the Investigator deems it is necessary.

5.2.3 Safety laboratory parameters

For the sampling time points please see Part A Flow Chart, Part B Flow Chart, and Part C Lung Flow Chart for each part. All analyses will be performed locally. Patients do not have to be fasted for the blood sampling for the safety laboratory tests.

Instructions regarding sample collection, sample handling/ processing and sample shipping are provided in the Laboratory Manual in the ISF.

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 5.2.6.4.5 and the Potential DILI Checklist provided in the ISF). The amount of blood taken from the patient concerned will be increased due to this additional sampling.

Safety laboratory tests will include the following parameters:

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

Biochemistry
The standard biochemistry panel will consist of glucose, sodium, potassium, chloride, calcium, phosphate, venous bicarbonate HCO_3, creatinine, AST, ALT, alkaline phosphatase, lactate dehydrogenase, total, direct and indirect bilirubin, total protein, albumin, urea nitrogen (or urea in lieu of urea nitrogen), uric acid and creatinine kinase (CK). If CK is elevated, then CK-MB [cardiac], Troponin I/Troponin T, and myoglobin should be reactively tested.

A thyroid panel (TSH, free T4, and free T3) will be done during Parts B and C 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.

Coagulation
Activated partial thromboplastin time (aPTT) and prothrombin time (PT) (expressed either in seconds or as percentage) will be tested according to the timing in Part A Flow Chart, Part B Flow Chart, and Part C Lung Flow Chart.

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

Pregnancy test
A beta human chorionic gonadotropin (β-HCG) pregnancy test in serum will be performed for women of childbearing potential at screening. Thereafter, this test may be done in serum or urine on Day 1 of each cycle, at the EOT visit, and at the 30-day safety follow-up visit.

Virology
At screening, tests according to local standards for HIV infection and hepatitis B (and if positive, anti-HBs, anti-HBc antibodies, and HBV DNA) and hepatitis C should not be older than 28 days.

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).

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

5.2.4 Electrocardiogram

Standard 12-lead (I, II, III, aVR, aVL, aVF, V1 - V6) resting electrocardiograms (ECGs) will be digitally recorded at various time points throughout the trial. The Part A Flow Chart, Part B Flow Chart, and Part C Lung Flow Chart outline which visits will require ECGs, and Appendix 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. While all ECGs will be transmitted to the central vendor, only the baseline, 6-hour, 8-hour, and 24-hour readings will be reviewed directly. The other readings would be analyzed only if the PK analysis points to a t_{max} deviating from the predicted t_{max}.

ECGs may be repeated for quality reasons and the repeated recording used for analysis. If necessary, additional ECGs may be recorded for safety reasons. In Part C, triplicate readings are required with pharmacokinetic sample collection as indicated in Table 10.3: 3. When triplicate ECGs are not done, single readings will be done for safety purposes as indicated in Part C Lung Flow Chart.

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. 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) 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.

Central morphological analyses of the ECGs (cardiologic assessments) will be performed by a board-certified cardiologist or equivalent. The cardiologist will interpret one ECG per time point. In case of triplicate ECG recordings per time point, this ECG will be selected randomly. In case additional (unscheduled) ECGs due to safety reasons are recorded at the study site, all ECGs of this time point including the additional ECGs will undergo interpretation. The ECG interpretation will include an overall assessment (normal, abnormal, not assessable) as well as assessments concerning rhythm, conduction, presence of myocardial infarction, ST segment deviations, T wave morphology, and U wave morphology findings.

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

Not applicable.

5.2.6 Assessment of adverse events

5.2.6.1 Definition of adverse event

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

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

5.2.6.2 Definition of serious adverse event

An SAE is defined as any AE which fulfils at least one of the following criteria:

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

Patients may be hospitalised for administrative reasons during the trial, including hospitalisation for respite care. These as well as hospitalisations/surgical procedures which were planned before the patient signed informed consent need not be reported as SAEs if they have been documented at or before signing of the informed consent and have been performed as planned (the condition requiring hospitalisation/surgical procedure has not changed/worsened after signing the informed consent).

5.2.6.3 Adverse events considered "Always Serious"

Every new occurrence of cancer of new histology must be classified as a serious event regardless of the duration between discontinuation of the trial medication and must be reported as described in Section 5.2.6.7, 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 Study Reference Manual in the ISF. These events should always be reported as SAEs as described above.

5.2.6.4 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 within the same time frame that applies to SAEs and according to the information in Section 5.2.6.7.

5.2.6.4.1 Dose-limiting toxicities

DLTs are considered to be AESIs, and must be reported as such. The definition of DLTs is presented in Section 0.

5.2.6.4.2 BI 754091 infusion-related reactions

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 [redacted] Safety group 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.

5.2.6.4.3 Cytokine release syndrome

Events of CRS CTCAE Version 5.0 Grade ≥2 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.

For Part A:
- Patients will remain under surveillance for 10 hours after first administration of BI 891065 [redacted]
- Patients will remain under surveillance for at least 8 hours after the second and third administrations of BI 891065.

For Part B:
- Patients will remain under surveillance after the administration of BI 891065 [redacted] in combination with BI 754091 [redacted] during Cycles 1 and 2.
- Duration of surveillance will be for 8 hours after the first dose of BI 891065 during Cycle 1, and for 6 hours after the first dose of BI 891065 in Cycle 2

For Part C:
- Patients will remain under surveillance after the administration of BI 891065 [redacted] in combination with BI 754091 [redacted] during Cycles 1 and 2.
- Duration of surveillance will be for 4 hours after the first dose of BI 891065 during Cycles 1 and 2.

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. Thereafter, patients will

be monitored with regular safety visits. All trial sites will have emergency resuscitation services and access to intensive care available.

Monitoring will include measurement of body temperature, heart rate, and blood pressure at regular intervals as presented in Part A Flow Chart, Part B Flow Chart, and Part C Lung 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 the case of a CRS CTCAE Version 5.0 Grade 2, 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 3.3.4.4 regarding replacement of patients.
- In the case of a CRS CTCAE Version 5.0 Grade 2, 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 CRS CTCAE Version 5.0 Grade 3 or 4, the patient must not be re-exposed to BI 891065 and BI 754091. Please refer to Section 3.3.4 for details.

5.2.6.4.4 Immune-related adverse events (irAE)

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 in Table 10.1: 1 in Appendix 10.1. These irAEs must be reported as AESIs. 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. Immune-related AEs should be reported as AESIs only for patients who received immunotherapy.

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

5.2.6.4.5 Hepatic injury

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

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

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

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (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.

Lab values meeting this definition of hepatic injury will need to be reported as an AESI. Please follow the flowchart below (Figure 5.2.6.4.5: 1) for reporting hepatic injury / potential DILI cases.

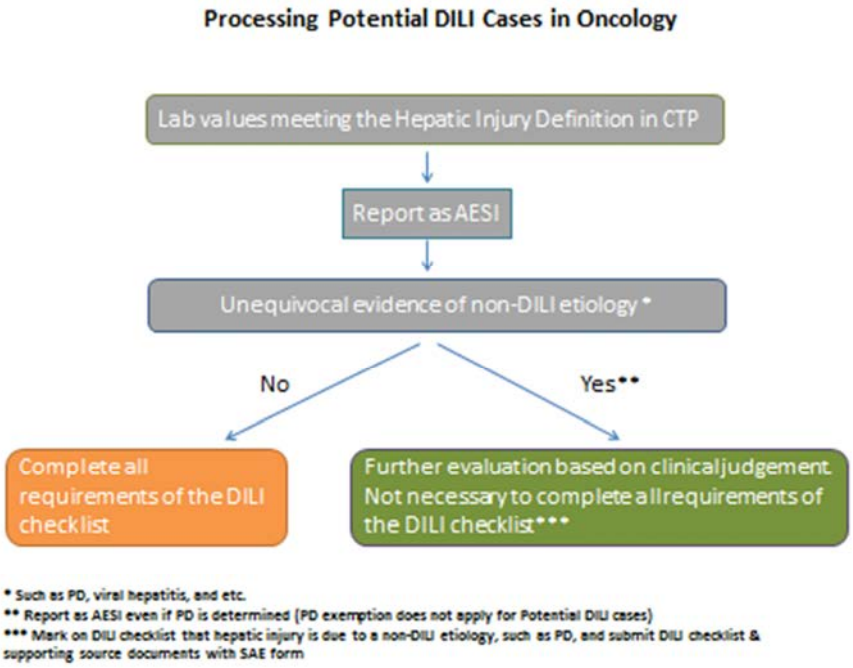


Figure 5.2.6.4.5: 1 Processing Potential DILI cases in oncology

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.

5.2.6.5 Severity of adverse events

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

5.2.6.6 Causal relationship of adverse events

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

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

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

Examples of 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.

5.2.6.7 Adverse event collection and reporting

5.2.6.7.1 Adverse event collection

The adverse event reporting scheme is presented in Figure 5.2.6.7.1: 1. The Investigator shall maintain and keep detailed records of all AEs in the patient files. The following must be collected and documented on the appropriate eCRF by the Investigator:

- From signing the informed consent onward until the end of treatment including residual effect period (REP):
  - all AEs (non-serious and serious) and all AESIs.
- After the end of treatment including REP 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 only report related SAEs and related AESIs of which the Investigator may become aware of by any means of communication (e.g., phone call). Those AEs should however, not be reported in the CRF.

The rules for Adverse Event Reporting exemptions still apply.

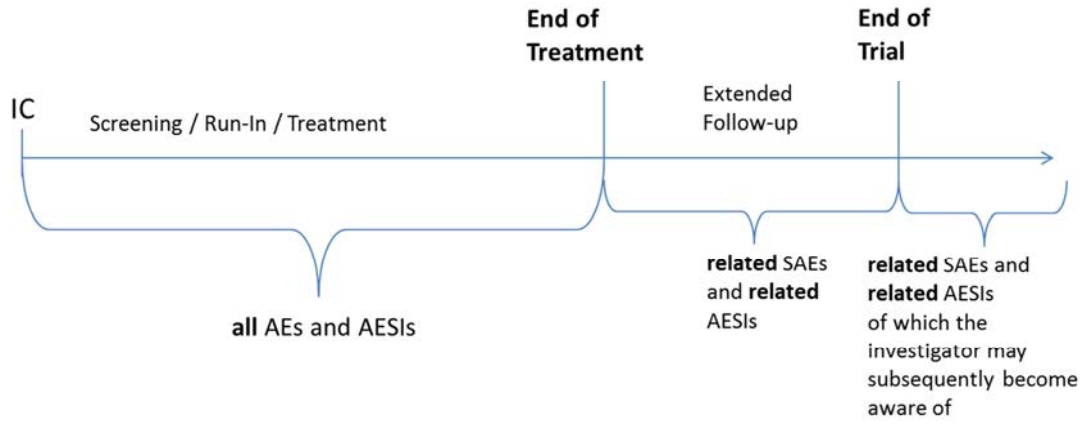


Figure 5.2.6.7.1: 1 Adverse event reporting scheme

The REP is defined as 30 days after the last trial medication application. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment. Events which occurred after the REP will be considered as post treatment events.

5.2.6.7.2 Adverse event reporting to Sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via secure e-mail connection or via fax immediately (within 24 hours) to the [redacted]

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

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

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

5.2.6.7.3 Information required

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

The following should also be recorded as an (S)AE in the CRF and BI SAE form (if applicable):
- Worsening of pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the Investigator.

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

5.2.6.8 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. 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). 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 ISF will contain the Pregnancy Monitoring Form for Clinical Trials (the form consists of Parts 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.

5.2.6.9 Exemptions to AE/SAE reporting

Progressive disease is a trial endpoint for analysis of efficacy and as such is exempted from reporting as an AE/SAE. Progression of the patient's underlying malignancy will be recorded on the appropriate pages of the eCRF as part of efficacy data collection only and will not be reported on the SAE Form. Death due to disease progression is also to be recorded on the appropriate eCRF page and not on the SAE Form.

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

Exempted events include:
- Progression of underlying malignancy
- Hospitalisation / procedures due solely to the progression of the underlying malignancy
- Clinical symptoms and/or signs of PD (without confirmation by objective criteria [e.g., imaging, clinical measurement]): if the symptom can exclusively be determined to be due to the progression of the underlying malignancy and does meet the expected pattern of progression for the disease under study.

Exempted events are collected and tracked following a protocol specified monitoring plan. Exempted events are monitored at appropriate intervals throughout the study at SRC meetings.

Lab values meeting the hepatic injury definition as defined in Section 5.2.6.4.5 will need to be reported as an AESI. PD reporting exemption does not apply to hepatic injury.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Standard pharmacokinetic parameters of BI 891065 will be determined from plasma and urine analyses after a single oral dose and after repeated dosing, at steady state. After multiple dose administration, the influence of food intake on the PK of BI 891065 will be investigated by comparison of $C_{max,ss}$ and $AUC_{0-\tau,ss}$, if feasible (for further details see Section 7.3.5).

Dose proportionality of the single and multiple dose pharmacokinetic parameters $C_{max,ss}$, $AUC_{\tau,ss}$ and $AUC_{0-24(,ss)}$ of BI 891065 in Cycle 1 of Part A will be assessed as described in Section 7.3.5.

If data allow, the PK parameters of BI 754091 will be evaluated using noncompartmental analysis methods according to BI internal SOP (001-MCS-36-472_RD-01 [actual version]).

Food interaction analyses are described in Section 6.2.2.1.

5.3.2 Methods of sample collection

The planned PK analyses will require blood and urine sampling at the time points indicated in Part A Flow Chart, Part B Flow Chart, and Part C Lung 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.

Pharmacokinetic sampling times and periods may be adapted by the Sponsor during the trial based on information obtained during trial conduct (e.g., preliminary PK data). Such changes would be implemented via non-substantial Clinical Trial Protocol Amendments.

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

5.3.2.1 Plasma sampling for BI 891065 pharmacokinetics

For quantification of analyte plasma concentrations, blood will be taken from an antecubital or forearm vein at the times indicated in Part A Flow Chart, Part B Flow Chart, and Part C Lung Flow Chart. 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 BI 754091 pharmacokinetics

For quantification of analyte plasma concentrations, samples will be drawn at the time points listed in Part A Flow Chart, Part B Flow Chart, Part C Lung Flow Chart and specified in PK time schedules in Appendix 10.3.

For Parts B and C, 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 Plasma sampling for metabolism analysis of BI 891065

Backup samples for PK analysis might be investigated for the identification of drug metabolites beginning with the first cohort of BI 891065 monotherapy. Based on the knowledge gained during the trial conduct, e.g., from preliminary PK results, the dose group for analysis will be determined.

The blood samples will be drawn together with the PK samples on Days 1, 15, and 16 (see Part A Flow Chart). Details on sample processing, shipment and handling are provided in the Laboratory Manual in the ISF.

Only data related to the parent compound and its metabolites will be acquired. Evaluation of the drug metabolism will be reported separately and not included in the clinical trial report of this trial. The trial samples will be discarded after completion of the assessments, but not later than 5 years after the final trial report has been signed.

5.3.2.5 Urine sampling and analysis for pharmacokinetics of BI 891065 (Part A only)

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 indicated in Table 10.3: 1 will be collected and stored. Subjects will be told to empty their bladders at the end of each sampling interval:

Cycle 1 Day 1:
- Spot urine pre-dose
- Pool 0 to 3 hours
- Pool 3 to 8 hours
- Pool 8 to 10 hours
- Pool 10 to 24 hours
- Pool 24 to 48 hours

Cycle 1 Day 15
- Spot urine pre-dose
- Pool 0 to 3 hours
- Pool 3 to 8 hours
- Pool 8 to 10 hours
- Pool 10 to 24 hours

In order to facilitate urine sampling, subjects 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 in the ISF.

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.

5.3.4 Pharmacokinetic – pharmacodynamic relationship

No formal analysis of a PK/PDc relationship is planned.

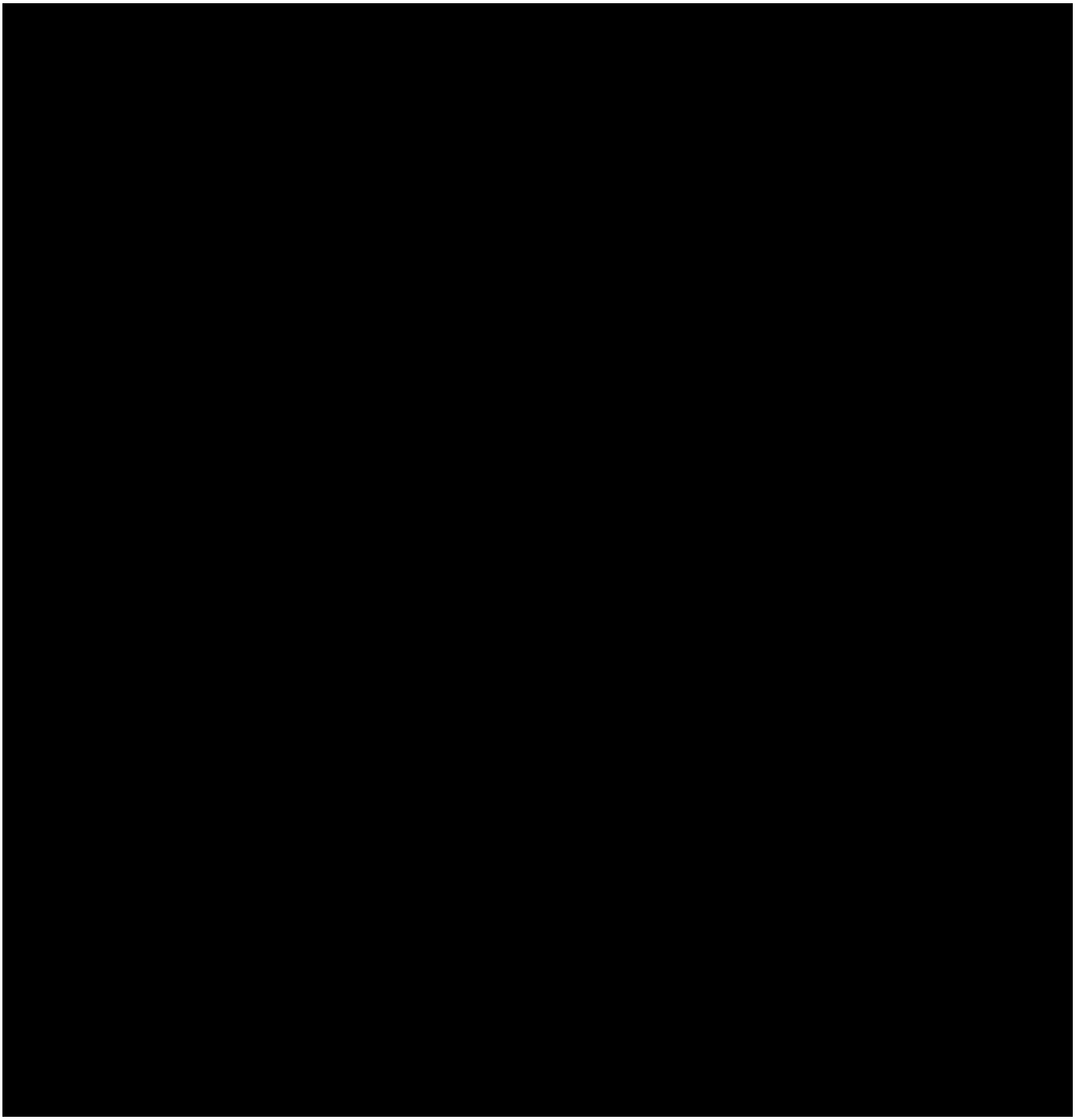
5.4 [redacted]

[redacted]

5.4.1 Methods of sample collection

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

[redacted]



5.4.3 Biobanking (solid tumours)

Participation in biobanking is voluntary and not a prerequisite for participation in the trial. Biobanking will be realised only after a separate biobanking informed consent has been given in accordance with local ethical and regulatory requirements. Banked samples may be analysed in the future for scientific evaluations or to further explore, for example, the mechanistic understanding of drug effects and/or to identify genetic or other factors associated with response to therapy or the risk of adverse drug reactions.

The leftovers of the following biomarker samples as specified in Section 5.4.2 will be banked:

- FFPE blocks of pre- and on-treatment biopsies.

5.5 OTHER ASSESSMENTS

5.6 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 Part A Flow Chart, Part B Flow Chart, and Part C Lung Flow Chart specific to each part. If a patient misses a scheduled visit, and reports to the Investigator between the missed visit and the next scheduled visit, the assessments for the missed visit must be done with the actual date and the reason must be given for the delayed visit. The next visit must then take place at the scheduled time after the first administration of the trial drug in the respective treatment cycle.

Once the decision 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 stopping 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 PD follow-up visits 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) with the exception of those who may continue treatment for a time after initial radiologic progression.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

The procedures required at each trial visit in all portions of the trial are presented in Part A Flow Chart, Part B Flow Chart, and Part C Lung Flow Chart at the beginning of this protocol. The key procedures required include:

- PK samples throughout the trial
- Reporting of all AEs occurring after the ICF has been signed
- Baseline and on-treatment blood biomarker and immunogenicity assessments
- Tumour biopsy biomarker assessments (Parts B and C only)
- Tumour assessments (based on CT/positron emission tomography [PET]/ and/or magnetic resonance imaging [MRI] scan) according to RECIST Version 1.1 and/or iRECIST must be performed once every 2 cycles (meaning every 6 weeks if there are no delays in cycles but as close as possible to the end of the second of the 2 cycles of treatment if there was a delay) after the start of BI 891065 for the first 6 months, and then every 3 cycles (9 weeks) thereafter.

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 28 days prior to first administration of trial medication. The screening period can be extended for up to a total of 12 weeks, if deemed clinically justified by the Investigator. The following given situations are examples that might trigger an extension of the screening period, e.g., an intermittent disease, or adverse event or an exacerbation of a concomitant disease that needs to be recovered before administration of trial medication, or a single episode of an abnormal laboratory value that needs to be repeated for proper evaluation. Investigations during the screening period, such as laboratory examinations, can be repeated during extended screening to meet the time period allowed between a respective examination and the first treatment with the trial medication. Patients

who do not meet all inclusion/exclusion criteria for eligibility at the end of the extended screening period are not allowed to be re-screened.

If the required baseline imaging is older than 28 days due to extended screening, imaging needs to be repeated.

6.2.1.2 Baseline conditions

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

6.2.1.3 Medical history

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

Previously administered chemotherapy, tyrosine kinase inhibitor treatment, vaccine therapy, antibodies therapy, immune therapy, and hormone therapy will be reported, including start and end dates (month and year may be sufficient), as well as whether therapy was given as neoadjuvant, adjuvant, or palliative therapy. The date of tumour progression after previous lines of treatment will be recorded, if known.

6.2.1.4 Concomitant therapies

Relevant concomitant diagnoses and/or therapies present at trial entry and/or during screening and relevant to the patient's safety during the trial as judged by the Investigator will be recorded in the eCRF (see Section 4.2.2.1 for details on concomitant medications). Post-trial therapy for advanced or metastatic disease will also be documented.

6.2.2 Treatment period

Patients will remain on treatment as long as, in the opinion of the Investigator, they are deriving benefit and the criteria listed in Section 3.3.4.1 are not met. Please refer to Part A Flow Chart, Part B Flow Chart, and Part C Lung Flow Chart for detailed presentations of each visit during the treatment period for each part of the trial.

6.2.2.1 Food-interaction assessment

An explorative food effect will be assessed for q.d. patients in Part B. Patients will fast for at least 10 hours prior to Cycle 1 Day 15 then receive BI 891065 together with approximately 240 mL water. Patients will remain fasted until at least 2 hours after drug intake. Water will be allowed except 30 minutes before and 1 hour after administration of BI 891065.

Patients will fast for at least 10 hours prior to Cycle 1 Day 16. At this visit, within 30 minutes of planned BI 891065 dose administration time, patients will be given a standard continental breakfast (see below) which they should consume within the 30 minutes prior to drug administration. Then patients will receive BI 891065 with approximately 240 mL water within 5 minutes of consuming the standard meal. If the patients are not able to eat or eat almost nothing, the information should be recorded on the eCRF.

The following definition of the standard continental breakfast is given in order to standardise the food intake prior to assessing food effects on BI 891065 (rough approximation): 2 bread rolls, 20 g butter, 25 g cheese, 25 g ham, 25 g jam, and 1 cup (~250 mL) of decaffeinated tea or coffee (average energy value per breakfast: ~688 kcal or 2880 kJ). Note: Alternative food components/quantity can be proposed by the Investigator, but it should be ensured that the caloric breakdown of the test meal is roughly in line with the breakfast indicated above.

6.2.3 Follow up periods 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, as soon as possible (preferably within 7 days but no later than 14 days) after permanent discontinuation of the trial medication or when the Investigator decided with the patient to permanently discontinue the trial medication or became aware that the trial medication had been terminated.

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 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.

A patient will be considered as having completed the trial if he/she discontinues because of PD and has performed the safety follow-up visit 30 days after EOT, or was lost to follow up, or withdrew consent for further evaluation at the EOT visit. If the patient discontinues for any other reason, he/she will be considered as withdrawn.

6.2.3.3 Extended follow-up period

Additional follow-up visits after the 30-day safety follow-up visit will be performed every 6 weeks if the patient has withdrawn prior to completing 6 months of treatment and/or every 9 weeks following 6 months of treatment until PD or another withdrawal criterion is met. The last follow-up visit will be considered the “end-of-follow-up” visit.

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

- Disease progression based on RECIST v1.1 and iRECIST
- Start of a new anti–cancer therapy
- Lost to follow-up
- Death
- 6 months after the last patient completed the 30-day safety follow-up visit in Parts A and B, and 12 months after the last patient completed the 30-day safety follow-up in Part C
- End of whole trial as specified in Section 8.6.

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

- For each reportable SAE/AESI, the Investigator should provide the information with regard to concomitant medication and the medication administered to treat the AE on the appropriate CRF pages and the SAE form including trade name, indication and dates of administration
- Record performance score/status (e.g., ECOG)
- Perform tumour assessment and imaging
- Treatment and date with any subsequent anti-cancer drug / therapy including the name and type of the anti-cancer drug and/or best supportive care (if applicable)
- Home care information
- Outcome (date of and reason for death [if applicable], in case the patient had PD the actual date of PD shall be recorded).

These visits may also be performed by telephone interview or via written correspondence in case the patient is unable to visit the Investigator.

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.

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 study. The objective of the design is to determine the MTD of BI 891065 defined as the highest dose with less than 25% risk of the true DLT rate being equal or above 33% (EWOC criterion). The dose-finding in Part A will be guided by a Bayesian 2-parameter logistic regression model with overdose control (R13-4803; R13-4806).

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 summarised using the following intervals:

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

The BLRM recommended dose for the next dose level is the level with the highest posterior probability of the DLT rate falling in the target interval [0.16, 0.33) among the doses fulfilling EWOC. Applying the EWOC criterion it should be unlikely (<25% posterior probability) that the DLT rate at that dose will be ≥0.33. In addition, for dose levels ≥25 mg BI 891065, the maximum allowable dose increment for the subsequent cohort will be no more that 100% from cohort to cohort.

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 18 patients have been treated in the dose escalation phase of the trial, of which at least 6 at the MTD.

The SRC may recommend stopping the dose finding 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 SRC may decide to include additional number of patients at this dose level and to declare this dose as the dose recommended for further testing.

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

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

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

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

Prior derivation:
For the current trial, no relevant information in the form of human data was available, since no trial in a comparable population with comparable dosing schedule has been conducted. Therefore, the three mixture components were established as follows:

- A weakly informative prior was derived reflecting the a priori assumption that the median DLT rate at the dose of 25 mg would equal 0.01, and the median DLT rate at the highest dose of 400 mg would equal 0.10. This yields μ_1 = (-2.787, -0.145). The standard deviations were set such that large uncertainty about the parameter means is reflected, and the correlation was set to 0, thus yielding $\sigma_{1,11} = 2$, $\sigma_{1,22} = 1$ and $\rho_1 = 0$, respectively. The prior weight a_1 for the first component was chosen as 0.9.
- A high-toxicity weakly informative prior was derived reflecting the case that the compound would be much more toxic than expected. For this prior component, it was assumed that the median DLT rate at the dose of 25 mg would equal 0.10, and the median DLT at the highest dose of 400 mg would equal 0.60. These assumptions yield μ_2 = (-0.245, -0.063). The standard deviations and correlations were set identical to the weakly informative prior, i.e. $\sigma_{2,11} = 2$, $\sigma_{2,22} = 1$ and $\rho_2 = 0$, respectively. The prior weight a_2 for the second component was chosen as 0.05.
- A low-toxicity weakly informative prior was derived reflecting the case that the compound would be much less toxic than expected. For this prior component, it was assumed that the median DLT rate at the dose of 25 mg would equal 0.001, and the median DLT at the highest dose of 400 mg would equal 0.05. These assumptions yield μ_3 = (-3.935, 0.357), i.e. basically a flat curve. The standard deviations and correlations were set to $\sigma_{3,11} = 5$, $\sigma_{3,22} = 0.01$, therefore almost fixing the slope parameter to its mean. The correlation was set to 0, i.e. $\rho_3 = 0$. The prior weight a_3 for the third component was chosen as 0.05.

A summary of the prior distribution is provided in Table 7.1.1: 1. Additionally, the prior probabilities of DLTs at different doses, as well as the corresponding probability of under-, targeted and overdosing, are shown in Table 7.1.1: 2. Graphically, the prior medians with accompanying 95% credible intervals are shown in Figure 7.1.1: 1. As can be seen from both, the table and the figure, the prior medians of the DLT probabilities are in-line with the prior medians derived from the weakly informative prior, and the uncertainty around the medians is large, showing the low amount of information this prior provides. This is also supported by the prior sample size, i.e., the information contained in the prior. This is approximately equal to 1.8 patients. Furthermore, it can be seen that the overdose prior probability of the starting dose of 5 mg is 0.029 and therefore well below the EWOC boundary of 0.25. A detailed evaluation of the model using hypothetical data scenarios and operating characteristics is provided in the statistical appendix (see Appendix 10.5).

Table 7.1.1: 1 Summary of prior distribution

Prior Component	Mixture Weight	Mean Vector	SD Vector
1: Weakly inf.	0.900	(-2.797, -0.145)	(2, 1, 0)
2: High Tox.	0.050	(-0.245, -0.063)	(2, 1, 0)
3: Low Tox.	0.050	(-3.935, 0.357)	(5, 0.01, 0)

Table 7.1.1: 2 Prior probabilities of DLTs at selected doses

Dose	Probability of true DLT rate in					Quantiles		
	[0-0.16)	**[0.16-0.33)**	**[0.33-1)**	**Mean**	**SD**	**2.5%**	**50%**	**97.5%**
5 mg	0.939	0.032	0.029	0.035	0.106	0.000	0.002	0.370
15 mg	0.912	0.045	0.042	0.050	0.128	0.000	0.004	0.470
25 mg	0.894	0.055	0.051	0.059	0.140	0.000	0.007	0.537
50 mg	0.859	0.072	0.069	0.078	0.159	0.000	0.013	0.631
100 mg	0.803	0.096	0.101	0.107	0.158	0.000	0.026	0.732
200 mg	0.691	0.135	0.174	0.164	0.224	0.001	0.061	0.847
400 mg	0.530	0.157	0.313	0.269	0.296	0.001	0.138	0.972

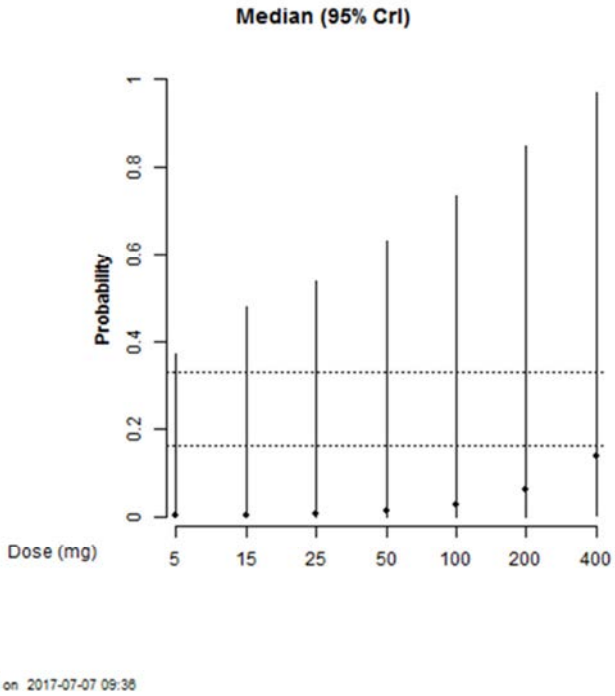


Figure 7.1.1: 1 Prior medians and 95% credible intervals

7.1.2 Part B

The primary objective of this part is to determine the MTD of BI 891065 in combination with BI 754091. To determine the MTD, patients are entered sequentially into escalating dose cohorts. The dose finding will be guided by a Bayesian 5-parameter logistic regression model with overdose control (R15-4233, Chapter 6).

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 $d_2^* = 3200$ 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 (k=1, 2) 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.

The priors for θ_k (k=1, 2) will be derived using the meta-analytic predictive approach. They will take into account available data from Part A of this trial and available data from the monotherapy dose escalation part of BI trial 1379.6 for the prior of BI 891065 and available data from the BI trial 1381.1 that aims to determine the MTD of BI 754091.

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

The derivation of these prior distributions is described in Appendix 10.5.

The estimated probability of DLT $\pi_{12,d1,d2}$ at each dose combination d_1, d_2 from the model will be summarised using the following intervals:
Under dosing: [0.00, 0.16)
Targeted toxicity: [0.16, 0.33)
Over dosing: [0.33, 1.00]

The BLRM recommended dose combination for the next cohort 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 be ≥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 12 patients have been treated in 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. This conversion is based on the assumption that safety events are triggered by C_{max} at steady state. For example, based on Table 7.1.2: 1, the 200 mg b.i.d. regimen will be modelled as equivalent to a 300 mg q.d regimen. For any other b.i.d. doses considered, their conversions will be specified in the TSAP.

The posterior probabilities of over toxicity are evaluated based on historical data for BI 891065 in Table 7.1.2: 2 and Table 7.1.2: 3, historical data for BI 754091 in Table 7.1.2: 4 and current data for the combination therapy of BI 891065 and BI 754091 in Table 7.1.2: 5. For example, as seen in Table 7.1.2: 6, the dose combination of 200 mg b.i.d. BI 891065 and 240 mg BI 754091 has a posterior probability of over toxicity below 25% and would therefore be suitable as a dose combination to select.

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.

Table 7.1.2: 1 Simulated C_{max} at steady state with 95% confidence intervals.

Possible Regimen	Cmax (nmol/L)
200 mg q.d.	2457.12 (771.53 - 6835.05)
300 mg q.d.	3421.69 (1286.11 - 9653.55)
400 mg q.d.	4357.98 (1672.88 - 12541.8)
200 mg b.i.d.	3502.75 (1458.73 - 10986.75)

Table 7.1.2: 2 Historical data for BI 891065 from Part A (status as of 16 Dec 2019)

Dose	N of patients with DLTs during MTD evaluation period / N of evaluable patients
5 mg q.d.	0/2
15 mg q.d.	0/1
25 mg q.d.	0/3
50 mg q.d.	0/4
100 mg q.d.	0/3

200 mg q.d.	0/3
400 mg q.d.	0/6

Table 7.1.2: 3 Historical data for BI 891065 from BI trial 1379.6 (status as of 16 Dec 2019)

Dose	N of patients with DLTs during MTD evaluation period / N of evaluable patients
100 mg q.d.	1/2

Table 7.1.2: 4 Historical data for BI 754091 from BI trial 1381.1 (status as of 30 Sep 2019)

Dose	N of patients with DLTs during MTD evaluation period / N of evaluable patients
80 mg	0/3
240 mg	0/71
400 mg	0/3

Table 7.1.2: 5 Data for combination of BI 891065 and BI 754091 from Part B (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

Table 7.1.2: 6 Posterior 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%**
50 mg q.d.	**240 mg**	0.977	0.023	0.000	0.071	0.036	0.019	0.065	0.158
200 mg q.d.	**240 mg**	0.853	0.147	0.000	0.110	0.050	0.035	0.102	0.229
200 mg b.i.d. [1]	**240 mg**	0.708	0.274	0.018	0.132	0.073	0.031	0.118	0.313
400 mg q.d.	**240 mg**	0.615	0.313	0.072	0.154	0.105	0.02	0.130	0.423

							3		

[1] The 200 mg b.i.d. dose is modeled as equivalent to a 300 mg q.d. dose in terms of dose-toxicity relationship in the BLRM.

7.1.3 Part C

The analysis in this trial is descriptive in nature. No statistical model will be used.

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

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

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

7.3.1 Primary endpoint analyses

Part A:

- In order to identify the MTD of BI 891065, the number of evaluable patients with DLTs during the MTD evaluation period at each dose level must be presented. Patients who are replaced during the MTD evaluation period will be excluded from the determination of MTD.

For the analysis of tolerability and safety, please refer to Section 7.3.4.

Part B:

- In order to identify the MTD of BI 891065 in combination with BI 754091, the number of evaluable patients with DLTs during the MTD evaluation period at each dose level must be presented. Patients who are replaced during the MTD evaluation period will be excluded from the determination of MTD.

For the analysis of tolerability and safety, please refer to Section 7.3.4.

Part C:

- The OR by Investigator assessment will be analysed descriptively in terms of objective response rate (ORR), defined as the proportion of patients with best overall response of

CR or PR. The primary analysis of Part C will take place after the last patient was treated for at least 18 weeks.

7.3.2 Secondary endpoint analyses

Part A:

- The number of patients with DLTs during the entire on-treatment period will be presented in a summary table.
- PK parameters will be analysed as described in Section 7.3.5.
- OR based on RECIST v1.1 will be analysed descriptively in terms of objective response rate, defined as the proportion of patients with objective response.

Part B:

- The number of patients with DLTs during the entire on-treatment period will be presented in a summary table.
- PK parameters will be analysed as described in Section 7.3.5.
- OR will be analysed descriptively in terms of ORR, defined as the proportion of patients with OR based on RECIST v1.1.

Part C:

- Duration of OR (based on RECIST v1.1) will analysed descriptively.

7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events

with an onset between start of treatment and end of the residual effect period (REP), a period of 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 residual effect period. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

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

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

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

Analyses of the centrally evaluated ECG data will be specified in the TSAP.

7.3.5 Pharmacokinetic and pharmacodynamic analyses

The pharmacokinetic parameters listed in Section 5.3.1 and Appendix 10.4 will be calculated according to the relevant BI internal procedures.

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 provided in the bioanalytical report, (that is, to the same number of decimal places provided in the bioanalytical report).

The following descriptive statistics will be calculated for plasma concentrations and PK parameters: number (N), arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. The exception to this is t_{max}, where only median, minimum and maximum will be calculated. The data format for descriptive statistics of concentrations will be identical to the data format of the respective concentrations. Thereafter, the individual values, as well as the descriptive statistics, will be reported with three significant digits in the clinical trial report.

For handling of missing data, please refer to Section 7.5.

Analyses will be carried out using Phoenix® WinNonlin® 6.3 (or later) and/or SAS® software, Version 9.4 (or later).

7.4 INTERIM ANALYSES

The Sponsor will continuously monitor the safety. The dose escalation design in parts A and B foresees that the Sponsor and the SRC perform regular safety evaluations. These evaluations will be unblinded to dose.

If considered necessary, as soon as the MTDs in Part A and Part B are determined or when the highest dose levels are reached, evaluations of the safety and other relevant aspects will be performed. Results of these evaluations will be documented and archived. If needed, each part will be analysed and reported in separate clinical trial reports. If applicable, such analyses will be defined in more detail in the TSAP.

An interim futility analysis will be performed by the SRC in Part C after 20 patients have been treated for at least 18 weeks. Until a decision from this futility analysis is made, the enrolment for that trial part will not be stopped. Enrolment will only be stopped if the defined efficacy boundary (see Table 7.7: 1) is not met. The SRC will document the decision, whether the futility bound is met or not in the SRC meeting minutes.

7.5 HANDLING OF MISSING DATA

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

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

Pharmacokinetic parameters
In the non-compartmental analysis, concentration data identified with NOS, NOR, and NOA will not be considered. BLQ values in the lag phase will be set to zero. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit. All other BLQ values of the profile will be ignored.

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

- If a concentration is only excluded from half-life determination, it will be used for all other calculations (e.g., descriptive statistics) and for graphical presentation.
- If a concentration value is excluded from all calculations, it will not be presented graphically or used for the calculation of descriptive statistics and parameter determination. However, the excluded concentration itself will be listed in the tables in Section 15 of the clinical trial report associated with an appropriate flag.

Descriptive statistics of parameters are calculated only when at least 2/3 of the individual parameter estimates of a certain parameter are available. If the actual sampling time is not recorded or is missing for a certain time point, the planned time will generally be used for this time point instead. Pharmacokinetic parameters which cannot be determined will be identified by "not calculated" (NC).

7.6 RANDOMISATION

No randomisation will be performed. In Part A and Part B, patients will be assigned to escalating dose groups by order of admission into the trial. In Part C, patients will be assigned to the expansion cohorts according to their diagnosis.

7.7 DETERMINATION OF SAMPLE SIZE

The number of patients to be enrolled in Part A and B cannot be predicted. Only estimation is provided in this section.

Part A:
No formal statistical power calculations to determine sample size were performed for this trial part. Approximately 30 patients (including patients at the MTD) are expected to be enrolled into Part A of this trial based on the number of dose levels/cohorts that are tested. Fewer patients might be needed based on the recommendation of the SRC and the criteria specified (see Section 8.7). However, the actual number of patients will depend on the number of dose cohorts tested. Based on the simulation study to evaluate operating characteristics of the BLRM (see statistical appendix), at least 20 evaluable patients (where evaluable patients refer to patients not fulfilling the criteria for replacement [Section 3.3.4.4]) are expected to be treated in the dose escalation part for the model to have reasonable operating characteristics relating to its MTD recommendation.

Part B:
No formal statistical power calculations to determine sample size were performed for this trial part. Approximately 31-37 patients (including patients at the MTD) will be expected for this part based on the number of dose levels/cohorts that are tested. Fewer patients might be needed based on the recommendation of the SRC and the criteria specified (see Section 8.7). However, the actual number of patients will depend on the number of dose cohorts tested.

Part C NSCLC:
A justification of the cohort size for this expansion cohort is based on assumed OR rates. A futility check will be performed by the SRC when 20 evaluable patients have been treated for at least 18 weeks. If an efficacy signal, i.e. at least 2 patients with OR, is observed out of 20 evaluable patients, the total intended 40 evaluable patients will be recruited into this trial part. If this efficacy signal cannot be observed, enrolment into the trial will be stopped.

Table 7.7: 1 summarises the probabilities to stop the trial after the futility analysis assuming different true underlying OR rates.

Table 7.7: 1 Probabilities to stop the trial at the futility analysis

Assumed true OR rate (%)	Cohort size	P(< 2 patients with OR)	P(≥ 2 patients with OR)
10	20	0.39	0.61
30	20	0.01	0.99
45	20	<0.01	>0.99

Table 7.7: 2 displays the probability of observing at least 2 patients with OR in the first 20 evaluable patients and then observing a certain number of patients with OR out of a total of 40 evaluable patients given different assumed true underlying OR rates. For example, assuming a true underlying OR rate of 10%, the probability to observe 2 or more patients with OR out of 20 evaluable patients is 0.61. This means that the probability to stop the trial is 0.39 in this scenario. Overall, the probability to observe 4 patients with OR out of 40 patients, given that at least 2 patients with OR had been seen already in the first 20 patients, is only 0.473 which is considered as acceptable for this trial.

Assuming a true underlying OR rate of 45%, the probability to observe 2 or more patients with OR out of 20 patients is almost 1. Overall, the probability to observe 18 patients with OR out of 40 patients, given that at least 2 patients with OR had been seen already in the first 20 patients, is 0.561 which is considered satisfactory for this trial.

Table 7.7: 2 Probabilities for objective response rates of the expansion cohort under different assumptions given the trial has not been stopped at the futility analysis

Assumed true OR rate (%)	Cohort size	At least 2 patients with OR in the first 20 patients and probability to observe at least 18 patients with OR in total						
		4	8	10	12	14	16	18
10	40	0.473	0.041	0.005	< 0.001	< 0.001	< 0.001	< 0.001
30	40	0.992	0.942	0.803	0.559	0.297	0.115	0.032
45	40	>0.999	>0.999	0.997	0.982	0.925	0.786	0.561

Probabilities in Table 7.7: 2 are calculated as P(n1 + n2 ≥ c AND n1 ≥ 2), where n1 is the number of patients with OR out of the first 20 patients, n2 is the number of additional patients with OR after more patients are enrolled after the futility check. c is the required minimum number of patients with OR displayed in Table 7.7: 2 (i.e. 4, 8, 10, 12, 14, 16, or 18 respectively). The calculations in this section were performed using R version 3.5.1.
It is assumed that 44 patients need to be enrolled in order to end up with 40 evaluable patients for the primary analysis.

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), and other relevant regulations.

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

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

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

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

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

The Investigator or delegate must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible.

The patient must be given sufficient time to consider participation in the trial. The Investigator or delegate obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The Investigator or his/her 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.

Following the initial radiologic progression, patients may be allowed to continue on treatment if, in the opinion of the Investigator, they are experiencing clinical benefit and criteria for withdrawal are not met (see Section 3.3.4.1). In this case, an additional informed consent form specific for this circumstance will be signed by the patient prior to treatment continuation.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the Sponsor, Sponsor's designees, or by an IRB 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

Electronic CRFs for individual patients will be provided by [redacted]

8.3.1 Source documents

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

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

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

Before providing any copy of patients' source documents to the Sponsor, the Investigator must ensure that all patient identifiers (e.g., patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents before sending them to the Sponsor.

Copies of tumour assessments scans may be collected by the Sponsor upon request. This could include CT scans of the chest and abdomen and/or imaging of any other known or suspected sites of disease (e.g., pelvis, brain) using an appropriate method (CT scan or MRI).

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

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

- Patient identification: gender, year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- 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.

- Technical information collected on PK sampling days (e.g., PK sampling times, repeated vital signs linked with PK) may be collected on specific paper PK logs, which will be considered as source data for related entries in the eCRF and are considered part of the ISF.

8.3.2 Direct access to source data and documents

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

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

8.3.3 Storage period of records

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

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements. Exemptions from expedited reporting are described in Section 5.2.6.9, if applicable.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

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

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

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

8.6 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 (including all follow-up visits) of the last patient in the whole trial ("Last Subject Completed" = 6 months after the last patient completed the 30-day safety follow-up visit in Parts A and B, and 12 months after the last patient completed the 30-day safety follow-up in Part C).

The "**Last Subject Last Treatment"** date is defined as the date on which the last patient at an individual trial site ends trial medication (as scheduled per protocol or prematurely). Individual Investigators will be notified of SUSARs occurring with the trial medication until 30 days after this date at their site.

The "**Last Patient Last Visit Primary Endpoint (LPLV PE)**" is defined as the date at which the last patient was examined or received an intervention for the purposes of final collection of data for the primary endpoint (according to the protocol specified schedule or after premature discontinuation) for each part of the trial. Patient treatment and follow up may continue after this time point. For Parts A and B, this is the last visit in the first cycle of the last patient in the respective part. A CSR will be considered at these time points. For Part C, this is the date when the last subject was treated for at least 18 weeks. At this time, the CSR will report the analysis of all primary and secondary endpoints. The CSR will be revised after "last subject completed".
Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

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

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

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

A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report. The Sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

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

A Safety Review Committee (SRC) will be established. Members of the SRC will include:
- [redacted] Medical Monitor for the trial, or delegate
- Principal Investigators, or delegates, from each investigational site
- BI Safety Physician, or delegate
- BI Clinical Program Leader, or delegate, responsible for the project.

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

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

The SRC will be responsible for assessing the progress of the clinical trial, including making safety and efficacy assessments at specified intervals, making dose-escalation decisions for BI 891065, making dose selection decisions for BI 754091, making decisions on the next cohort size, and recommending to the Sponsor whether to continue, modify, or stop the trial. To support their decision making, the SRC will have unblinded access to data from this trial and the ongoing studies, BI 1381.1 and BI 1381.2, which evaluate BI 754091. Minutes from these meetings will be prepared and circulated to the trial team and each investigator for comment prior to finalisation.

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

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

The statistical analysis will be done by BI according to BI Standard Operating Procedures (SOPs).

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

An Interactive Response Technology (IRT) vendor will be used in this trial for development of shipment orders and assignment of trial medication.

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

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

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial.

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

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

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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*

Immune-related adverse events of special interest
Pneumonitis (reported as an irAE if ≥ Grade 2)
• Acute interstitial pneumonitis • Interstitial lung disease • Pneumonitis
Colitis (reported as an irAE if ≥ 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 (reported as an irAE if ≥ 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
Endocrine (reported as an irAE)
• Type 1 diabetes mellitus (if new onset)

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

Hematologic (reported as an irAE if ≥ 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 (reported as an irAE if ≥ 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 (reported as an irAE for any grade)
• Allergic reaction • Anaphylaxis • Cytokine release syndrome • Serum sickness • Infusion reactions • Infusion-like reactions
Neurologic (reported as an irAE for any grade)
• Autoimmune neuropathy • Guillain-Barre syndrome • Demyelinating polyneuropathy • Myasthenic syndrome
Ocular (report as an irAE if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)
• Uveitis • Iritis

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

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

*Immune-related AEs should be reported as AESIs only for patients who received immunotherapy.

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 and BI 891065 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 and BI 891065 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 and BI 891065 has to be withheld, and treatment with high-dose corticosteroids (1-2mg/kg/d 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 and BI 891065 may be considered for selected irAEs, but caution is advised, in particular in patients with early-onset irAEs. Expert consultancy and agreement with medical monitor is recommended prior to restart of therapy.
- Most Grade 4 irAEs warrant permanent discontinuation of BI 754091 and BI 891065.
- 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 andconsideration 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.

BI 754091 and BI 891065 should be permanently discontinued for immune related

- 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 and BI 891065 besides interrupting or permanently discontinuing BI 754091 and BI 891065 are not allowed.

In rare situations when benefit and risk assessment is considered positive for a patient to continue BI 754091 and BI 891065 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 and BI 891065 until improvement or resolution; BI 754091 and BI 891065 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 and BI 891065 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 BI 891065 and immediately initiate treatment according to available guidelines.

Diarrhoea/Colitis:

- For Grade 1 diarrhoea/colitis, consider interruption of BI 754091 and BI 891065 therapy.
- For Grade 2 diarrhea/colitis, withhold BI 754091 and BI 891065 until patient's symptoms recovered to grade 1 or less. Consider initiating treatment with steroids.
- For Grade 3 diarrhoea/colitis, withhold BI 754091 and BI 891065 and immediately start treatment (steroids, non-steroidal immunosuppressents) as per available guidelines.
- For Grade 4 diarrhoea/colitis, permanently discontinue BI 754091 and BI 891065 and immediately commence adequate therapy (e.g. i.v. corticosteroids).
- For Grade 1-3 colitis, restart of BI 754091 and BI 891065 may be considered once symptoms improve to Grade 1 or less without need for continued steroids. After careful benefit risk assessment, BI 754091 and BI 891065 may also be restarted after recovery to grade 1 or less, and on corticosteroid ≤ 10 mg per day
- BI 754091 and BI 891065 should be permanently discontinued for recurrent diarrhoea/colitis of any grade.

Diabetes

- Consider withholding BI 754091 and BI 891065 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 and BI 891065 should be withheld until glucose level is controlled with insulin with no sign of ketoacidosis.
- BI 754091 and BI 891065 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 and BI 891065 may be continued, with regular monitoring of thyroid values.
    - For Grade 2 hypothyroidism, consider withholding BI 754091 and BI 891065
    - For Grade 3-4 hypothyroidism, withhold BI 754091 and BI 891065, consider admission and IV therapy, especially in case of myxedema
    - BI 754091 and BI 891065 may be restarted once symptoms resolve to baseline with appropriate thyroid hormone supplementation
- Primary hyperthyroidism
    - For Grade 1 hyperthyroidism, BI 754091 and BI 891065 may be continued , with regular monitoring of thyroid values.
    - For Grade 2 hyperthyroidism, consider withholding BI 754091 and BI 891065, initiate therapy as per available guidelines.

- For Grade 3-4 hyperthyroidism, withhold BI 754091 and BI 891065. Consider hospitalization, especially in case of thyreotoxicosis.
- BI 754091 and BI 891065 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 and BI 891065 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 and BI 891065 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 and BI 891065 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 and BI 891065 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 and BI 891065 should be suspended. Monitoring of liver values every 3 days is recommended. Initiate treatment according to available guidelines. Restarting of BI 754091 and BI 891065 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 and BI 891065 has to be permanently discontinued.

Nephritis:

- For Grade 1 nephritis, consider temporarily withholding BI 754091 and BI 891065.
- For Grade 2 nephritis, withhold BI 754091 and BI 891065. Consult nephrology. Initiate treatment according to guidelines. In case of no improvement or worsening, permanently discontinue BI 754091 and BI 891065.BI 754091 and BI 891065 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 and BI 891065. 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 and BI 891065 should also be permanently discontinued for recurrent nephritis grade 2 or higher.

Rash
- For Grade 1 rash, continue BI 754091 and BI 891065. Initiate topical treatment.
- For Grade 2 rash, BI 754091 and BI 891065 may be continued, in case of no improvement upon weekly monitoring, consider interruption of BI 754091 and BI 891065 therapy. Treat topically, add systemic corticosteroid therapies as clinically appropriate.
- For Grade 3 rash, withhold BI 754091 and BI 891065. 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 and BI 891065 might be restarted, especially in case no alternative anti-neoplastic therapy is available.
- For Grade 4 rash, BI 754091 and BI 891065 should be permanently discontinued.
- BI 754091 and BI 891065 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 and BI 891065 can be continued.
- For Grade 2 bullous dermatosis, withhold BI 754091 and BI 891065. Administer topical therapy, add systemic therapy as clinically adequate.
- For Grade 3 bullous dermatosis, withhold BI 754091 and BI 891065, initiate topical and systemic therapy as per available guidelines. Restarting of BI 754091 and BI 891065 may be considered after dermatology consultation.
- For Grade 4 bullous dermatosis, permanently discontinue BI 754091 and BI 891065.

Severe cutaneous adverse reaction (SCAR), Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN)
- For Grade 2 events, withhold BI 754091 and BI 891065, initiate treatment as per available guidelines. Closely monitor for improvement or worsening.
- For Grade 3 events, withhold BI 754091 and BI 891065. 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 and BI 891065, 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 and BI 891065 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 and BI 891065 should be permanently discontinued for any grade.

Myasthenia gravis
- For Grade 2 myasthenia gravis, withhold BI 754091 and BI 891065,
- For Grade 3 or 4 myasthernia gravis, permanently discontinue BI 754091 and BI 891065

Guillain Barré Syndrome (GBS)
- Discontinue BI 754091 and BI 891065 permanently for any grade GBS.

Transverse Myelitis
- Discontinue BI 754091 and BI 891065 permanently for any grade transverse myelitis.

Peripheral neuropathy, autonomic neuropathy
- For Grade 1 events, may continue BI 754091 and BI 891065, but with low threshold to discontinue while monitoring closely for worsening.
- For Grade 2 events, withhold BI 754091 and BI 891065 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 and BI 891065.

Inflammatory Arthritis
- For Grade 1 arthritis, BI 754091 and BI 891065 can be continued. Administer analgetic treatment (acetaminophen, NSAID).
- For Grade 2-4 arthritis, withhold BI 754091 and BI 891065. Initiate treatment as per available guidelines, cave regarding reactivation of tuberculosis/opportunistic infections in case of prolonged immunosuppressive/DMARD therapy.

BI 754091 and BI 891065 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 and BI 891065 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 and BI 891065, 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 and BI 891065 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 and BI 891065.
- BI 754091 and BI 891065 should be permanently discontinued if there is any evidence of myocardial involvement.

Polymyalgia-like syndrome
- For Grade 1 event, BI 754091 and BI 891065 can be continued.

- For Grade 2 event, withhold BI 754091 and BI 891065 and promptly initiate adequate therapy. If no improvement, treat as grade 3.
- For Grade 3 or G4 event, withhold BI 754091 and BI 891065, promptly initiate adequate therapy Rheumatology consultancy is highly recommended.

BI 754091 and BI 891065 may be resumed after careful assessment of risks and benefits, rheumatology consultancy highly recommended prior to reinitiation. BI 754091 and BI 891065 may only be re-started upon recovery to grade 1 or less and on corticosteroid ≤ 10 mg per day.

Myocarditis

- Discontinue BI 754091 and BI 891065 permanently for any grade of myocarditis.

Uveitis/Iritis, Episcleritis

- For Grade 1 events, treatment with BI 754091 and BI 891065 can continue. Treat topically as needed.
- For Gade 2 events, withhold therapy with BI 754091 and BI 891065, urgent ophthalomology referral is recommended. Initiate topical treatment, consider systemic therapy if needed. Restart of BI 754091 and BI 891065 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 and BI 891065 therapy.
- For Grade 3 or 4 events, permanently discontinue BI 754091 and BI 891065 therapy. Seek emergent ophthalmology consultation.. Initiate adequate local and systemic treatment.

Autoimmune-hemolytic anemia (AIHA)

- For Grade 1 AIHA, continue treatment with BI 754091 and BI 891065. Close follow-up of anemia and other lab values.
- For Grade 2-4 AIHA, discontinue BI 754091 and BI 891065 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 and BI 891065.
- For HUS (TTP excluded), withhold BI 754091 and BI 891065 for grade 1 and grade 2, provide supportive care. Upon full recovery, BI 754091 and BI 891065 may be restarted after carefuly weighing of risks and benefits.
- For Grade 3 or Grade 4 HUS, discontinue BI 754091 and BI 891065 permanently.

Immune thrombocytopenia (ITP)

- In case of Grade 1 ITP, BI 754091 and BI 891065 can be continued.
- For Grade 2 or Grade 3 ITP, withhold BI 754091 and BI 891065 and initiate systemic therapy. BI 754091 and BI 891065 may be restarted upon resolution to at least grade 1.
- For Grade 4 ITP, permanently discontinue BI 754091 and BI 891065.

10.3 TIME SCHEDULES FOR PHARMACOKINETIC (PK) [redacted] SAMPLING

Table 10.3: 1 Time schedule for PK blood and urine samplings, [redacted], and ECG measurements - Part A BI 891065 Monotherapy

						Blood samples				Urine samples[c]
Cycle	**Visit**	**Day**	**Time Point [hh:min]/ event**	**CRF Time /PTM**	**Sample No.**	**Triplicate ECGs***	**Plasma for BI 891065[b]**	[redacted]	[redacted]	
1	2	1	-1:00 (+/-10min	-1:00		X				
			-30 min (+/-15min)	-30 min		X				
			Predose (within 15 min)	Predose		X				
			Just before drug intake	-0:05[a]	1		X	X	X	X
			BI 891065 intake	0:00	---					
			0:30	0:30	2	X	X			
			1:00	1:00	3	X**	X			
			2:00	2:00	4	X**	X			
			3:00	3:00	5	X**	X	X		
			5:00	5:00	6	X**	X			
			6:00	6:00	7	X	X			
			7:00	7:00	8	X**	X			
			8:00	8:00	9	X	X	X		
			10:00	10:00	10	X**	X			
	3	2	**No drug intake**	24:00	11	X	X	X	X	
			36:00	36:00	12		X			
	4	3	Just before drug intake	47:55	13		X			
			BI 891065 intake	48:00	---					
	5	8	Just before drug intake	167:55	14		X	X	X	
			BI 891065 intake	168:00	---					

BI = Boehringer Ingelheim; CRF = Case Report Form; ECG = electrocardiogram; IAP = inhibitor of apoptosis; PBMC = Peripheral blood mononuclear cells; PTM = planned time
a PK to be taken following an overnight fast (minimum 10 hours) on this day

b The following windows of time are allowed for PK sampling:

- Predose samples (PTM -0:05, 47:55, 167:55, etc.): within 1 hour before drug intake
- On Day 1 (PTM 1:00 through PTM 3:00): within ±10 minutes of designated time
- On Day 1 (PTM 5:00, 6:00, 7:00, 8:00, and 10:00): within ±15 minutes of designated time
- Days 2 and beyond post first drug intake (PTM 24:00, 47:55, 167.55, etc.): ±1 hour.

Time windows are specified for procedural reasons; deviations do not automatically lead to exclusion of samples from data evaluation. The new PK and urine schedule will be implemented upon availability of updated lab kits.

c 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 5.3.2.5.

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

** ECGs will be taken throughout, as it is possible that time of maximum concentration is not accurately estimated; for safety, time of maximum concentration is one of the most relevant time points, so should not be missed. As such, some ECGs may only be evaluated at later points or, if deemed unnecessary, not at all.

Table 10.3: 1 Time schedule for PK blood and urine samplings, [redacted] and ECG measurements - Part A BI 891065 Monotherapy (continued)

						Blood samples				Urine samples[d]
Cycle	**Visit**	**Day**	**Time Point [hh:min]/ event**	**CRF Time /PTM**	**Sample No.**	**Triplicate ECGs***	**Plasma for BI 891065[b,c]**	[redacted]	[redacted]	
1	6	12	Just before drug intake	263:55	15		X			
			BI 891065 intake	264:00						
	7	15	Just before drug intake	335:55 [a]	16	X	X	X	X	X
			BI 891065 intake	336:00	---					
			0:30	336:30	17	X	X			▲
			1:00	337:00	18	X**	X			▲
			2:00	338:00	19	X**	X			▲
			3:00	339:00	20	X**	X			▲
			5:00	341:00	21	X**	X			▲
			6:00	342:00	22	X	X			▲
			7:00	343:00	23	X**	X			▲
			8:00	344:00	24	X	X			▲
			10:00	346:00	25	X**	X			▼
	8	16	Just before drug intake	359:55	26	X	X			
			BI 891065 intake	360:00	---					
2	9	1	Just before drug intake	-0:05	27		X			
EOT								X	X	

BI = Boehringer Ingelheim; CRF = Case Report Form; ECG = electrocardiogram; EOT = end of treatment; IAP = inhibitor of apoptosis; PBMC = Peripheral blood mononuclear cells; PTM = planned time

a PK to be taken following an overnight fast (minimum 10 hours) on this day

b The following windows of time are allowed for PK sampling:

- Predose samples (PTM 335:55, 359:55, etc.): within 1 hour before drug intake
- Day 15 (PTM 336:30 through PTM 339:00): within ±10 minutes of the designated time
- Day 15 (PTM 341:00 through 346:00):within ±15 minutes of the designated time

Time windows are specified for procedural reasons; deviations do not automatically lead to exclusion of samples from data evaluation.

c Serum aliquot B samples for PK might be used for identification of metabolites on Days 1 (prior to treatment), 15, and 16 at the same time points as the PK samples.

d 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, and 10-24 (Cycle 1 Days 1 and 15) and detailed in Section 5.3.2.5.

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

** ECGs will be taken throughout, as it is possible that time of maximum concentration is not accurately estimated; for safety, this is one of the most relevant time points, so should not be missed. As such, some ECGs may only be evaluated at later points or, if deemed unnecessary, not at all.

Table 10.3: 2 Time schedule for PK blood, [redacted] during Part B including food effect in q.d. treatment group

						Samples				
Cycle	**Visit**	**Day**	**Time Point [hh:min]/ event**	**CRF Time /PTM**	**Triplicate ECG***	**Plasma[b] BI 891065**	**Plasma[b] BI 754091**	[redacted]	**Biopsy[c]**	[redacted]
1	2	1	Predose (between screening and C1D1 dosing)						X	
			-30 min (+/-15min)	-30 min	X					
1	2	1	Just before drug admin	Predose[a]	X		X	X		X
			BI 754091 admin	0:00						
			Just before infusion end	1:00			X			
			1:25	1:25	X**	X	X			
			BI 891065 admin	1:30						
			2:00	2:00		X	X			
			2:30	2:30	X**	X	X			
			3:30	3:30	X**	X	X			
			4:30	4:30	X**	X	X	X		
			6:30	6:30	X**	X	X			
			7:30	7:30	X	X	X			
			8:30	8:30	X**	X	X			
			9:30	9:30	X	X	X	X		
			11:30	11:30	X**	X	X			
	3	2	Just before drug intake	25:25	X	X	X	X		
			BI 891065 intake	25:30						
	4	8	Just before drug intake	167:55		X	X	X		
			BI 891065 intake	168:00						
	5	12	Just before drug intake	263:55		X	X			
			BI 891065 intake	264:00						

ADA = anti-drug antibodies; BI = Boehringer Ingelheim; CRF = Case Report Form; IAP = inhibitor of apoptosis; PTM = planned time

a PK to be taken following an overnight fast (minimum 10 hours) on this day

b The following windows of time are allowed for PK and ECG sampling (ECGs should be performed PRIOR to PK sampling):

- Predose samples (PTM -0:05, 25:25, 167:55, etc.): within 1 hour before drug intake
- One hour to 4:30 hours post first drug intake (PTM 1:00 through PTM 4:30): within ±10 minutes of designated time
- 6:30 to 11:30 hours post first drug intake (PTM 6:30 through 11:30): within ±15 minutes of designated time

Time windows are specified for procedural reasons; deviations do not automatically lead to exclusion of samples from data evaluation.

c Biopsy for IAP degradation to be taken as noted in Part B Flow Chart.

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

** ECGs will be taken throughout, as it is possible that time of maximum concentration is not accurately estimated; for safety, this is one of the most relevant time points, so should not be missed. As such, some ECGs may only be evaluated at later points or, if deemed unnecessary, not at all.

Table 10.3: 2 Time schedule for PK blood, [redacted] during Part B including food effect in q.d. treatment group (continued)

						Samples				
Cycle	**Visit**	**Day**	**Time Point [hh:min]/ event**	**CRF Time /PTM**	**Triplicate ECGs ***	**Plasma [b] BI 891065**	**Plasma [b] BI 754091**	**[redacted]**	**Biopsy [c]**	**[redacted]**
1	6	15	Just before drug admin	335:55[a]	X	X	X			
			BI 891065 intake	336:00						
			0:30	336:30	X	X				
			1:00	337:00	X**	X				
			2:00	338:00	X**	X				
			3:00	339:00	X**	X				
			5:00	341:00	X**	X				
			6:00	342:00	X	X				
			7:00	343:00	X**	X				
			8:00	344:00	X	X				
			10:00	346:00	X**	X				
	7	16	-0:30 Breakfast	359:30[a]	X	X	X			
			BI 891065 intake	360:00						
			0:30	360:30		X				
			1:00	361:00		X				
			2:00	362:00		X				
			3:00	363:00		X				
			5:00	365:00		X				
			6:00	366:00		X				
			7:00	367:00		X				
			8:00	368:00		X				
			10:00	370:00		X				
	8	17	Just before drug admin	383:55		X	X			
			BI 891065 intake	384:00						
2-5, then every 2nd cycle	9-12 then every 2nd cycle	1	Just before drug admin	-0:05		X (C2 only)	X		X	X
			Just before infusion end	1:00			X			
EOT							X	X		X
30-Day FU							X			X

ADA = anti-drug antibodies; BI = Boehringer Ingelheim; CRF = Case Report Form; ECG = electrocardiogram; EOT = end of treatment; FU = follow up; IAP = inhibitor of apoptosis; PTM = planned time
a PK to be taken following an overnight fast (minimum 10 hours) on this day
b The following windows of time are allowed for PK and ECG sampling (ECGs should be performed PRIOR to PK sampling):

- Predose samples (PTM 335:55 [Day 15], 359:30 [Day 16], 383:55 [Day 17], etc.): within 1 hour before drug intake
- On Day 15 (PTM 336:30 through 339:00) and Day 16 (PTM 360:30 to 363:00): within ±10 minutes of designated time

- On Day 15 (PTM 341:00 through 346:00) and Day 16 (PTM 365:00 through 370:00): within ±15 minutes of designated time

Time windows are specified for procedural reasons; deviations do not automatically lead to exclusion of samples from data evaluation.
c Biopsy for IAP degradation to be taken as noted in Part B Flow Chart.
* In order not to confuse an ECG recording, all PK samples should be taken after performing the ECGs.
** ECGs will be taken throughout, as it is possible that time of maximum concentration is not accurately estimated; for safety, this is one of the most relevant time points, so should not be missed. As such, some ECGs may only be evaluated at later points or, if deemed unnecessary, not at all.

Table 10.3: 3 Time schedule for PK blood, [redacted] during Part B excluding food effect in b.i.d. treatment group

					Samples				
Cycle	**Visit**	**Day**	**Time Point [hh:min]/ event**	**CRF Time /PTM**	**Triplicate ECG***	**Plasma[b] BI 891065**	**Plasma[b] BI 754091**	**[redacted]**	**Biopsy[c]**	**[redacted]**
1	2	1	Predose (between screening and C1D1 dosing)						X	
			-30 min (+/-15min)	-30 min	X					
1	2	1	Just before drug admin	Predose[a]	X		X	X		X
			BI 754091 admin	0:00						
			Just before infusion end	1:00			X			
			1:25	1:25	X**	X	X			
			BI 891065 admin	1:30						
			2:00	2:00		X	X			
			2:30	2:30	X**	X	X			
			3:30	3:30	X**	X	X			
			4:30	4:30	X**	X	X	X		
			6:30	6:30	X**	X	X			
			7:30	7:30	X	X	X			
			8:30	8:30	X**	X	X			
			9:30	9:30	X	X	X	X		
			11:30	11:30	X**	X	X			
			No drug intake	13:30						
	3	2	Just before drug intake	25:25	X	X	X	X		
			BI 891065 intake	25:30						
	4	8	Just before drug intake	167:55		X	X	X		
			BI 891065 intake	168:00						
	5	12	Just before drug intake	263:55		X	X			
			BI 891065 intake	264:00						

ADA = anti-drug antibodies; BI = Boehringer Ingelheim; CRF = Case Report Form; IAP = inhibitor of apoptosis; PTM = planned time

a PK to be taken following an overnight fast (minimum 10 hours) on this day

b The following windows of time are allowed for PK and ECG sampling (ECGs should be performed PRIOR to PK sampling):

- Predose samples (PTM -0:05, 25:25, 167:55, etc.): within 1 hour before drug intake
- One hour to 4:30 hours post first drug intake (PTM 1:00 through PTM 4:30): within ±10 minutes of designated time
- 6:30 to 11:30 hours post first drug intake (PTM 6:30 through 11:30): within ±15 minutes of designated time

Time windows are specified for procedural reasons; deviations do not automatically lead to exclusion of samples from data evaluation.

c Biopsy for IAP degradation to be taken as noted in Part B Flow Chart.

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

** ECGs will be taken throughout, as it is possible that time of maximum concentration is not accurately estimated; for safety, this is one of the most relevant time points, so should not be missed. As such, some ECGs may only be evaluated at later points or, if deemed unnecessary, not at all.

Table 10.3: 3 Time schedule for PK blood, [redacted] during Part B excluding food effect in b.i.d. treatment group (continued)

						Samples			
Cycle	**Visit**	**Day**	**Time Point [hh:min]/ event**	**CRF Time /PTM**	**Triplicate ECGs***	**Plasma[b] BI 891065**	**Plasma[b] BI 754091**	[redacted]	**Biopsy[c]**	[redacted]
1	6	15	Just before drug admin	335:55[a]	X	X	X			
			BI 891065 intake	336:00						
			0:30	336:30	X	X				
			1:00	337:00	X**	X				
			2:00	338:00	X**	X				
			3:00	339:00	X**	X				
			5:00	341:00	X**	X				
			6:00	342:00	X	X				
			7:00	343:00	X**	X				
			8:00	344:00	X	X				
			10:00	346:00	X**	X				
			No drug intake	348:00						
	7	16	Just before drug intake	359:30***	X	X	X			
			BI 891065 intake	360:00						
2-5, then every 2nd cycle	9-12 then every 2nd cycle	1	Just before drug admin	-0:05		X (C2 only)	X		X	X
			Just before infusion end	1:00			X			
EOT							X	X		X
30-Day FU							X			X

ADA = anti-drug antibodies; BI = Boehringer Ingelheim; CRF = Case Report Form; ECG = electrocardiogram; EOT = end of treatment; FU = follow up; IAP = inhibitor of apoptosis; PTM = planned time

a PK to be taken following an overnight fast (minimum 10 hours) on this day

b The following windows of time are allowed for PK and ECG sampling (ECGs should be performed PRIOR to PK sampling):

- Predose samples (PTM 335:55 [Day 15]): within 1 hour before drug intake
- On Day 15 (PTM 336:30 through 339:00): within ±10 minutes of designated time
- On Day 15 (PTM 341:00 through 346:00): within ±15 minutes of designated time
- On Day16 (PTM 359:30): within 30 min before drug intake

Time windows are specified for procedural reasons; deviations do not automatically lead to exclusion of samples from data evaluation.

c Biopsy for IAP degradation to be taken as noted in Part B Flow Chart.

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

** ECGs will be taken throughout, as it is possible that time of maximum concentration is not accurately estimated; for safety, this is one of the most relevant time points, so should not be missed. As such, some ECGs may only be evaluated at later points or, if deemed unnecessary, not at all.

***Central lab kits provided will contain extra tubes (for post-dose timepoints 360:30-370:00 on Day 16 and 383:55 on Day 17). These tubes should not be used for b.i.d patients.

Table 10.3: 4 Time schedule for PK blood, [redacted] during Part C – NSCLC

						Samples						
Cycle	**Visit**	**Day**	**Time Point [hh:min] / event**	**CRF Time /PTM**	**Triplicate ECGs ***	**Plasma[b] BI 891065**	**Plasma[b] BI 754091**	[redacted]	[redacted]	**Biopsies**	[redacted]
Scr	1									X	
1	2	1	-30 min (±15min)	-0:30	X						
			Just before drug admin	-0:05[a]	X	X	X	X	X		X
			BI 754091 admin	0:00							
			Just before infusion end	1:00			X				
			1:25	1:25	X	X					
			BI 891065 intake	1:30							
			2:00	2:00	X	X					
			2:30	2:30	X	X					
			3:30	3:30	X	X					
			4:30	4:30	X	X					
			6:30	6:30	X	X					
			7:30	7:30	X	X					
	3	2	24:00	24:00	X	X	X	X			
	4	8	Just before drug intake	167:55		X	X	X	X		
			BI 891065 intake	168:00							

Table 10.3: 4 Time schedule for PK blood, [redacted] sampling during Part C – NSCLC (continued)

						Samples					
Cycle	**Visit**	**Day**	**Time Point [hh:min] / event**	**CRF Time /PTM**	**Triplicate ECGs ***	**Plasma[b] BI 891065**	**Plasma[b] BI 754091**	[redacted]	[redacted]	**Biopsies**	[redacted]
1	5	15	Just before drug intake	335:55		X	X	X	X		
			BI 891065 intake	336:00							
			0:30	336:30	X	X					
			1:00	337:00	X	X					
			2:00	338:00	X	X					
			3:00	339:00	X	X					
			5:00	341:00	X	X					
			6:00	342:00	X	X					
	6	16	24:00	360:00	X	X	X				
2-5, then every 2nd cycle	7-10 then every 2nd cycle	1	Just before drug admin (both)	-0:05		X (only cycle 2)	X	X (only cycle 2,4)	X (only cycle 2.4)	X (only cycle 3)	X
			Just before infusion end	1:00			X				
EOT							X			(X)	X
30-Day FU							X				X

ADA = anti-drug antibodies; BI = Boehringer Ingelheim; CRF = Case Report Form; PTM = planned time; EOT = end of treatment; FU = follow up; MDSC = myeloid-derived suppressor cells; PBMC = Peripheral blood mononuclear cells; PTM = planned time

a PK to be taken following an overnight fast (minimum 10 hrs) on this day

b The following windows of time are allowed for PK and ECG sampling (ECGs should be performed PRIOR to PK sampling):

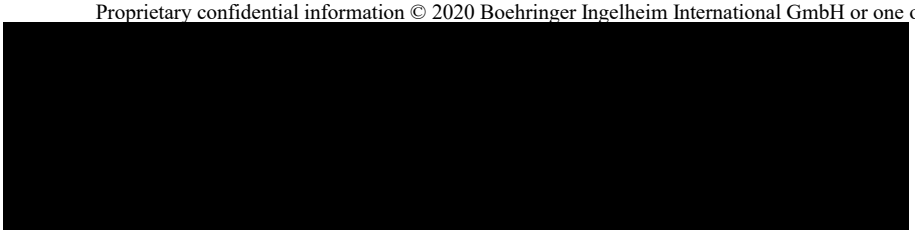
- Predose samples (PTM -0:05, 167:55, etc.): within 1 hour before drug intake
- Just before end of infusion (PTM 1:00): within ±10 minutes of designated time
- On Day 1 (PTM 1:25 through 8:30) and on Day 15 (PTM 336:30 through 339:00): within ±10 minutes of designated time
- On Day 1 (PTM 0:30 through 6:00) and on Day 15 (PTM 341:00 through 342:00): within ±15 minutes of designated time

Time windows are specified for procedural reasons; deviations do not automatically lead to exclusion of samples from data evaluation.

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

Optional assessments are noted in parentheses. Please refer to the footnotes in Part C Lung Flow Chart for details.

[redacted]



10.5 STATISTICAL APPENDIX

Part A:
A BLRM with overdose control will be used to guide dose escalation in this part of the trial. The BLRM is introduced in Section 7, 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 summarised in Table 10.5: 3. In addition, recommendations of the next dose level by the BLRM with overdose control principle are also provided under various hypothetical outcome scenarios in early cohorts to show how it facilitates on-trial dose-escalation decisions (see Table 10.5: 1). For simplicity reasons, a cohort size of 3 patients who are all evaluable starting at 25 mg is assumed for calculation of the operating characteristics.

Hypothetical data scenarios
Hypothetical data scenarios are shown in Table 10.5: 1. These scenarios reflect potential on-trial 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 where 1 patient has been treated at the starting dose of 5 mg and did not experience a DLT. Then, the BLRM would recommend escalating to 200 mg as the next dose. Since escalation is only allowed up to 15 mg per protocol, the next dose to be tested in the trial would be 15 mg.

Similarly, Scenario 4 represents the case where 1 patient has been treated at 5 mg and 1 at 15 mg, none of them with a DLT. In this case, the model recommends escalating to 200 mg. As this exceeds the per protocol margin, the next dose to be tested would be 25 mg.

Scenario 3 shows the case that already the starting dose level is quite toxic, with 2 out of 3 treated patients experiencing DLTs. The overdose control implemented in the model then does not allow going to any of the pre-specified doses.

Finally, Scenario 14 and 15 illustrate a case where escalation has proceeded up to the highest dose of 400 mg. Scenario 15 represents a scenario where the MTD could be declared at 400 mg.

Table 10.5: 1 Hypothetical data scenarios

Scenario	Dose (mg)	# Patients	# DLT	Current Dose: P(OD)	Next recommended dose	Next recommended dose:		
						P(UD)	P(TD)	P(OD)
1	5	1	0	0.012	200* [15]	0.701	0.143	0.156
2	5	3	1	0.161	5	0.592	0.246	0.161
3	5	3	2	0.607	NA	NA	NA	NA
4	5 15	1 1	0 0	0.012	200* [25]	0.724	0.137	0.140
5	5 15	1 3	0 1	0.131	25	0.540	0.273	0.186
6	5 15 25	1 1 3	0 0 0	0.003	200* [50]	0.769	0.127	0.104
7	5 15 25	1 1 3	0 0 1	0.095	50	0.522	0.281	0.196
8	5 15 25	1 1 3	0 0 2	0.415	5	0.571	0.282	0.147
9	5 15 25 50	1 1 3 3	0 0 0 0	0.002	400*[100]	0.626	0.148	0.226
10	5 15 25 50	1 1 3 3	0 0 0 1	0.055	100	0.550	0.280	0.170
11	5 15 25 50 100	1 1 3 3 3	0 0 0 0 0	0.003	400*[200]	0.674	0.124	0.202

Table 10.5: 1 Hypothetical data scenarios (continued)

12	5 15 25 50 100	1 1 3 3 3	0 0 0 0 2	0.290	50	0.654	0.284	0.062
13	5 15 25 50 100 200	1 1 3 3 3 3	0 0 0 0 0 0	0.011	400	0.760	0.111	0.129
14	5 15 25 50 100 200 400	1 1 3 3 3 3 3	0 0 0 0 0 0 0	0.021	400	0.899	0.080	0.021
15	5 15 25 50 100 200 400	1 1 3 3 3 3 6	0 0 0 0 0 1 1	0.158	400	0.450	0.392	0.158

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 10.5: 2 describes 4 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

Table 10.5: 2 Assumed true dose-toxicity scenarios

Scenario		Dose (mg)				
		25	50	100	200	400
1: Prior	P(DLT)	0.059	0.078	0.107	0.164	0.269
2: High Tox		0.259	0.278	0.307	0.364	0.469
3: Low Tox		0.009	0.028	0.057	0.114	0.219
4: Non-Logistic		0.048	0.147	0.193	0.312	0.348

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%, or if at least 18 patients have been treated in the trial, of which at least 6 at the MTD. 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 10.5: 3.

Table 10.5: 3 Simulated operating characteristics

Scenario	% of trials declaring a MTD with true DLT rate in				# Patients	# DLTs
	underdose	target dose	overdose	Stopped	Mean (Min-Max)	Mean (Min-Max)
1	20.8	77.6	0.0	1.6	20.350 (3 - 42)	2.669 (1 - 8)
2	0.0	44.7	8.9	46.4	13.250 (3 - 30)	3.816 (1 - 9)
3	46.2	53.7	0.0	0.1	20.830 (6 - 39)	2.179 (1 - 6)
4	19.4	68.5	10.4	1.7	19.250 (3 - 33)	3.612 (1 - 9)

In Scenario 1 which reflects the case that the true dose-toxicity is aligned with prior means almost 78% of trials have found a MTD with true DLT rate in the target interval. 412 trials

declared 400 mg as the MTD, 364 trials declared 200 mg as the MTD. In Scenario 2 (high-toxicity scenario), almost as many trials declared a MTD with true DLT rate in the target interval, as trials that were stopped without declaring a MTD since all dose levels were too toxic. The high number of prematurely stopped trials is an expected situation for such a high toxicity scenario. Only few trials declared MTDs with true DLT rates in the overdose interval.

Scenario 3 (low-toxicity scenario) shows that more than 50% of trials (537 of 1000) declared MTDs with true DLT rate in the target interval although only one dose level (400 mg) has assumed true DLT rate in the target interval. The majority of the rest of the trials (393 trials) declared 200 mg as the MTD. Only one trial has been stopped prematurely due to too toxic doses. Scenario 4 represents a case where the assumed true dose-toxicity curve does not follow a logistic shape. In this scenario, more than 60% of trials determined MTDs with true DLT rate in the target interval an only a few trials declared MTDs with true DLT rate in the overdose interval. The mean patient numbers range from 13.25 patients (Scenario 2) to 20.83 patients (Scenario 3) and the maximum number of patients was 39. Therefore, the patient numbers are as expected and increase when moving away from the high-toxicity scenario.

By reviewing the metrics presented in Table 10.5: 3, it can be seen that the model is not sensitive to different scenarios of truth, even under misspecification results are satisfactory. In general, this model is conservative due to the overdose control criteria. In all scenarios, the probabilities of recommending a dose with true P(DLT) ≥33% as MTD are much smaller than probabilities of recommending a dose with true P(DLT) between 16% and 33% as MTD.

On-trial 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 3.2.2 was used for data scenarios and simulations.

Part B:
Dose finding in Part B of the trial will be guided by a Bayesian 5-parameter logistic regression model with overdose control. For a description of the model refer to Section 7.1.2.

To determine the prior distributions for θ_1 and θ_2, a meta-analytic predictive approach will be used. Toxicity information on BI 891065 from Part A of the trial and toxicity information on BI 754091 from the Trial 1381.1 will be incorporated.

Data of the 400 mg cohort of Part A was not completely available by the time of the finalisation of this version of the CTP. Therefore, two possible scenarios of how the prior to be used for Part B could be defined are presented. The first scenario represents the case that none of the patients treated with 400 mg in Part A experiences a DLT. The second scenario represents that case that one of the 6 patients treated with 400 mg in Part A experiences a DLT.

The historical data for BI 891065 can be found in Table 10.5: 4 for Scenario 1 and in Table 10.5: 5 for Scenario 2. [redacted]

Table 10.5: 4 Historical data for BI 891065 assuming no DLTs happen at 400 mg (status as of 17 Oct 2018)

Dose	N of patients with DLTs during MTD evaluation period / N of evaluable patients
5 mg	0/2
15 mg	0/1
25 mg	0/3
50 mg	0/4
100 mg	0/3
200 mg	0/3
400 mg	0/6

Table 10.5: 5 Historical data for BI 891065 assuming one patient has a DLT at 400 mg (status as of 17 Oct 2018)

Dose	N of patients with DLTs during MTD evaluation period / N of evaluable patients
5 mg	0/2
15 mg	0/1
25 mg	0/3
50 mg	0/4
100 mg	0/3
200 mg	0/3
400 mg	1/6

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

1. θ_1:
    1. The meta-analytic-predictive prior was derived using the information in Table 10.5: 4 (for Scenario 2 information is in Table 10.5: 5), allowing for small to moderate between-trial heterogeneity. This mixture component was assigned 90% mixture weight.
    2. A second, weakly-informative component was added with 10% mixture weight.
2. θ_2:
    1. The meta-analytic-predictive prior was derived using the information in Table 10.5: 6, allowing for moderate to substantial between-trial heterogeneity. This mixture component was assigned 90% mixture weight.
    2. A second, weakly-informative component was added with 10% mixture weight.
3. 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% credible interval covers an up to 1.4-fold increase (or decrease) in the odds of a DLT over no interaction.

The prior distributions for both scenarios are given in Table 10.5: 7 and Table 10.5: 8. 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 10.5: 9 and Table 10.5: 10.

Table 10.5: 7 Prior distributions for Scenario 1 (no DLTs at 400 mg in Part A)

Parameter	means, standard deviations, correlation	mixture weight
$\log(\alpha_1)$, $\log(\beta_1)$: component 1	(-2.404, -0.364), (0.679, 0.737), -0.036	0.9
$\log(\alpha_1)$, $\log(\beta_1)$: component 2	(-2.404, -0.364), (2, 1), 0	0.1
$\log(\alpha_2)$, $\log(\beta_2)$: component 1	(-2.946, -0.193), (0.690, 0.884), -0.037	0.9
$\log(\alpha_2)$, $\log(\beta_2)$: component 2	(-2.946, -0.193), (2, 1), 0	0.1
η	0, 0.56	N/A

Table 10.5: 8 Prior distributions for Scenario 2 (one DLT at 400 mg in Part A)

Parameter	means, standard deviations, correlation	mixture weight
$\log(\alpha_1)$, $\log(\beta_1)$: component 1	(-2.040, -0.093), (0.644, 0.716), -0.095	0.9
$\log(\alpha_1)$, $\log(\beta_1)$: component 2	(-2.040, -0.093), (2, 1), 0	0.1
$\log(\alpha_2)$, $\log(\beta_2)$: component 1	(-2.946, -0.193), (0.690, 0.884), -0.037	0.9
$\log(\alpha_2)$, $\log(\beta_2)$: component 2	(-2.946, -0.193), (2, 1), 0	0.1
η	0, 0.56	N/A

Table 10.5: 9 Prior probabilities of DLTs for Scenario 1 (no DLTs at 400 mg in Part A)

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%**
50 mg	**240 mg**	0.831	0.140	0.030	0.113	0.097	0.023	0.089	0.357
100 mg	**240 mg**	0.743	0.214	0.043	0.134	0.107	0.029	0.108	0.417
200 mg	**240 mg**	0.565	0.324	0.110	0.179	0.135	0.032	0.143	0.544
400 mg	**240 mg**	0.408	0.274	0.318	0.274	0.225	0.018	0.207	0.839

Table 10.5: 10 Prior probabilities of DLTs for Scenario 2 (one DLT at 400 mg in Part A)

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%**
50 mg	**240 mg**	0.804	0.162	0.033	0.118	0.102	0.022	0.093	0.376
100 mg	**240 mg**	0.684	0.263	0.053	0.147	0.113	0.030	0.119	0.451
200 mg	**240 mg**	0.450	0.387	0.162	0.211	0.147	0.040	0.174	0.600
400 mg	**240 mg**	0.297	0.268	0.435	0.342	0.248	0.026	0.282	0.905

As can be seen from Table 10.5: 9 and Table 10.5: 10, the dose combinations 50 mg BI 891065 and 240 mg BI 754091, 100 mg BI 891065 and 240 mg BI 754091, and 200 mg BI 890165 and 240 mg BI 754091 have prior probabilities of over toxicity below 25% in both scenarios. They fulfill the overdose criterion and are therefore suitable starting dose combinations.

Since prior probabilities for both scenarios shown above are similar, only Scenario 2 with a starting dose combination 100 mg BI 891065 and 240 mg BI 754091 will be used to evaluate the model in terms of performance metrics and data scenarios.

Performance metrics (operating characteristics) illustrate the precision of the design in estimating the MTD under various dose-toxicity relationships through computer simulation. These results are summarized in Table 10.5: 13. In addition, recommendations of the next dose combination 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 10.5: 11). For simplicity reasons, a cohort size of 3 patients who are all evaluable is assumed.

Hypothetical data scenarios

Hypothetical data scenarios are shown in Table 10.5: 11. These scenarios reflect potential on-study data constellations and related escalation as allowed by the model and the 100% escalation limit. For each scenario, the probability of overdose for the current dose combination, as well as the next potential dose combination and related probabilities of under-dosing, target dose, and over-dosing are shown.

Scenario 1 represents the case that 3 patients are treated at the starting dose combination 100 / 240 and none of these patients experiences a DLT. The model recommendation then is to escalate to the combination 200 / 240. Even if one of these 3 patients experiences a DLT, the model still recommends to escalate to 200 / 240 (see Scenario 2).

Scenario 3 describes a case where de-escalation to 50 / 240 would be required. In case 2 of 3 patients at 100 / 240 experience DLTs, the overdose probability at 100 / 240 exceeds 25%, which implies that 100 / 240 cannot be tested without further data at lower dose levels.

Scenarios 4 and 5 illustrate that when 3 patients have been treated at 100 / 240 without DLT and then additional 3 patients have been treated at 200 / 240 without DLT, the model would still recommend to treat the next patient with 200 / 240. Only in the case 4 or more patients are treated with 200 / 240 without experiencing a DLT, the model recommends to escalate to 400 / 240. Scenarios 9 and 10 show that in case one patient experiences a DLT at 200 / 240, the model requires 9 additional patients without DLT to allow escalating to 400 / 240.

Scenarios 11 and 12 illustrate possible ways to declare 400 / 240 as the MTD.

Table 10.5: 11 Hypothetical data scenarios

Scenario	Dose [combination] (mg)	# Patients	# DLT	Current Dose [combination]: P (OD)	Next recommended dose [combination]	Next dose [combination]:		
						P (UD)	P (TD)	P (OD)
1	100 / 240	3	0	0.012	200 / 240	0.548	0.369	0.083
2	100 / 240	3	1	0.066	200 / 240	0.335	0.453	0.212
3	100 / 240	3	2	0.256	50 / 240	0.444	0.381	0.175
4	100 / 240 200 / 240	3 3	0 0	0.027	200 / 240	0.691	0.282	0.027
5	100 / 240 200 / 240	3 4	0 0	0.021	400 / 240	0.488	0.277	0.234
6	100 / 240 200 / 240	3 3	0 1	0.117	200 / 240	0.420	0.463	0.117
7	100 / 240 200 / 240	3 3	0 2	0.308	100 / 240	0.534	0.412	0.054
8	100 / 240 200 / 240	3 6	0 1	0.048	200 / 240	0.547	0.405	0.048
9	100 / 240 200 / 240	3 10	0 1	0.014	400 / 240	0.434	0.318	0.249
10	100 / 240 200 / 240 400 / 240	3 4 6	0 0 0	0.017	400 / 240	0.819	0.164	0.017
11	100 / 240 200 / 240 400 / 240	3 4 6	0 0 1	0.101	400 / 240	0.522	0.377	0.101
12	100 / 240 200 / 240 400 / 240	3 10 6	0 1 1	0.107	400 / 240	0.488	0.405	0.107

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 combination with true DLT rate in the target interval can be approximated via simulation. Table 10.5: 12 describes 4 assumed

true dose-toxicity scenarios that 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

Table 10.5: 12 Assumed true dose-toxicity scenarios

Scenario		Dose combination (mg/mg)			
		50 / 240	100 / 240	200 / 240	400 / 240
1: Prior	P(DLT)	0.118	0.147	0.211	0.342
2: High Tox		0.156	0.298	0.379	0.514
3: Low Tox		0.051	0.092	0.137	0.254
4: Non-Logistic		0.098	0.112	0.317	0.675

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

1. 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 of BI 891065
2. If the recommended dose combination satisfying the overdose criterion is >100% increase in dose of BI 891065, then escalate to the highest dose combination which is ≤100% increase from the current dose of BI 891065.

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 if in total at least 12 patients have been included in the trial or if the posterior probability of targeted toxicity was at least 50% for the dose combination which is the model's recommendation for the next dose cohort and if in total at least 12 patients have been included in the trial.

It was then assessed how often a dose combination was declared as MTD with true DLT rate in the under-dose, targeted dose, 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 10.5: 13.

Table 10.5: 13 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	19.4	70.4	9.3	0.9	12.711 (3 - 30)	2.601 (1 - 8)
2	6.9	51.1	35.5	6.5	11.538 (3 - 30)	3.648 (1 - 12)
3	76.2	23.1	0.0	0.7	13.752 (6 - 30)	2.048 (0 - 7)
4	34.5	64.9	0.2	0.4	12.414 (6 - 27)	3.007 (1 - 9)

In Scenario 1, which reflects the case that the true dose-toxicity is aligned with prior means, 70.4% of the simulated trials declared the combination 200 / 240 mg as MTD. Only 9.3% of the simulated trials declared the dose combination 400 / 240 mg as MTD, which has an assumed true toxicity probability in the overdose interval.

In Scenario 2 (high-toxicity scenario), more than 50% of simulated trials declared a dose as MTD with assumed true toxicity probability in the target interval. 35.2% of simulated trials declared 200 / 240 as MTD which has a true toxicity probability of 0.379 which is close to boundary between target dose interval and overdose interval. The high-toxicity scenario has the biggest number of stopped trials (6.5%). This is expected for such a scenario.

In Scenario 3 (low-toxicity scenario) the MTD was more often chosen as a dose combination with true toxicity probability in under-dose interval than in the target dose interval. In the majority of simulated trials (70.4%) the MTD was chosen as 200 / 240, which has an assumed true toxicity probability of 0.137 which is close to the boundary of the target dose interval.

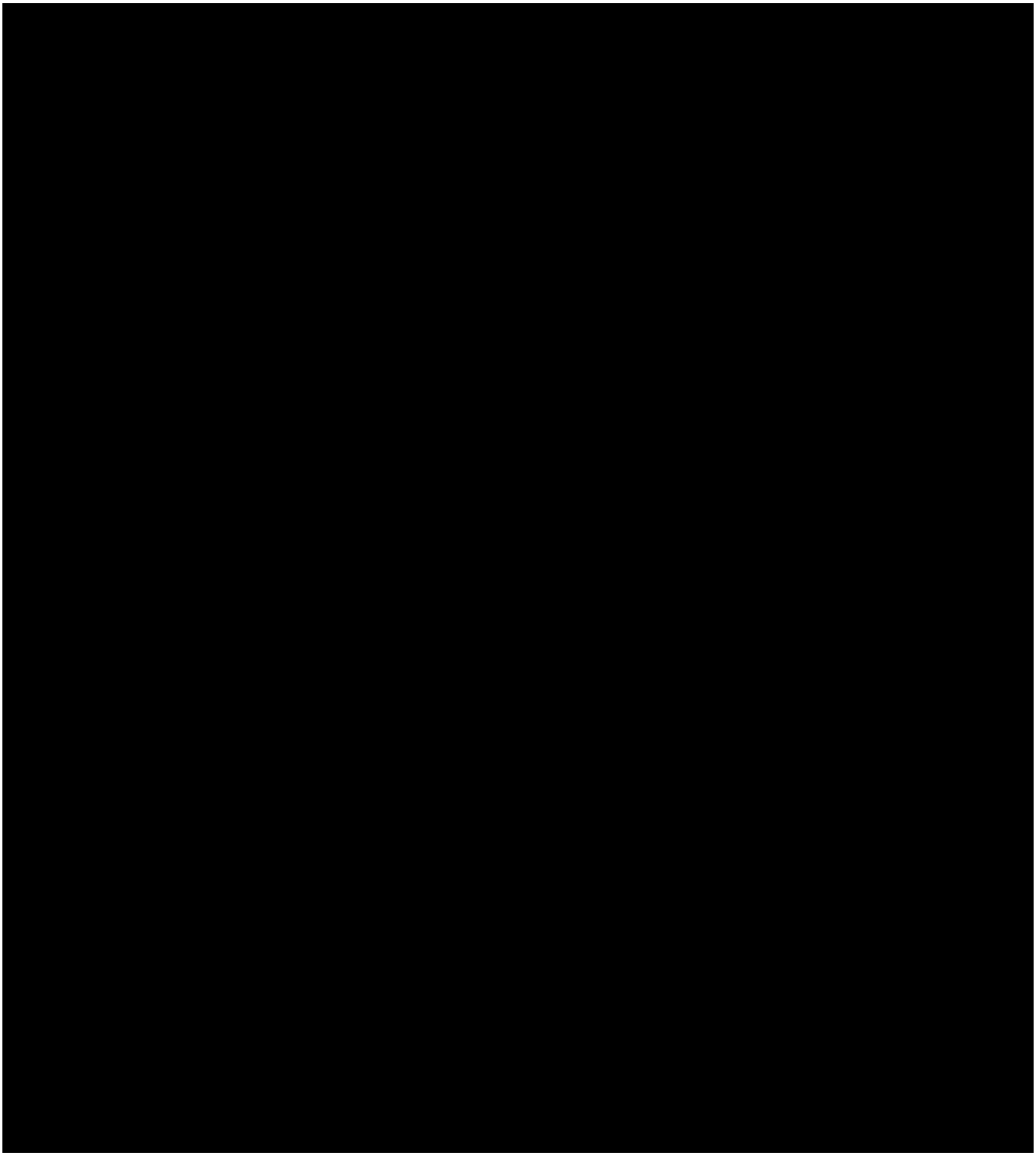
Scenario 4 (non-logistic scenario) illustrates that even if the model assumption of a logistic dose-toxicity relationship is not fulfilled, the model still selects doses with true toxicity probability in the target interval as MTD in almost 65% of simulated trials. This illustrates that the model is not sensitive to model misspecification.

The mean patient numbers range from 11.5 patients (Scenario 2) to 13.8 patients (Scenario 3) and the maximum number of patients was 30. Therefore, the patient numbers are as expected and increase when moving away from the high-toxicity scenario.

By reviewing the metrics presented in Table 10.5: 13, it can be seen that the model is not sensitive to different scenarios of truth. In general, this model is conservative due to the overdose control criteria. In all scenarios, the probabilities of recommending a dose combination with true P(DLT) ≥33% as MTD are much smaller than probabilities of recommending a dose combination 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 version 4.3.0 were used for data scenarios and simulations for Part B.



[redacted]

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		27 July 2017
EudraCT number		2017-000465-74
BI Trial number		1379.1
BI Investigational Products		BI 891065 and BI 754091
Title of protocol		An open-label Phase I dose finding trial with BI 891065 alone and in combination with BI 754091 to characterise safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy in patients with advanced and/or metastatic malignancies
To be implemented only after approval of the IRB / IEC / Competent Authorities		X
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Additions to the text are bolded and deletions from the text are crossed-off. Only the parts of sections with changes are presented. Please note that formatting changes and minor changes to punctuation, spelling, and abbreviations that do not affect meaning are not noted in this summary.		
Section to be changed		All sections, tables, etc. pertaining to Part C Cohort 2 (Multiple Myeloma) have been removed. Details are not provided in this description. In addition, the NSCLC portion is no longer designated Cohort 1, because it is the only Part C cohort currently planned. This change is also not detailed here.

Rationale for change		The FDA requested that the multiple myeloma cohort planned for Part C be removed from this protocol at this time and be submitted as a stand-alone protocol at the discretion of the Sponsor.
Section to be changed		Title page
Description of change		Trial Medical Monitor changed to: [redacted] Phone: [redacted] Fax: [redacted]
Rationale for change		Logistical change due to the location of the trial sites.
Section to be changed		Synopsis, Section 1.2.2 BI 754091, and Section 4.1.2 Selection of doses in the trial (changes to Sections 1.2.2 and 4.1.2 are presented here)
Description of change		1.2.2 BI 754091 BI 754091 is currently being tested in patients in the BI 1381.1 BI 1381.2 clinical trials and will be closely monitored during the conduct of this trial. **The dose of 240 mg BI 754091 once every 3 weeks was taken forward into the expansion portion of the BI 1381.1 trial and will be the starting dose of BI 754091 used in this trial.**
Rationale for change		Based on recommendations of the FDA, the starting dose of BI 754091 has been set at 240 mg.
Section to be changed		4.1.2.1 Starting dose of BI 891065
Description of change		~~A dose~~ **Based on the toxicities and exposures in the GLP-compliant dog study (the more sensitive species), a starting dose** of ~~25~~**5** mg BI 891065 daily ~~is expected to be a safe first-in-human starting dose for~~ **has been chosen. To minimize the number of** patients ~~in Part A, which is supported by the low overdose prior probability of 0.05~~**1exposed to doses of BI 891065 presumed to be below the threshold of activity, an adapted dose-escalation approach (see Section 4.1.3) will be used for doses of BI 891065 below 25 mg.** For details please refer to the

		Investigator's Brochure (c14463420).
Rationale for change		Based on the toxicities and exposures in the GLP-compliant dog study, a starting dose of 5 mg BI 891065 daily has been chosen. Because of the lowering of the original planned starting dose, the dose escalation plan has been adjusted for cohorts using doses <25 mg BI 891065.
Section to be changed		4.1.2.2 Starting dose of BI 754091
Description of change		**A fixed dose of BI 754091 once every 3 weeks will be administered.** The **anticipated** starting dose ~~of BI 754091~~ **is 240 mg (i.e., the dose currently selected** in ~~this trial will be determined by the SRC using~~ the ~~most recent safety information from another ongoing trial, BI~~**Phase I Trial** 1381.1~~. In the BI~~ **of BI 754091 monotherapy for expansion cohort patients and** 1381.~~1 trial, 80 mg was~~**2). Based on further data for BI 754091,** the starting dose ~~of BI 754091 the dose of 240 mg has been cleared. Escalating doses are selected~~ **may be adapted** by the SRC (informed by a BLRM with overdose control design). ~~The dosing schedule of BI 754091 will be once every 3 weeks (q3w) and is not anticipated to change.~~
Rationale for change		Based on recommendations of the FDA, the starting dose of BI 754091 has been set at 240 mg.
Section to be changed		All flow charts
Description of change		A row for virology testing at screening was added to all flow charts.
Rationale for change		To clarify that if recent virology tests (≤28 days) are not available, virology testing must be done at screening.
Description of change		A row for cardiac testing (only if cardiac disease suspected) was added to all flow charts. In addition, a new Footnote f was added for this row. All subsequent footnotes were reordered.

Rationale for change		To clarify the criteria for cardiac testing at screening by adding a link to the exclusion criteria.
Description of change		A row for reviewing patient diaries was added.
Rationale for change		To reinforce compliance during study conduct.
Description of change		All charts follow-up for PD visits footnotes: tumour assessment by imaging […] should be performed every 6 weeks (±~~-~~5 days) for the first 6 months […]
Rationale for change		Corrected from -5 days to ±5 days
Section to be changed		Part A flow chart
Description of change		Blood, **urine** sampling for pharmacokinetics
Rationale for change		To clarify that blood and urine samples are taken during Part A.
Section to be changed		Part B flow chart
Description of change		This row was added to the Part B Flow Chart: **Food administration for Food Interaction Assessment**
Rationale for change		To clarify for the sites exactly when the meal is administered during the food interaction assessment.
Section to be changed		Flow chart footnotes
Description of change		All charts Footnote a: Treatment cycles (C) are 21 days (3 weeks). Patients **may**~~will~~ continue treatment with BI 891065 as long as they are deriving clinical benefit ~~or until undue drug toxicity (both~~ according to the Investigator**'**s judgment~~) or withdrawal of consent, whichever occurs first~~. **All circumstances for withdrawal of trial treatment are presented in Sections 3.3.4.1.**
Rationale for change		To provide consistency throughout the protocol concerning withdrawal of patients from treatment.
Description of change		The following was added to Part A Footnote l, Part B Footnote n: **Patients will be observed after their first 3 doses of BI 891065 as outlined in Section**

		5.2.6.4.3. Patients will fast a minimum of 10 hours prior to select visits as outlined in Section 4.1.5.1. Patients should not take BI 891065 prior to certain visits that require pre-dose blood sampling as detailed in Table 10.3: 1. The following was added to Part C Footnote m: **Patients will be observed after their first 3 doses of BI 891065 as outlined in Section 5.2.6.4.3. Patients should not take BI 891065 prior to certain visits that require pre-dose blood sampling as detailed in Table 10.3: 1.**
Rationale for change		To clarify intense observation during the first doses of BI 891065 and the timing of doses for PK sampling days.
Description of change		Parts A and C Footnote m and Part B Footnote o: An EOT visit should be performed for all patients who permanently discontinue~~d~~ trial medication. If the decision to permanently discontinue treatment is taken at a scheduled visit, the EOT visit should be performed instead of the scheduled visit (preferably within 7 days and no later than 14 days after the last treatment). **Please note that a patient with an initial radiologic PD does not have to be automatically withdrawn from treatment (see Sections 3.3.4.1).**
Rationale for change		To clarify that patients will be allowed to continue treatment following the first radiologic progression and details are provided in Section 3.3.4.1.
Section to be changed		Part A Flow Chart Footnote l
Description of change		Added: **Patients will be observed after their first 3 doses of BI 891065 as outlined in Section 5.2.6.4.3. Patients will fast a minimum of 10 hours prior to select visits as outlined in Section 4.1.5.1. Patients should not take BI 891065 prior to certain visits that require pre-dose blood sampling as detailed in Table 10.3: 1.**
Rationale for change		To reinforce the extent of fasting and add links to sections describing patient observation and drug dosing details.
Section to be changed		2.1.2 Primary endpoints

		2.1.2.1 Part A
Description of change		[…] **For doses below 25 mg, single patient cohorts will be treated at 5 mg and 15 mg if not specified otherwise by the SRC. For doses above 25 mg, a~~A~~** BLRM employing the escalation with overdose control (EWOC) principle will be used during the escalation phase for selection of doses to investigate and for estimation of the MTD. Cohorts of patients will receive escalating doses of BI 891065 until the MTD is reached or the highest possible dose has been tested. Each cohort will consist of newly enrolled patients. Estimation of the MTD during the escalation phase of the trial will be based upon the estimation of the probability of a DLT in Cycle 1 in the set of evaluable patients **(where evaluable patients refer to patients not fulfilling the criteria for replacement [Section 3.3.4.4])** for MTD. Another BLRM employing the EWOC principle will be used during the escalation phase for selection of dose combinations and for estimation of the MTD. **It is planned that c~~C~~**ohorts of patients will receive escalating doses of BI 891065 in combination with ~~a stable dose of~~ BI 754091 **(at the dose pre-specified by the SRC)** until the MTD is reached or the highest tolerated dose of BI 891065 determined in Part A has been tested.
Rationale for change		Based on the recommendation by the FDA, doses <25 mg BI 891065 will be tested. Description of evaluable patient was moved forward in the protocol for this section and for Section 7.7. Clarified that the SRC can change the dose of BI 754091, if needed.
Section to be changed		2.1.2 Primary Endpoints 2.1.2.2 Part B Last paragraph
Description of change		Another BLRM employing the EWOC principle will be used during the escalation phase for selection of dose combinations and for estimation of the MTD. **It is planned that ~~C~~c**ohorts of patients will receive escalating doses of BI 891065 in combination with ~~a stable dose of~~ BI 754091 **(at the dose pre-specified**

		by the SRC) until the MTD is reached or the highest tolerated dose of BI 891065 determined in Part A has been tested.
Rationale for change		To clarify that the fixed dose of BI 754091 may be changed for future cohorts if deemed necessary by the SRC. Dosing of BI 754091 will not change within an individual patient's study participation.
Section to be changed		2.1.2 Primary endpoints 2.1.2.3 Part C
Description of change		**The dose of each of the study drugs used for Part C will be determined from the data of Parts A and B.** […]
Rationale for change		To clarify this point under primary endpoints
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		3.1 Overall trial design and plan
Description of change		[…] Dose-escalation will in addition be restricted to a maximum of 100% from the previous dose **for any dose ≥15 mg BI 891065 (see Section 4.1.3)**. Successive cohorts of patients will receive increasing or decreasing doses of BI 891065 until the MTD is reached; the maximum dose level planned is 400 mg. For any dose-escalation cohort **>15 mg BI 891065**, at least 3 patients will be required (refer to Section 7).

		[…] […]Part B will be a dose escalation of BI 891065 in combination with **a dose of 240 mg** BI 754091 **once every 3 weeks (the dose used for the expansion portion of Trial 1381.1.**~~at the biologically relevant dose as determined in the BI 754091 development program (Trials 1381.1 and 1381.2). The dose of BI 754091 will be kept stable during this part of the trial while escalating the dose of BI 891065.~~ **Should it be decided that a higher starting dose of BI 754091 is warranted in the combination with BI 891065, this BI 754091 dose is not to exceed the highest dose assessed as safe for BI 754091 monotherapy, and in any case must not exceed 2000 mg for the single dose (technical limit). […]** […] **For dose levels above 25 mg, i**~~i~~f DLTs are observed in the first two consecutive patients of a previously untested dose level, subsequent enrolment to that cohort will be stopped. The BLRM will be re-run to confirm that the dose level still fulfils the EWOC principle. Based on this information, the SRC will evaluate whether the next patients will be enrolled at the same dose level, or if they will be enrolled at a lower dose level~~. In the unlikely event that the initial dose of 25 mg once daily is considered as not tolerated by the SRC, cohorts on lower dose level(s) may be initiated based on the decision of the SRC~~. […] […]Patients will continue treatment as long as they are deriving clinical benefit in the opinion of the Investigator, **or until** withdrawal of consent, ~~or~~occurrence of unacceptable toxicity, ~~whichever occurs first. Patients will be allowed to stay on treatment~~**or for additional reasons detailed in Section 3.3.4.1**~~the case of initial radiological PD, if the Investigator feels that it is in the patient's best interest~~.
Rationale for change		Based on recommendations of the FDA, the starting dose of BI 891065 has been set at 5 mg, the starting dose of BI 754091 has been set at 240 mg, and it is clarified that the dose of BI 754091 cannot exceed 2000 mg.

		Because of the lowering of the original planned starting dose, the dose escalation plan has been adjusted for cohorts using doses <25 mg BI 891065.
Section to be changed		3.3.3 Exclusion criteria
Description of change		10 Any of the following cardiac criteria: […] • **Patients with an e**~~E~~jection fraction <55% or the lower limit of normal of the institutional standard **will be excluded. Only in cases where the Investigator or the treating physician or both suspects cardiac disease with negative effect on the ejection fraction, the ejection fraction will 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.**
Rationale for change		To clarify that echocardiograms or MUGAs need not be done for all patients at screening and to detail the circumstances for doing them.
Description of change		14 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.
Rationale for change		To clarify that echocardiograms are only done at screening if the Investigator suspects cardiac disease and therefore patients with know cardiac disease must

		be excluded.
Description of change		19 Patients receiving systemic treatment with any immunosuppressive medication **within 1 week prior treatment start** (steroids of max. 10 mg prednisolone equivalent per day are allowed, topical ~~[e.g.,~~**and** inhaled~~]~~ steroids are not considered as immunosuppressive~~) within 1 week prior treatment start.~~**)**.
Rationale for change		To clarify details for pre-study steroid use and to refine the definition of steroids not considered to be immunosuppressive.
Description of change		20 For Parts A and B: Patients with **known** epidermal growth factor receptor (EGFR~~) or~~**), known** anaplastic lymphoma kinase (ALK**), or known ROS Proto-Oncogene 1 (ROS1**) genomic tumour aberrations, unless disease has progressed following available EGFR or ALK targeted therapy (including osimertinib for EGFR T790M-mutated NSCLC) 22 For Part C: Patients with EGFR**,** ALK, **or (if known) ROS1** genomic tumor aberrations
Rationale for change		At the request of the FDA, ROS1 genomic tumour aberrations were added to the relevant exclusion criteria.
Section to be changed		3.3.4.1 Withdrawal from trial treatment
Description of change		An individual patient is to be withdrawn from trial treatment**(s)** if: […] • **Recurring radiologic progression. Note: In the case of initial radiological PD, patients will be allowed to stay on treatment if the following criteria are met:** – **The Investigator feels that it is in the patient's best interest** – **The patient signed an informed consent form specific for this circumstance after acknowledging that this practice is not considered standard in the treatment of cancer. The specific informed consent process for this circumstance includes**

		discussion of alternative treatment options, including any available approved therapies (if applicable) and participation in alternative clinical trials. – **Absence of clinical symptoms or signs indicating clinically significant PD** – **No decline in performance status** – **Absence of rapid PD or threat to vital organs or critical anatomical sites (e.g., central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention** – **No significant, unacceptable, or irreversible toxicities related to study treatment.** • **A pause of treatment or delayed start of treatment of more than 12 weeks due to SAEs/AEs** • **The following adverse event(s) occur:** – Cytokine release syndrome CTCAE Version 4.03 Grade 3 or 4 – Immune related AEs requiring permanent study drug discontinuation as described in Guidelines for Management of Immune-Related AEs (Appendix 10.2): - **Grade 3 to 4 pneumonitis** - **Grade 3 to 4 adrenal insufficiency** - **Grade 4 diabetes mellitus** - **Any grade encephalitis** - **Grade 4 hypophysitis** - **Grade 4 rash** - **Grade 3 to 4 colitis or recurrent colitis of any grade** - **Any recurrent Grade 3 to 4 AE** - **Transaminase increases >5 times ULN or total bilirubin >3 times ULN** - **Inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks** - **SAEs/AEs of Grade ≥2 deemed intolerable by the**

		patient or the treating physician and not responding to medical management and any SAEs/AEs of ≥ Grade 3 that do not recover to Grade 1 or less within 12 weeks - **Persistent Grade 2-3 AEs that do not recover to Grade 1 or less within 12 weeks** - **Grade 3 to 4 AEs that are classified as immune-related by the Investigator but are not listed in Appendix 10.1 if they do not resolve to Grade ≤ 1 or baseline with immunosuppressive therapy within 2 weeks.** - **≥ Grade 4 drug-related AEs.**
Rationale for change		To consolidate all circumstances for withdrawal in one section. Based on recommendations of the FDA, specifics were added for circumstances where a patient will be allowed to stay on treatment after initial radiologic progression. It is also clarified that these patients must sign an additional informed consent in order to do so.
Section to be changed		**4.1.3.1 Cohorts at dose levels <25 mg BI 891065 daily**
Description of change		**Enrolment into the first cohort at 5 mg BI 891065 daily will begin with 1 patient. If no drug-related AE ≥ Grade 2 (CTCAE Version 4.03) is observed for the single patient (observation period is 3 weeks), a 15 mg daily single patient cohort will be initiated, unless the SRC recommends another dose for the second cohort. If no drug-related AE ≥ Grade 2 (CTCAE Version 4.03) is observed for the single patient on 15 mg BI 891065 (observation period is 3 weeks), the 25-mg cohort will be initiated as described in Section 4.1.3.2, unless the SRC recommends another dose. Therefore, dose escalation to the second cohort will NOT be**

		restricted to a maximum of 100% from the previous dose as in cohorts that follow the 15 mg cohort. **If drug-related AEs ≥ Grade 2 are observed in the above described single-patient cohorts (5 and 15 mg), the cohort and subsequent cohorts will be expanded to at least 3 patients.** **The SRC will meet at the end of each of these treatment cohorts to decide on the next dose level based on available safety data.**
Rationale for change		Based on recommendations of the FDA, the starting dose of BI 891065 has been set at 5 mg. Because of the lowering of the original planned starting dose, the dose escalation plan has been adjusted for cohorts using doses <25 mg BI 891065.
Section to be changed		**4.1.3.2 Cohorts at dose levels ≥25 mg BI 891065 daily**
Description of change		The dose of BI 891065 is planned to be escalated in the Part A cohorts **≥25 mg daily** at pre-defined provisional dose levels based on a maximum escalation of 100%. The provisional dose levels **≥25 mg daily** to be assigned to separate cohorts of patients are listed in Table 4.1.3: 1. Intermediate or lower dose levels, depending on the number of DLTs observed in the trial may be investigated as long as they fulfil the EWOC criterion if agreed upon by the SRC. Table 4.1.3: 1 was updated by the addition of the **5 mg and 15 mg dose levels as Doses 1 and 2**. The rest of the table items were subsequently shifted. At the end of each treatment cohort, BI will convene a meeting with the SRC members. At the dose escalation meeting the clinical course (safety information including both DLTs and all Common Terminology Criteria for Adverse Events [CTCAE; R18-1357] ≥ Grade 2 toxicity data during the MTD evaluation period and additional data if needed) for each patient in the current dose cohort will be described in detail. Updated safety data on other

		ongoing patients, including data in later cycles, as well as cIAP degradation in PBMCs **(for dose cohorts above 25 mg BI 891065)**, will be discussed as well. Based on that, a decision on the next dose level to be tested will be made. For Part B (combination therapy), the dose of BI 891065 is planned to be escalated in cohorts at dose levels which will be determined based on the results of Part A. However, the starting dose of BI 891065 in Part B will be maximally 75% of the highest tolerated dose from Part A. **It is planned that**~~The~~ **a** fixed dose of **240 mg** BI 754091 will be used as determined in ~~t~~**T**rial 1381.1 (**the dose chosen for the expansion cohorts**~~and possibly Trial 1381.2~~). Based on emerging safety information in the 1381.1 and 1381.2 studies, the SRC may amend the dose of BI 754091 used in this trial. The SRC will determine the selected dose of BI 754091 for each combination cohort of this trial and communicate it to the investigators. The dose of BI 891065 in combination with BI 754091 to be used in Part C will be determined based on the safety and PK/PDc data of Parts A and B including data of target engagement in tumour tissue.~~ The fixed dose of BI 754091 will be used as determined in trial 1381.1 (and possibly trial 1381.2)~~. The dose of BI 891065 might be changed during conduct of Part C, if needed. ~~In Part C Cohort 2 (MM), the dose of BI 891065 will be assessed by the SRC and confirmed after the number of patients specified in the SRC documentation have been treated for at least one cycle~~.
Rationale for change		Based on recommendations of the FDA, the starting dose of BI 891065 has been set at 5 mg. Because of the lowering of the original planned starting dose, the dose escalation plan has been adjusted for cohorts using doses <25 mg BI 891065.
Section to be changed		4.1.5.1 Administration of BI 891065
Description of change		[…] Patients need to be ~~advised~~**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 and all meals on the PK days should be recorded in the patient diary.** **Refer to flowcharts and Appendix 10.3 for information about sampling that is required prior to dose administration.** BI 891065 doses should be taken orally at approximately the same time each morning with the exception of ~~certain trial visit days. For clinic visits on PK days following a single dose of BI 891065 (~~**prior to Part A** Cycle 1 Day ~~1) and for the food effect assessment in Part B (see the flow charts and tables in Section), patients~~**2 where study drug is not taken**. **Patients** will be asked to fast overnight (minimum of 10 hours) prior to the **following intensive PK days:** **Part A: Cycle 1 Day 1, 15** **Part B: Cycle 1 Day 1,15, 16** **Refer to Section 10.3**~~visit. Pre-dose laboratory samples will be collected prior to receiving the single morning dose.~~ **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 (approximately 8 US ounces).~~ The fasting status and all meals on the PK days should be recorded in the patient diary.~~ Additional information about the food-interaction assessments in Part B are presented in Section 6.2.2.1. ~~For clinic visits on non-PK days, patients will be asked to fast overnight (minimum of 10 hours) prior to the visit. Pre-dose laboratory samples will be collected prior to receiving the single morning dose. The fasting status on non-PK days should be recorded in the patient diary.~~

		Missed doses should not be made up if more than 6 hours have passed since scheduled dosing time. Missed doses must be recorded in the patient's Dosing Diary, and then should be recorded in the eCRF.
Rationale for change		Increased detail on fasting requirements and timing in relation to PK sampling to add clarity.
Section to be changed		4.1.7 Dose reductions and dose delays
Description of change		If the treatment pause is ≤**12**~~6~~ weeks, the patient can be re-exposed to BI 891065 at one dose level lower than the dose administered before the pause **(except for the 5 mg monotherapy dose)** and the same fixed dose of BI 754091 ~~(applicable for Part A monotherapy and Part B combination therapy)~~ as long as the re-exposure is considered clinically indicated by the Investigator. Figure 4.1.7: 1 was updated to reflect the new timing. ~~BI 891065 and BI 754091 should be permanently discontinued together for Grade 3 to 4 pneumonitis, Grade 3 to 4 adrenal insufficiency, Grade 4 diabetes mellitus, any grade encephalitis, Grade 4 hypophysitis, Grade 4 rash, Grade 3 to 4 colitis or recurrent colitis of any grade, any recurrent Grade 3 to 4 AE, transaminase increases >5 times ULN or total bilirubin >3 times ULN, inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2 to 3 AEs that do not recover to Grade 1 or less within 12 weeks. BI 754091 and BI 891065 should be permanently discontinued together for Grade 3 to 4 AEs that are classified as immune-related by the Investigator that are not listed in Appendix .Please see Appendix for guidelines for management of immune-related adverse events.~~ […] **Criteria leading to permanent discontinuation of BI 891065 and BI 754091 are presented in Section 3.3.4.1.** Section 4.1.7.1 Permanent discontinuation of

		BI 891065 and BI 754091 was removed and included in Section 3.3.4.1.
Rationale for change		!" #$%&'()+,%'$"(&:++/0"-1&+," 23 456789 ("$$":';< %0%1-+"(=6> :++?-@ !A+ 0%&%<&%0A *+-#&'B';< 0+&C%;+;, *'-#";,';1%,'"; "(,A+-,1*) ,&+%,C+;,:%- C"D+*," E+#,'"; F@F@G@6 -" ,A%%$$'-#";,';1%,'"; #&',+&:%1$* B+'; ,A+ -%C+-+#,'";@
Section to be changed		G@6@67 H+(';','"; "(D%$1%B$%,'+;,
Description of change		~~Please refer to Section 7.2.~~ **Patients that are evaluable for MTD are those who do not fulfil criteria for replacement as outlined in Section 3.3.4.4.**
Rationale for change		!" %**,A+*+(';','"; &%,A;+&%;';$) 0&+-+;,';<% $';?@
Section to be changed		G@>@>@> I+-,&'#,'";- "; *'+, %;* $'(+ -,)$+
Description of change		[…] 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** • **Part B patients will be asked to eat a specific meal per Section 6.2.2.1.**
Rationale for change		A link was added to the fasting requirements and details around the fed portion of the food interaction assessment.
Section to be changed		G@!&+%,C+;#"C0$'%;#+
Description of change		The investigational products should only be used as directed in this protocol. **For BI 754091 administration days,** BI 891065 will be administered orally approximately 30 minutes after the end of the infusion of BI 754091, and only if considered safe by the Investigator.
Rationale for change		JA%;<+*," %**#$%&',)@

Section to be changed		9@K--+--C+;, "(+(('#%#)
Description of change		Copies of scans ~~may~~**will** be collected by the Sponsor ~~upon request~~.
Rationale for change		!" +C0A%-'L;A%,A+E0";-"& :'$$ #"$$+##"0'+- "(+(('#%#) %--+--C+;, -#%;-@
Section to be changed		5.1.1 NSCLC tumour assessment and solid tumour assessment
Description of change		[…] If the patient stops with the trial medication for ~~another~~ reason **other** than progression, the tumour assessment according to RECIST v1.1 and iRECIST will be performed according to standard of care until the last follow-up needed according to **the** protocol (progression, death, lost to follow-up, end of the trial). **Patients will be allowed to stay on treatment in the case of initial radiological PD, if the Investigator feels that it is in the patient's best interest, the patient signs an informed consent form specific for this circumstance, and the criteria listed in Section 3.3.4.1 are met.**
Rationale for change		Based on recommendations of the FDA, specifics are added for circumstances where a patient will be allowed to stay on treatment after initial radiologic progression. It is also clarified that these patients must sign an additional informed consent in order to do so.
Section to be changed		5.2.3 Safety laboratory parameters
Description of change		Biochemistry The standard biochemistry panel will consist of glucose, sodium, potassium, chloride, calcium, phosphate, venous bicarbonate HCO_3, urea, creatinine, AST, ALT, alkaline phosphatase, lactate dehydrogenase, bilirubin (direct and indirect bilirubin in case of elevated total bilirubin values), total protein, albumin, urea nitrogen, uric acid and creatinine kinase (CK~~; if~~**). If** CK is elevated, then CK-MB [cardiac], Troponin I, and myoglobin should be reactively tested**)**. **C-peptide , serum cholesterol, serum triglycerides**

		will be done at baseline only.
Rationale for change		To clarify C-peptide, cholesterol, and triglycerides testing.
Description of change		Virology At screening, tests **according to local standards** for HIV infection ~~(PCR)~~ and hepatitis B (~~HBs-Ag~~, and if positive, anti-HBs, anti-HBc antibodies, and HBV DNA) and hepatitis C ~~(PCR)~~ should not be older than 28 days.
Rationale for change		To clarify that virology testing should be according to local standards, and therefore specific types of testing are not mandated.
Section to be changed		5.2.4 Electrocardiograms
Description of change		Electrocardiogram machines will be provided for Part A 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. While all ECGs will be transmitted to the central vendor, only the baseline, 6-hour, 8-hour, and 24-hour readings will be reviewed directly. The other readings **would**~~will~~ be analyzed only **if**~~after~~ the PK analysis points to a t_{max} deviate from the predicted t_{max}.
Rationale for change		To clarify when additional ECG reading time points might be read by the central vendor.
Section to be changed		5.2.6.3 Adverse events considered “Always Serious”
Description of change		[…] The latest list of “Always Serious AEs” can be found in the **Study Reference Manual**~~electronic document system~~. These events should always be reported as SAEs as described above.
Rationale for change		Clarification that the latest list of “Always Serious AEs” will be located in the Study Reference Manual.
Section to be changed		5.2.6.4.3 Cytokine release syndrome

Description of change		• […] In the case of a CRS CTCAE Version 4.03 Grade 2, 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 3.3.4.4 regarding replacement of patients.
Rationale for change		To clarify the intention of the 50% dose of BI 754091 when BI 891065 is being restarted.
Section to be changed		5.3.2 Methods of sample collection
Description of change		[…] **Pharmacokinetic sampling times and periods may be adapted by the Sponsor during the trial based on information obtained during trial conduct (e.g., preliminary PK data). Such changes would be implemented via non-substantial Clinical Trial Protocol Amendments.** […]
Rationale for change		To clarify that PK sampling times may be changed based on new data.
Section to be changed		6.1 Visit schedule
Description of change		Additional PD follow-up visits 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) **with the exception of those who may continue treatment for a time after initial radiologic progression**.
Rationale for change		To clarify that patients will be allowed to continue treatment following the first radiologic progression if deemed appropriate by the Investigator

Section to be changed		6.2.2 Treatment period
Description of change		Patients will remain on treatment as long as, in the opinion of the Investigator, they are deriving benefit **and the criteria listed in Section 3.3.4.1 are not met**. Please refer to the respective flow charts for detailed presentations of each visit during the treatment period for each part of the trial.
Rationale for change		To provide a link for the reviewer to new criteria specified in Section 3.3.4.1 explaining the criteria for patients to continue on treatment after the initial radiologic progression.
Section to be changed		6.2.2.1 Food-interaction assessment
Description of change		At all dose levels in Part B, an explorative food effect will be assessed. ~~Consecutive patients~~**Patients** will ~~be assigned~~**fast for at least 10 hours prior** to ~~a fixed sequence of a fasted treatment followed by a fed treatment the next day. For the fasted condition (~~**Cycle 1** Day 15~~), patients will~~**then** receive BI 891065 ~~after an overnight fast of at least 10 hours,~~ together with **approximately** 240 mL water. Patients will remain fasted until at least 2 hours after drug intake. Water will be allowed except 30 minutes before and 1 hour after administration of BI 891065. ~~The fed condition~~ **Patients** will ~~occur on Day 16; after an overnight~~ fast ~~off~~**for** at least 10 hours ~~and following~~**prior to Cycle 1 Day 16**. **At this visit, within 30 minutes of planned BI 891065 dose administration time, patients will be given** a standard continental breakfast (see below**) which they should consume within the 30 minutes prior to drug administration. Then** patients will receive BI 891065~~together~~ with **approximately** 240 mL water within 5 minutes of consuming the standard meal. ~~Patients should start and consume the breakfast within the 30 minutes prior to administration of BI 891065.~~ If the patients are not able to eat or eat almost nothing, the information should be recorded on the eCRF. The following definition of the standard continental breakfast is given in order to standardise the food

		intake prior to assessing food effects on BI 891065 **(rough approximation):** 2 bread rolls, 20 g butter, 25 g cheese, 25 g ham, 25 g jam, and 1 cup (~250 mL) of decaffeinated tea or coffee (average energy value per breakfast: ~688 kcal or 2880 kJ. **Note: Alternative food components/quantity can be proposed by the Investigator, but it should be ensured that the caloric breakdown of the test meal is roughly in line with the breakfast indicated above.**
Rationale for change		Additional details are added for the sites to increase compliance with the food interaction assessment part of the study.
Section to be changed		7.1 Statistical design model 7.1.1 Part A
Description of change		The BLRM recommended dose for the next dose level is the level with the highest posterior probability of the DLT rate falling in the target interval [0.16, 0.33) among the doses fulfilling EWOC. Applying the EWOC criterion it should be unlikely (<25% posterior probability) that the DLT rate at that dose will be ≥0.33. ~~However~~**In addition, for dose levels ≥25 mg BI 891065**, the maximum allowable dose increment for the subsequent cohort will be no more that 100% from cohort to cohort. […] A summary of the prior distribution is provided in Table 7.1.1: 1. Additionally, the prior probabilities of DLTs at different doses, as well as the corresponding probability of under-, targeted and overdosing, are shown in Table 7.1.1:2. Graphically, the prior medians with accompanying 95% credible intervals are shown in Figure 7.1.1:1. As can be seen from both, the table and the figure, the prior medians of the DLT probabilities are in-line with the prior medians derived from the weakly informative prior, and the uncertainty around the medians is large, showing the low amount of information this prior provides. This is also supported by the prior sample size, i.e., the information contained in the prior. This is approximately equal to 1.8 patients. **Furthermore, it can be seen that the overdose prior probability of**

		the starting dose of 5 mg is 0.029 and therefore well below the EWOC boundary of 0.25. A detailed evaluation of the model using hypothetical data scenarios and operating characteristics is provided in the statistical appendix (see Appendix 10.5). In the following paragraphs of this section, it was clarified that the starting dose was no longer 25 mg. Table 7.1.1: 2 and Figure 7.1.1:1 were updated to add the 5 mg and 15 mg doses as dose levels 1 and 2.
Rationale for change		To clarify that there will be new dose levels at 5 and 15 mg and that the BLRM will be initiated for doses ≥25 mg BI 891065.
Section to be changed		7.7 DETERMINATION OF SAMPLE SIZE
Description of change		Part A: No formal statistical power calculations to determine sample size were performed for this trial part. Approximately 30 patients (including patients at the MTD) are expected to be enrolled into Part A of this trial based on the number of dose levels/cohorts that are tested. Fewer patients might be needed based on the recommendation of the SRC and the criteria specified (see Section 8.7). However, the actual number of patients will depend on the number of dose cohorts tested. Based on the simulation study to evaluate operating characteristics of the BLRM (see statistical appendix), at least 20 evaluable patients **(where evaluable patients refer to patients not fulfilling the criteria for replacement [Section 3.3.4.4])** are expected to be treated in the dose escalation part for the model to have reasonable operating characteristics relating to its MTD recommendation. Part C […] With only 20 evaluable patients **(at least one post-baseline response assessment is available),** the probability of observing 7 ORs assuming a true underlying response rate of 30% is only 39%.

Rationale for change		Descriptions of evaluable patients are moved forward in the protocol for this section and for Section 7.7, and the differences in definitions are highlighted between Parts A and C.
Section to be changed		8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT
Description of change		[…] **Following the initial radiologic progression, patients may be allowed to continue on treatment if, in the opinion of the Investigator, they are experiencing clinical benefit. In this case, an additional informed consent form specific for this circumstance will be signed by the patient prior to treatment continuation.**
Rationale for change		Based on recommendations of the FDA, it is clarified that patients staying on treatment after initial radiologic progression must sign an additional informed consent in order to do so.
Section to be changed		References
Description of change		Reference to the BI 891065 Investigator's Brochure was updated to Edition 3. All references used in the multiple myeloma sections were removed.
Rationale for change		The BI 891065 Investigator's Brochure has been updated. The multiple myeloma cohort has been removed from the protocol.
Section to be changed		Table 10.3: 1
Description of change		Footnote **c 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 (◄—│—│—►) 0-4, 4-8, 8-12, 12-24 (Cycle 1 Days 1 and 15) and 24-48 h (Cycle 1 Day 1 only) and detailed in Section 5.3.2.4**.

Rationale for change		The table was updated by adding Footnote c and by making it clear that the pre-dose sampling is a spot urine sample and not a pool.
Description of change		It was confirmed that overnight fasting is required before the first PK sampling on Day 15.
Rationale for change		Correction: the footnote was mistakenly not added to the table.
Section to be changed		10.5 Statistical Appendix
Description of change		This appendix has been updated to include the 2 new doses <25 mg.
Rationale for change		Based on recommendations of the FDA, the starting dose of BI 891065 has been set at 5 mg. Because of the lowering of the original planned starting dose, the dose escalation plan has been adjusted for cohorts using doses <25 mg BI 891065.

Number of global amendment		2
Date of CTP revision		27 February 2018
EudraCT number		2017-000465-74
BI Trial number		1379.1
BI Investigational Products		BI 891065 and BI 754091
Title of protocol		An open-label Phase I dose finding trial with BI 891065 alone and in combination with BI 754091 to characterise safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy in patients with advanced and/or metastatic malignancies
To be implemented only after approval of the IRB / IEC / Competent Authorities		X
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Additions to the text are **bolded** and deletions from the text are ~~crossed-off~~. Only the parts of sections with changes are presented. Please note that formatting changes and minor changes to punctuation, spelling, and abbreviations that do not affect meaning are not noted in this summary.		
Section to be changed		All flow charts Footnote c
Description of change		[…]clinical chemistry (sodium, potassium, phosphate, chloride, creatinine, calcium, venous bicarbonate HCO_3, albumin, total protein, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, bilirubin, lactate dehydrogenase, serum glucose, ~~c-peptide [baseline only], serum cholesterol [baseline only], serum triglycerides [baseline only],~~ creatinine kinase [CK:

		if CK is elevated, then CK-MB, Troponin I, and myoglobin should be reactively tested, with further follow-up as clinically warranted], serum urea nitrogen, serum uric acid, and thyroid panel [TSH, free T4, and free T3]), […]
Rationale for change		It has been determined that these tests are not needed.
Section to be changed		Part A flow chart Footnote c
Description of change		[…] and **single**/triplicate ECGs required ~~prior to first trial dose~~**as outlined in Section 5.2.4 and Table 10.3: 1**.[…]
Rationale for change		To clarify that single or triplicate ECGs are taken in relation to specific PK sampling times as presented in the Section 10 tables.
Section to be changed		Part A flow chart Footnote e
Description of change		**Triplicate or single** 12-lead electrocardiograms (ECGs) will be done **at the time points as outlined in Section 5.2.4 and Table 10.3: 1**~~in triplicate before blood work or other procedures after 10 minutes of rest at screening, during Cycle 1 on Days 1, 2, 15, and 16 at every PK sampling point, and pre-treatment on Cycle 2 Day 1, Cycle 3 Day 1, and Day 1 of every third cycle thereafter (Cycles 6, 9, 12, etc.), at the EOT visit~~, and whenever […]
Rationale for change		To clarify that not all ECGs taken in Part A will be triplicate ECGs. Triplicate ECGs are taken in relation to specifc PK sampling times as defined in the Section 10 tables.
Section to be changed		Part A flow chart Footnotes h and p
Description of change		Tumour assessments should be done according to RECIST v1.1 **and iRECIST** […]
Rationale for change		To clarify that there are iRECIST parameters in Part A in addition to Parts B and C.
Section to be changed		Part B flow chart Footnote c
Description of change		[…] and single/**triplicate** ECGs **as outlined in Section 5.2.4 and Table 10.3: 2** required prior to

		first administrations of trial treatments. […]
Rationale for change		To clarify that not all ECGs taken in Part B will be single ECGs. Some triplicate ECGs are taken in relation to specific PK sampling times as defined in Section 5.2.4 and the Section 10 tables.
Section to be changed		Part B flow chart Footnote e
Description of change		**Triplicate or** ~~**Ss**~~**single** 12-lead electrocardiograms (ECGs) will be done **at time points as outlined in Section 5.2.4 and Table 10.3: 2** ~~before blood work or other procedures after 10 minutes of rest at screening, and pre-treatment during Cycle 1 on Days 1, 2, 15, and 16, single ECGs will be done during Cycle 2 on Day 1, during Cycle 3 on Day 1, and on Day 1 of every third cycle thereafter (Cycles 6, 9, 12, etc.), at the EOT visit,~~ and whenever the Investigator deems it necessary (see Section 5.2.4 and Table 10.3: 2 ~~Table 10.3.1~~). **ECG machines will be provided for Part B to facilitate central readings. While all ECGs will be transmitted to the central vendor, only the baseline, 6-hour, 8-hour, and 24-hour readings will be reviewed directly. The other readings will be analysed only after the PK analysis points to a t_{max}.**
Rationale for change		To clarify that not all ECGs taken in Part B will be single ECGs. Some triplicate ECGs are taken in relation to specific PK sampling times as defined in the Section 10 tables.
Section to be changed		Part B flow chart Footnote l
Description of change		Blood samples for biomarkers - samples for the quantification of cytokines will be taken during Cycle 1 on Day 1 pre-treatment and at 5.5 and 9.5 hours post treatment, on Day 2 ~~(no treatment day)~~ at 24 hours after first drug intake on the previous day, pre-treatment on Day 8, and at the EOT visit (see Section 5.4.2 and Appendix 10.3).
Rationale for change		Correction

Section to be changed		Section 1.3 Rationale for conducting the trial
Description of change		[…] **Parts A and B of the trial will be undertaken in patients with advanced/refractory solid tumours. Part A will determine the MTD and/or the recommended dose for Part B as well as investigate the safety, PK, and pharmacodynamics (PDc) of BI 891065 monotherapy. Target engagement will be determined in peripheral blood (cIAP degradation in peripheral blood mononuclear cells [PBMCs]). Dose escalation in Part A will be guided by a BLRM with overdose control. The data obtained from the trial will determine the MTD estimate based on a BLRM employing an escalation with overdose control (EWOC) principle (R13-4803). The BLRM estimates the MTD by updating estimates of the probability of observing a DLT in the MTD evaluation period (first treatment cycle) 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 criterion (refer to Section 7).** **In both Parts A and B, the Safety Review Committee (SRC) will recommend and decide on the size for the next dose escalation cohort. After all patients in a cohort in Part A and Part B 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.** ~~Parts A and B will be undertaken in patients with advanced/refractory solid tumours to determine the MTD and/or the recommended dose for later development (Part C).~~ Part C will be in the selected indication (NSCLC) in order to assess efficacy (objective response [OR]) and reconfirm safety and tolerability **at the combination doses determined in Part B**. […]
Rationale for change		Clarification of the BLRM estimates.

Section to be changed		Section 1.4 Benefit Risk Assessment
Description of change		[…] Since this is the first-in-human trial for BI 891065, patients in Part A will remain under surveillance for **10**~~12~~ hours after first administrations of BI 891065 and for at least 8 hours after administration of the second and third administrations of BI 891065. For Parts B and C, patients will remain under surveillance for **10**~~12~~ hours after the administration of BI 891065 in combination with BI 754091 in Cycles 1 and 2, and for at least 8 hours after the second and third administrations of BI 891065 in Cycle 1 (see Section 5.2.6.4.3). All trial sites will have emergency resuscitation services and access to intensive care available. […]
Rationale for change		Preliminary data supports the shortening of the length of required surveillance following the first administration of BI 891065 to make it easier for the patients.
Section to be changed		Section 2.1.2.1 Part A (Primary endpoints)
Description of change		[…] For doses below 25 mg, single patient cohorts will be treated at 5 mg and 15 mg if not specified otherwise by the SRC. ~~For doses above 25 mg, a~~ **A** BLRM employing the ~~escalation with overdose control (~~EWOC~~)~~ principle will be used during the escalation phase for selection of doses to investigate and for estimation of the MTD. […]
Rationale for change		Clarification of when the BLRM will be used in Part A.
Section to be changed		Section 2.1.2.3 Part C (NSCLC)
Description of change		[…] Tumor imaging will be performed at baseline and then every 6 weeks for the first 6 months and then every 9 weeks thereafter **as required by RECIST / iRECIST (R17-0923)** until the earliest of PD, death or **the** last evaluable tumour assessment before start of subsequent anti-cancer therapy or until the end of

		the trial as defined in Section 8.6.
Rationale for change		To clarify that the requirements of RECIST and iRECIST will be followed for continued tumour imaging.
Section to be changed		Section 3.1 Overall Trial Design and Plan
Description of change		[…] In both Parts A and B, the SRC will recommend and decide on the size for the next dose escalation cohort. After all patients in a cohort **in Part A and Part B** 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. […] For dose levels above ~~25~~15 mg, if DLTs are observed in the first two consecutive patients of a previously untested dose level, subsequent enrolment to that cohort will be stopped. The BLRM will be re-run to confirm that the dose level still fulfils the EWOC principle. Based on this information, the SRC will evaluate whether the next patients will be enrolled at the same dose level, or if they will be enrolled at a lower dose level.
Rationale for change		To clarify that the BRLM will be run for both Parts A and B, and for all dose levels above 15 mg.

Section to be changed		Section 4.1.3.1 Cohorts at dose levels <25 mg BI 891065 daily
Description of change		Enrolment into the first cohort at 5 mg BI 891065 daily will begin with 1 patient. If no drug-related AE ≥ Grade 2 (CTCAE Version 4.03) **and no DLT** is observed for the single patient (observation period is 3 weeks), a 15 mg daily single patient cohort will be initiated, unless the SRC recommends another dose **or another cohort size** for the second cohort. If no drug-related AE ≥ Grade 2 (CTCAE Version 4.03) **and no DLT** is observed for the single patient on 15 mg BI 891065 (observation period is 3 weeks), the 25-mg cohort will be initiated as described in Section 4.1.3.2, unless the SRC recommends another dose. […] The SRC will meet at the end of each of these treatment cohorts to decide on the next dose level based on available safety data **and the BLRM recommendation**.
Rationale for change		To clarify the method of dose escalation in Part A and to clarify that a BLRM will be used in Part A.
Section to be changed		Table 4.1.3: 1 Provisional dose levels for dose escalation of BI 891065 in Part A
Description of change		Increase of Dose Level 2 over Dose Level 1 is corrected to 300%.
Rationale for change		Correction
Section to be changed		Section 4.1.5.1 Administration of BI 891065
Description of change		[…] Patients will be asked to fast overnight (minimum of 10 hours) prior to the following intensive PK days: Part A: Cycle 1 Day 1, 15 Part B: Cycle 1 Day 1, **15,** 16
Rationale for change		Correction
Section to be changed		Section 4.1.8 Definition of dose-limiting toxicity
Description of change		Dose-limiting toxicities (DLTs) will be recorded

		throughout the trial. Any DLT must be reported to the [redacted] Medical Monitor by the Investigator or designee within 24 hours of first knowledge, and to the [redacted] as an SAE when appropriate. All DLTs will be agreed upon between the Sponsor, the Study Chair, the [redacted] Medical Monitor, and the Investigators after review of the data from each cohort. […] […] Severity of AEs will be graded according to CTCAE Version 4.03. Any of the following AEs ~~that are not equivocally due to underlying malignancy or an extraneous cause~~ will be classified as DLTs following review by the Investigators and the [redacted] Medical Monitor **unless unequivocally due to underlying malignancy or an extraneous cause**. […]
Rationale for change		To clarify which Medical Monitor should be notified. In addition, the sentence was rewritten for better clarity.
Section to be changed		Section 4.2.2.1 Restrictions regarding concomitant treatments
Description of change		[…] **BI 891065 was found to be an inhibitor of various CYP450 enzymes *in vitro*, with Ki values in the range of 0.84 to 12 µM (see Section 1.2.1). 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). Table 4.2.2.1: 1 provides a list of restricted and permitted medications. Alternatives with less potential for CYP450 based interactions should be considered, where available. Close monitoring for potential adverse reactions is warranted and patients should be informed about potential signs and symptoms of such adverse reactions (e.g., muscle pain). BI 891065 was also found to be an inhibitor of the drug transporters P-glycoprotein and BCRP *in vitro*, with IC_{50} values of 0.034 uM and 0.18-0.59 µM,**

		respectively (see Section 1.2.1). Caution should be exercised when combining BI 891065 with P-gp and BCRP substrates. Table 4.2.2.1: 1 provides a list of restricted and permitted medications. **Table 4.2.2.1: 1 was added.** ~~BI 891065 is an *in vitro* inhibitor of various CYP450 enzymes, with Ki values in the range of 0.84 to 12 µM (see Section 1.2.1). 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. In particular, concomitant administration of BI 891065 and drugs metabolized by CYP3A4, e.g., HMG CoA-reductase inhibitors (such as lovastatin, simvastatin, and atorvastatin) or calcium antagonists (such as nisoldipine, less for verapamil or nifedipine), could result in increased exposure of the concomitant drug, depending on the currently yet uncharacterized bioavailability of BI 891065. Concomitant treatment with such drugs while the patient is receiving BI 891065 should occur only if strictly indicated, and with judicious dosing. 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).~~ *The following **caveat applies for** ~~concomitant medications~~ **immunosuppressive medications** ~~are prohibited~~: • ~~Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNFα 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 upon discussion with the [redacted] Medical Monitor. For the treatment of CRS, supportive therapy including steroids and / or interleukin 6 receptor (IL6R) antagonists (R15-0031) may be used as clinically indicated. • ~~Live attenuated vaccines are prohibited during the trial through 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 7 days prior to first dose of study treatment.~~
Rationale for change		In response to comments from the FDA, further restrictions were applied for concomitant medications. In addition, clarification of which Medical Monitor to contact was added.

Section to be changed		Section 5.1.1 NSCLC tumour assessment and solid tumour assessment
Description of change		Tumour response will be evaluated at the site according to RECIST Version 1.1 (R09-0262) and/or iRECIST (R17-0923 and Appendix 10.6) ~~(relevant during combination therapy)~~. 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). Duplicates of the images will be collected and stored by a BI-appointed representative, and **may be used**~~could be sent~~ for future independent central RECIST/**iRECIST** review, if deemed appropriate. **In addition, the images may be used for further future investigations (e.g., Radiomics).** […]
Rationale for change		To clarify that iRECIST applies to Part A in addition to Parts B and C, and to introduce that images collected may be used in future Radiomics investigations.
Section to be changed		Section 5.2.3 Safety laboratory parameters
Description of change		Biochemistry […] ~~C-peptide , serum cholesterol, serum triglycerides will be done at baseline only.~~ […]
Rationale for change		The Medical Monitors and Investigators have determined that these tests are not needed.
Section to be changed		Section 5.2.4 Electrocardiograms
Description of change		Standard 12-lead (I, II, III, aVR, aVL, aVF, V1 - V6) resting electrocardiograms (ECGs) will be digitally recorded ~~in triplicate (3 single ECGs within a maximum period of 5 minutes) and performed for each patient~~ at various time points **throughout the trial**. ~~during Part A of the trial according to~~ **The Part A Flow Chart and the Part B Flow Chart** ~~and Appendix 10.3~~ **outline which visits will require ECGs, and Appendix 10.3 outlines which time points (during Parts A and**

		B) require triplicate ECGs to be done along with certain PK samples. ~~This will include triplicate readings during Part A at every PK sampling time point during Cycle 1 on Days 1, 2, 15, and 16.~~ […] Electrocardiogram machines will be provided for Part**s** A **and B** to facilitate central readings.[…] ECGs may be repeated for quality reasons and the repeated recording used for analysis. If necessary, additional ECGs may be recorded for safety reasons. In Part~~s B and~~ C, single ECGs will typically be taken unless additional readings are indicated. 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. 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 4.03 will be used for the grading of prolonged QTcF intervals. ~~During the BI 891065 monotherapy dose escalation, ECGs will be done at screening, specified visits and at EOT.~~ […] ~~In Parts B and C, single 12-lead ECGs will be done as outlined in the flow charts and will be assessed by the sites locally; particular attention must be paid to T wave inversions. Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as AEs and will be followed up and/or treated as medically appropriate.~~
Rationale for change		To clarify that not all ECGs taken in Part A will be triplicate ECGs. Triplicate ECGs are taken in relation to PK sampling as defined in the Section 10 tables, while single ECGs are taken for safety

		reasons on non-PK days.
Section to be changed		Section 5.2.6.4.3 Cytokine release syndrome
Description of change		[…] For Part A: • Patients will remain under surveillance for **10**~~12~~ hours after first administration of BI 891065 [redacted] […] For Parts B and C: • Patients will remain under surveillance for **10**~~12~~ hours after the administration of BI 891065 [redacted] in combination with BI 754091 [redacted] during Cycles 1 and 2. […]
Rationale for change		Preliminary data supports the shortening of the length of required surveillance following the first administration of BI 891065 to make it easier for the patients.
Section to be changed		Section 5.3.2.4 Urine sampling and analysis for pharmacokinetics of BI 891065 (Part A only)
Description of change		[…] Cycle 1 Day 1: • Spot urine pre-dose • Pool 0 to **3**~~4~~ hours • Pool **3**~~4~~ to 8 hours • Pool 8 to ~~12~~**10** hours • Pool ~~12~~**10** to 24 hours • Pool 24 to 48 hours Cycle 1 Day 15 • Spot urine pre-dose • Pool 0 to **3**~~4~~ hours • Pool **3**~~4~~ to 8 hours • Pool 8 to ~~12~~**10** hours • Pool ~~12~~**10** to 24 hours […]
Rationale for change		To shorten the length of the PK testing days to make it easier for the patients.

Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		Section 5.4 Assessment of biomarkers
Description of change		[…] As medical knowledge in this field is constantly evolving, other tissue/blood biomarkers that may become relevant as predictive markers of treatment response **(e.g., 4β-OH cholesterol)** may also be explored via available tissues/blood or acquisition of additional tumour tissues/blood. […]
Rationale for change		To clarify that 4β-OH cholesterol may likely be explored in the future.
Section to be changed		Section 8.7 Administrative structure of the trial
Description of change		[…] A Safety Review Committee (SRC) will be established. Members of the SRC will include: • [redacted] Medical Monitor for the trial, **or delegate** […] The BI Safety Physician **(or delegate) and the** BI Clinical Program Leader **(**or delegate**)** should always attend the SRC to discuss safety issues.
Rationale for change		To clarify attendance at the SRC meetings.
Section to be changed		Tables 10.3: 1 and 10.3: 2
Description of change		Each of these tables was edited to add a separate column for ECGs clearly showing which ECGs are to be done in triplicate. Note to Footnote b was edited to: Time windows have been specified for procedural reasons; deviations do not automatically lead to exclusion of samples from data evaluation. **The new PK and urine schedule will be implemented upon availability of updated lab kits.**

		Footnote c (urine collections was edited to reflect the new timings as presented in the table and Section 5.3.2.4. The ECG footnote was edited to add: **In order not to confuse an ECG recording, PK samples should be taken after performing the ECG.**
Rationale for changes		To clarify that not all ECGs taken in Parts A and B will be triplicate ECGs. Triplicate ECGs are taken in relation to specific PK sampling times. Urine sampling has been changed to coincide with PK blood sampling. To clarify for the sites when PK samples should be taken in relation to ECGs.

Number of global amendment		3
Date of CTP revision		12 November 2018
EudraCT number		2017-000465-74
BI Trial number		1379.1
BI Investigational Products		BI 891065 and BI 754091
Title of protocol		An open-label Phase I dose finding trial with BI 891065 alone and in combination with BI 754091 to characterise safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy in patients with advanced and/or metastatic malignancies
To be implemented only after approval of the IRB / IEC / Competent Authorities		X
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Additions to the text are **bolded** and deletions from the text are ~~crossed-off~~. Only the parts of sections with changes are presented. Please note that formatting changes and minor changes to punctuation, spelling, and abbreviations that do not affect meaning are not noted in this summary.		
Section to be changed		Section 3.1 Overall trial design and plan
Description of change		Patients with **select** advanced/refractory solid tumours without established treatment options will be entered in order to determine the MTD and/or recommended dose for the expansion cohort in Part C of BI 891065 in combination with BI 754091, to assess safety and tolerability, and to explore PK/PDc.
Rationale for change		Amended to restricted eligibility for Part B

Section to be changed		Figure 3.1: 1 Design of trial 1379.1 including 2 dose-escalation parts and 1 expansion cohort
Description of change		Part B: ~~solid~~ select tumours
Rationale for change		Amended to restricted eligibility for Part B
Section to be changed		Section 3.3.1 Main diagnosis for trial entry
Description of change		Part A ~~and B~~: 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. **Part B: Patients with a confirmed diagnosis of advanced, unresectable and/or metastatic cancers who have failed standard treatment, or for whom no therapy of proven efficacy exists, or who are not amenable to standard therapies. Eligibility is limited to patients with the following cancer types: bladder, colon, breast, NSCLC, ovarian, pancreatic, renal, esophagogastric, sarcoma, prostate and melanoma.**
Rationale for change		Specify tumour types that are eligible for Part B
Section to be changed		Section 3.3.2 Inclusion criteria
Description of change		6. For Parts A and B: 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. Measurable lesions according to RECIST Version 1.1 must be present. **Eligibility is limited to the following tumour subtypes in Part B: bladder, colon, breast, NSCLC, ovarian, pancreatic, renal, esophagogastric, sarcoma, prostate and melanoma.**
Rationale for change		Specify tumour types that are eligible for Part B
Section to be changed		Figure 4.1.7: 1 Schematic of dose delays and reductions
Description of change		~~Must~~ **R**estart at one dose level lower ~~(unless at~~

		~~Cohort 1 dose, then restart at Cohort 1 dose)~~* ***The following caveat applies for restart of BI 891065:** • **If at Cohort 1 dose, then restart at Cohort 1 dose** • **If deemed in the best interest of the patient, may restart at the original assigned dose. If dose is lowered, may escalate from lower dose to the maximum of the originally assigned dose when deemed clinically appropriate.**
Rationale for change		To include option to restart BI 891065 at original dose
Section to be changed		Section 4.1.7 Dose reductions and dose delays
Description of change		As a general rule, serious **related** AEs/AEs of ≥ Grade 2 deemed intolerable by the patient or the treating physician and not responding to appropriate medical management and any SAEs/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 and C) until resolution to baseline or Grade 1. […] A maximum of 2 dose reductions of BI 891065 are allowed, if lower tested dose levels are available. Dose reductions will be only to doses previously explored in earlier cohorts. ~~In case of BI 891065 dose reductions, all future dose administrations will also be at the reduced dose.~~ If **a reduced dose** is intolerable (as previously described), the treatment of that patient should be discontinued. **Where deemed in the best interest of the patient, the investigator may restart at the originally assigned dose of BI 891065. If dose is lowered, the investigator may also escalate from the lower dose to the maximum of the originally assigned dose of BI 891065 as soon as deemed clinically appropriate (note: study treatment**

		can be restarted during tapering of immunosuppressive medications. See Table 4.2.2.1:1 for more information).
Rationale for change		To provide further information regarding dosing options after dose reductions.
Section to be changed		Section 4.2.1 Other treatments and emergency procedures
Description of change		**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.**
Rationale for change		To clarify guidance regarding blood transfusions
Section to be changed		Table 4.2.2.1:1 Restricted medication when coadministered with BI 891065
Description of change		An asterisk was added in the 2nd column for Immunosuppressive medications* at doses exceeding 10 mg/day; TNFα blockers
Rationale for change		To draw further attention to the footnote below the table
Section to be changed		Section 5.1 Assessment of efficacy
Description of change		In addition, the images may be used for further **analysis** ~~future investigations (e.g., Radiomics).~~ **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).**
Rationale for change		To clarify the purpose of radiomics assessments

Section to be changed		Throughout
Description of change		Updated all references to CTCAE from Version 4.03 to Version 5.0
Rationale for change		CTCAE has been updated to Version 5.0
Section to be changed		7.1.2 Part B
Description of change		[…] The derivation of these prior distributions ~~will be given in the TSAP and if applicable in the minutes of the SRC meetings.~~ **is described in Appendix 10.5.**
Rationale for change		The statistical methods for Part B were updated.
Section to be changed		7.3.2 Secondary endpoint analyses
Description of change		Part B […] • OR will be analysed descriptively in terms of ORR, defined as the proportion of patients with OR **based on RECIST v1.1**.
Rationale for change		To clarify that RECIST V1.1 criteria will be used for OR.
Section to be changed		8.1 Trial approval, patient information, informed consent
Description of change		[…] **The investigator or delegate must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible.** The patient must be given sufficient time to consider participation in the trial. The Investigator **or delegate** obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The Investigator **or his/her 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.
Rationale for change		To clarify that investigators may delegate the responsibility of consenting patients (where locally allowable).
Section to be changed		10.3 Time schedules for PK and biomarker sampling Table 10.3.2 Part B Food effect
Description of change		Visit column: 9-**12 then every 2nd cycle**
Rationale for change		To clarify visit numbers for Cycles 2-5 and every 2nd cycle
Section to be changed		10.3 Time schedules for PK and biomarker sampling Table 10.3.3 Part C
Description of change		Visit column: 5-**8 then every 2nd cycle**
Rationale for change		To clarify visit numbers for Cycles 2-5 and every 2nd cycle
Section to be changed		10.5 Statistical Appendix
Description of change		[…] Part B: ~~Operating characteristics and data scenarios for the BLRM used in Part B of the trial will be provided in the TSAP.~~ Thereafter, the operating characteristics and data scenarios for the BLRM used in Part B were added.
Rationale for change		The statistical methods for Part B were updated.

Number of global amendment		4
Date of CTP revision		08 May 2019
EudraCT number		2017-000465-74
BI Trial number		1379.1
BI Investigational Products		BI 891065 and BI 754091
Title of protocol		An open-label Phase I dose finding trial with BI 891065 alone and in combination with BI 754091 to characterise safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy in patients with advanced and/or metastatic malignancies
To be implemented only after approval of the IRB / IEC / Competent Authorities		X
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve		

logistical or administrative aspects only		
Additions to the text are **bolded** and deletions from the text are ~~crossed-off~~. Only the parts of sections with changes are presented. Please note that formatting changes and minor changes to punctuation, spelling, and abbreviations that do not affect meaning are not noted in this summary.		
Section to be changed		Part A, B, and C Flow chart footnote c and Section 5.2.3 Safety laboratory parameters
Description of change		[…] **total, direct and indirect** bilirubin ~~(direct and indirect bilirubin in case of elevated total bilirubin values)~~ […]
Rationale for change		To clarify that fractionated bilirubin needs to be collected in addition to total bilirubin as part of each clinical chemistry assessment.
Section to be changed		Section 3.3.1 Main diagnosis for trial entry and Synopsis
Description of change		Part C (NSCLC): Patients with **metastatic NSCLC who developed disease progression (per RECIST v1.1) after the first scan (where SD, PR, or CR was demonstrated at the first scan), and require new anti-cancer therapy after first line treatment with an anti PD-1/anti PD-L1 mAb (given either as single agent therapy or in combination with a platinum-based chemotherapy regimen)** ~~advanced NSCLC who have been treated with platinum-based chemotherapy as first-line therapy, and who are not responding to an anti-PD-1/anti-PD-L1 mAb therapy as second-line therapy~~.
Rationale for change		To update the NSCLC patient population for Part C
Section to be changed		Part C Flowchart
Description of change		The following tumour biopsies will be mandatory for all patients in Part C of the trial: - The equivalent of **two** ~~2 fine~~**-14-16G** needle biopsies must be freshly taken between screening and the day before the first trial drug treatment. If archival formalin-fixed paraffin-embedded (FFPE) tumour material is available that is not older than 6 months, ~~20~~ **26** 4-5µm sections would be acceptable as well. - The equivalent of **two** ~~2 fine~~**-14-16G** needle biopsies on treatment at the beginning of Cycle 3 (i.e., after 6 weeks of treatment) if possible from the same lesion as the pre-treatment biopsies.
Rationale for change		To update the requirements for needle size in Part C (to obtain sufficient material for transciptomic and genomic analyses) and the number of sections collected from archival FFPE block. Further details are provided

		in the lab manual.
Section to be changed		Section 3.3.2 Inclusion Criteria
Description of change		8. For Part C: **Patients with metastatic NSCLC who developed disease progression (per RECIST v1.1) after the first scan (where SD, PR, or CR was demonstrated at the first scan), and require new anti-cancer therapy after first line treatment with an anti PD-1/anti PD-L1 mAb (given either as single agent therapy or in combination with a platinum-based chemotherapy regimen).** ~~Patients with a confirmed diagnosis of advanced NSCLC who have been treated with combination of platinum-based chemotherapy as first-line therapy.~~ 9. ~~For Part C: Patients within 6 to 16 weeks are not responding to treatment with an anti PD-1/anti PD-L1 mAb second line therapy, and who are no longer benefitting from the previous therapy in the opinion of the Investigator~~.
Rationale for change		To update the NSCLC patient population for Part C
Section to be changed		Section 3.3.4 1 Withdrawal from trial treatment Section 4.1.5.1 Administration of BI 891065 Section 5.2.1 Physical examination Section 5.2.2 Vital Signs Section 5.2.3 Safety laboratory parameters Section 5.2.6.4.3 Cytokine release syndrome Section 5.3.2 Methods of sample collection Section 5.3.2.1 Plasma sampling for BI 891065 pharmacokinetics Section 5.3.2.2 Plasma sampling for BI 754091 pharmacokinetics Section 5.5.1 Immunogenicity testing Section 6.1 Visit Schedule Section 6.2 Details of Trial Procedures at Selected Visits Section 6.2.2 Treatment period
Description of change		[…] the respective ~~flow charts~~ **Part A Flow Chart, Part B Flow Chart, Part C Lung Flow Chart** […]
Rationale for change		To link the reader to the appropriate flow chart.
Section to be changed		Section 3.3.4.4 Replacement of patients who have received at least one dose of BI 891065 or BI 754091
Description of change		Patients in the NSCLC expansion cohort (Part C) will not be replaced unless it becomes apparent that probably less than ~~30~~ **40** patients will be evaluable for the assessment of the primary endpoint.
Rationale for change		To clarify the number of NSCLC patients for Part C

Section to be changed		Section 4.1.5.2 Administration of BI 754091 Section 5.2.6.3 Adverse events considered "Always Serious" Section 5.3.2 Methods of sample collection Section 5.3.2.3 Plasma sampling for metabolism analysis of BI 891065 Section 5.3.2.4 Urine sampling and analysis for pharmacokinetics of BI 891065 (Part A only) Section 5.3.3.2 BI 754091 plasma concentration Section 5.4.1 Methods of sample collection Section 5.5.1 Immunogenicity testing
Description of change		[…] manual **in the ISF**[…]
Rationale for change		To align terminology for ISF
Section to be changed		Section 4.1.7 Dose reductions and dose delays
Description of change		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 ~~754111~~ **891065** and BI 754091 will be permanently discontinued (see Section 5.2.6.4.2).
Rationale for change		Correction of typo
Section to be changed		Figure 4.1.7: 1 Schematic of dose delays and reductions
Description of change		Restart **at original dose or** at one dose level lower***** *The following caveat applies for restart of BI 891065: • […] • ~~If deemed~~ **Investigator to decided based on what is** in the best interest of the patient~~, may restart at the original assigned dose~~. If dose is lowered, may escalate from lower dose to the maximum of the originally assigned dose when deemed clinically appropriate.
Rationale for change		To clarify option to restart BI 891065 at original dose
Section to be changed		Section 5.2.3 Safety laboratory parameters and Section 5.2.6.4.5 Hepatic injury
Description		[…] **Potential** DILI checklist […]

of change		
Rationale for change		To clarify information around potential DILI requirements.
Section to be changed		Section 5.2.6.4.3 Cytokine release syndrome
Description of change		For Parts B and C: • Patients will remain under surveillance for at least 8 hours after the **first** ~~second~~ and **second** ~~third~~ administrations of BI 891065 during Cycle 1.
Rationale for change		To clarify surveillance time for Part B and C patients.
Section to be changed		Section 5.2.6.4.5 Hepatic injury
Description of change		**Lab values meeting this definition of hepatic injury will need to be reported as an AESI. Please follow the flowchart below (Figure 5.2.6.4.5: 1) for reporting hepatic injury / potential DILI cases.** **<u>Hy's Law cases have the following 3 components:</u>** • **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		To clarify the lab values that prompt the use of the Potential DILI Checklist.
Section to be changed		5.2.6.7.1 Adverse event collection
Description of change		[…] • After the individual patient's end of the trial: – the Investigator does not need to actively monitor the patient for **new** AEs but should **only** report related SAEs and related AESIs of which the Investigator may become aware of by any means of communication (e.g., phone call). Those AEs should however, not be reported in the CRF.
Rationale for change		To clarify AE collection process after the patient ends the trial.

Section to be changed		Section 5.2.6.8 Pregnancy
Description of change		[…] **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		Section 5.2.6.9 Exemptions to **AE**/SAE reporting
Description of change		[…] **Lab values meeting the hepatic injury definition as defined in Section 5.2.6.4.5 will need to be reported as an AESI. PD reporting exemption does not apply to hepatic injury.**
Rationale for change		To clarify that the lab values meeting hepatic injury definition need to be reported as an AESI.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		Section 7.7 Determination of Sample Size and Synopsis Part C NSCLC
Description of change		**A futility check will be performed by the SRC when 20 evaluable patients have been treated for at least 18 weeks. If an efficacy signal, i.e. at least two patients with OR, is observed out of 20 evaluable patients, the total intended 40 evaluable patients will be recruited into this trial part. If this efficacy signal cannot be observed, enrolment into the trial will be stopped.** **Table 7.7: 1 summarizes the probabilities to stop the trial after the futility analysis assuming different true underlying OR rates.**

Table 7.7: 1 Probabilities to stop the trial at the futility analysis

Assumed true OR rate (%)	Cohort size	P(< 2 patients with OR)	P(≥ 2 patients with OR)
10	20	0.39	0.61
30	20	0.01	0.99
45	20	<0.01	>0.99

Table 7.7: 2 displays the probability of observing at least 2 patients with OR in the first 20 evaluable patients and then observing a certain number of patients with OR out of a total of 40 evaluable patients given different assumed true underlying OR rates. For example, assuming a true underlying OR rate of 10%, the probability to observe 2 or more patients with OR out of 20 evaluable patients is 0.61. This means that the probability to stop the trial is 0.39 in this scenario. Overall, the probability to observe 4 patients with OR out of 40 patients, given that at least 2 patients with OR had been seen already in the first 20 patients, is only 0.473 which is considered as acceptable for this trial.

Assuming a true underlying OR rate of 45%, the probability to observe 2 or more patients with OR out of 20 patients is almost 1. Overall, the probability to observe 18 patients with OR out of 40 patients, given that at least 2 patients with OR had been seen already in the first 20 patients, is 0.561 which is considered satisfactory for this trial.

Table 7.7: 2 Probabilities for objective response rates of the expansion cohort under different assumptions given the trial has not been stopped at the futility analysis

Assumed true OR rate (%)	Cohort size	At least 2 patients with OR in the first 20 patients and probability to observe at least 18 patients with OR in total						
		4	8	10	12	14	16	18
10	40	0.473	0.041	0.005	< 0.001	< 0.001	< 0.001	< 0.001
30	40	0.992	0.942	0.803	0.559	0.297	0.115	0.032
45	40	>0.999	>0.999	0.997	0.982	0.925	0.786	0.561

Probabilities in Table 7.7: 2 are calculated as P(n1 + n2 ≥ c AND n1 ≥ 2), where n1 is the number of patients with OR out of the first 20 patients, n2 is the number of additional patients with OR after more patients are enrolled after the futility check. c is the required minimum number of patients with OR displayed in Table 7.7: 2 (i.e. 4, 8, 10, 12, 14, 16, or 18 respectively). The calculations in this section were performed using R version 3.5.1.
It is assumed that 44 patients need to be enrolled in order to end up with 40 evaluable patients for the primary analysis.

Table 7.7: 1 summarises the probabilities of observing certain OR rates based on different assumptions on sample size and on underlying OR rates. Assuming a true objective response rate of 30%, a sample size of 30 evaluable patients (where evaluable patients refer to patients having at least one post-baseline response assessment) leads to a probability of 84% of observing at least 7 ORs. If the true OR rate is higher, i.e. 45%, the probability of observing at least 7 ORs out of 30 evaluable patients is higher than 99%. The probability of observing a false positive signal, i.e. to observe at least 7 ORs if the underlying true OR rate is 10%, is only 7%.

With only 20 evaluable patients (at least one post-baseline response assessment is available), the probability of observing 7 ORs assuming a true underlying response rate of 30% is only 39%.

With a higher number of evaluable patients, the probabilities of observing responses increase, however the probabilities determined for 30 evaluable patients are considered satisfactory. Therefore, a sample size of 30 evaluable patients per cohort is deemed sufficient for Part C. It is assumed that 33 patients need to be enrolled to end up with 30 evaluable patients.

Table 7.7: 1 Probabilities for objective response rates of NSCLC expansion cohort under different assumptions

True OR rate	Patients	Probability to observe at least					
		6 events	7 events	8 events	9 events	10 events	11 events
10%	20	0.01	<0.01	<0.01	<0.01	<0.01	<0.01

		30%	**20**	**0.58**	**0.39**	**0.23**	**0.11**	**0.05**	**0.02**
		45%	**20**	**0.94**	**0.87**	**0.75**	**0.56**	**0.41**	**0.25**
		10%	**30**	**0.07**	**0.03**	**0.01**	**<0.01**	**<0.01**	**<0.01**
		30%	**30**	**0.92**	**0.84**	**0.72**	**0.57**	**0.41**	**0.27**
		45%	**30**	**>0.99**	**>0.99**	**0.99**	**0.97**	**0.93**	**0.86**
		10%	**40**	**0.21**	**0.10**	**0.04**	**0.02**	**0.01**	**<0.01**
		30%	**40**	**0.99**	**0.98**	**0.94**	**0.89**	**0.80**	**0.69**
		45%	**40**	**>0.99**	**>0.99**	**>0.99**	**>0.99**	**>0.99**	**0.99**
		The calculations in this section were performed using R version 3.2.2.							
Rationale for change		To clarify the sample size for Part C NSCLC							
Section to be changed		Section 10.3 Time schedules for PK and biomarker sampling Table 10.3.3 Part C							
Description of change		Added column for Triplicate ECGs and additional PK time points during Cycle 1 **Day 1** **-30 min (±15min) (pre dose)** **[…] 1:25 post dose […]** **[…] 2:00** **2:30** **3:30** **4:30** **6:30** **7:30** **Day 15** **0:30 post dose, 336:30** **1:00, 337:00** **2:00, 338:00** **3:00, 339:00** **5:00, 341:00** **6:00, 342:00** b The following windows of time are allowed for PK sampling: • Predose samples (PTM -0:05, 167:55, **335:55**, etc.): within 1 hour before drug intake • Just before end of infusion (PTM 1:00): within ±10 minutes of designated time • **On Day 1 (PTM 1:25 through 8:30) and on Day 15 (PTM 336:30 through 339:00): within ±10 minutes of designated time**							

		• **On Day 1 (PTM 0:30 through 6:00) and on Day 15 (PTM 341:00 through 342:00): within ±15 minutes of designated time** The following text was also added at the bottom of the table: * In order not to confuse an ECG recording, all PK samples should be taken after performing the ECGs. Optional assessments are noted in parentheses. Please refer to the footnotes in Part C Lung Flow Chart for details.
Rationale for change		To clarify Part C ECG/PK sample time points and provide clarifications

Number of global amendment		5
Date of CTP revision		26 July 2019
EudraCT number		2017-000465-74
BI Trial number		1379.1
BI Investigational Products		BI 891065 and BI 754091
Title of protocol		An open-label Phase I dose finding trial with BI 891065 alone and in combination with BI 754091 to characterise safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy in patients with advanced and/or metastatic malignancies
To be implemented only after approval of the IRB / IEC / Competent Authorities		X
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Additions to the text are **bolded** and deletions from the text are ~~crossed-off~~. Only the parts of sections with changes are presented. Please note that formatting changes and minor changes to punctuation, spelling, and abbreviations that do not affect meaning are not noted in this summary.		
Section to be changed		Part B Flowchart
Description of change		Removed ~~(C3)~~ from Tumour biopsy assessment row
Rationale for change		To allow flexibility for the timing of on-treatment biopsy collection and ensure that the necessary prerequisites for time on treatment are met prior to biopsy collection
Section to be changed		Part B Flowchart footnote m

Description of change		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**~~at the beginning of Cycle 3 (i.e., after 6 weeks of treatment)~~. **Biopsy collection should be delayed until these conditions are met.**
Rationale for change		To allow flexibility for the timing of on-treatment biopsy collection and ensure that the necessary prerequisites for time on treatment are met prior to biopsy collection
Section to be changed		Part B Flowchart footnote n
Description of change		[…] Patients will be observed after their ~~first 3~~ dose~~s~~ of BI 891065 **and BI 754091 given at Cycle 1 Day 1 (for 8 hours) and Cycle 2 Day 1 (for 6 hours)** as outlined […].
Rationale for change		To clarify surveillance period after administration of BI 891065 with BI 754091.
Section to be changed		Part C Flowchart
Description of change		**Added (single/triplicate), and footnote c** **Added "X" to Electrocardiograms row for the following time points:** • **Cycle 1 Day 15** **Added "(single)" to Electrocardiograms row for the following time points:** • **Screening** • **Cycle 1 Day 8** • **Cycle 2+ Day 1** • **EOT**
Rationale for change		To clarify timing for single and triplicate ECG collections.
Section to be changed		Part C Flowchart footnote e
Description of change		**Triplicate electrocardiograms (ECGs) are required in connection with pharmacokinetic sample collection as outlined in Table 10.3: 3.** ~~S~~**When triplicate ECGs are not done, s**ingle 12-lead **ECGs** ~~electrocardiograms (ECGs)~~ will be

		done **per the flow chart above for safety purposes** ~~before blood work or other procedures after 10 minutes of rest~~ at screening, ~~, and pre-treatment during Cycle 1~~ **on Cycle 1 Day 8, on Day 1 of each additional cycle,** ~~on Days 1 and 8, during Cycle 2 on Day 1, during Cycle 3 on Day 1, on Day 1 of every third cycle thereafter (Cycles 6, 9, 12, etc.),~~ at the EOT visit, and whenever the Investigator deems it necessary (see Section 5.2.4).
Rationale for change		To clarify timing of single and triplicate ECG collections.
Section to be changed		Part C Flowchart footnote l
Description of change		[…]**. I**~~i~~f possible **the biopsy should be collected** from the same lesion as the pre-treatment biopsies. **In case study drug was interrupted for 3 weeks or longer, consult with the Sponsor regarding whether or not to delay the biopsy.**
Rationale for change		To clarify biopsy collection procedure
Section to be changed		Part C Flowchart footnote m
Description of change		[…] Patients will be observed after their first ~~3~~ doses of BI 891065 during **on Day 1 of Cycles 1 and 2** as outlined in Section 5.2.6.4.3
Rationale for change		Revised for consistency with Section 5.2.6.4.3
Section to be changed		Section 1.4 Benefit – Risk Assessment
Description of change		For Parts B and C, patients will remain under surveillance ~~for 10 hours~~ after the administration of BI 891065 in combination with BI 754091 ~~in Cycles 1 and 2, and for at least~~ for 8 hours after the ~~second and third~~ **first** ~~administration~~**doses** ~~s~~ of BI 891065 in Cycle 1**, and then for 6 hours after the first dose of BI 891065 in Cycle 2**
Rationale for change		To reduce the patient burden of a surveillance period after BI 891065 administration with BI 754091 based on emerging data from Part B.
Section to be changed		Section 3.1 Overall Trial Design and Plan
Description of change		Once the combination dose is determined (to be confirmed by the Sponsor), the Part C expansion cohort will be initiated in patients with NSCLC who failed ~~previous treatment with~~ an anti-PD-1/anti-PD-L1 **treatment as a first-line** therapy, **either by itself or in combination with platinum-based therapy**

Rationale for change		To clarify Part C expansion cohort
Section to be changed		Section 3.3.2 Inclusion criteria
Description of change		7. For Parts B and C: Patients must have measurable disease per RECIST v1.1, must have at least 1 tumour lesion amenable to biopsy, and must be willing to undergo a biopsy prior to first treatment and ~~after 6 weeks~~ **another biopsy while** on therapy.
Rationale for change		To allow flexibility for the timing of on-treatment biopsy collection in Part B and ensure that the necessary prerequisites for time on treatment are met prior to biopsy collection
Section to be changed		Section 4.1. Investigational Treatments
Description of change		**Added BI 891065 tablet strength of 100 mg in Table 4.1.1:1 and in Section 4.1.5.1 (Administration of BI 891065) text**
Rationale for change		Update BI 891065 tablet strengths in this study because 100 mg tablet will become available. It will not be distributed to countries until all local regulatory requirements for adding a new dose strength are met.
Section to be changed		Figure 4.1.7: 1 Schematic of dose delays and reductions
Description of change		Modified box BI 891065: Restart at **original dose or** at one dose level lower* Figure footnote: ~~If deemed~~ **Investigator to decide based on what is** in the best interest of the patient~~, may restart at original assigned dose~~.
Rationale for change		To clarify criteria for restarting at original or a lower dose after a dose interruption
Section to be changed		Figure 4.1.7 Dose reduction and dose delays
Description of change		~~A maximum of 2 d~~**D**ose reductions of BI 891065 are allowed~~, if lower tested dose levels are available. Dose reductions will be only~~ to doses previously explored in earlier cohorts **if the Investigator anticipates a lower dose would be better tolerated**.
Rationale for change		To clarify criteria for dose reduction of BI 891065
Section to be changed		Section 5.2.3 Safety laboratory parameters
Description of change		The standard haematology panel will consist of:

		haemoglobin, red blood cell count, haematocrit, mean corpuscular volume, white blood cell count, ~~and~~ differential blood count (preferably expressed in absolute values), ~~and~~ platelets, **haptoglobin and reticulocytes.**
Rationale for change		To investigate the reason for isolated bilirubin increases observed.
Section to be changed		Section 5.2.4 Electrocardiogram
Description of change		In Part C, ~~single ECGs will typically be taken unless additional~~ **triplicate** readings are **required with pharmacokinetic sample collection as** indicated **in Table 10.3: 3**. **When triplicate ECGs are not done, single readings will be done for safety purposes as indicated in Part C Lung Flow Chart.**
Rationale for change		To clarify timing of single and triplicate ECG collections in Part C.
Section to be changed		Section 5.2.6.4.3 Cytokine release syndrome
Description of change		For Parts B and C: • Patients will remain under surveillance ~~for 10 hours~~ after the administration of BI 891065 [redacted] in combination with BI 754091 [redacted] during Cycles 1 and 2. • Patients will remain under surveillance for **about 8 hours after the first dose of BI 891065** ~~at least 8 hours after the first and second administrations of BI891065~~ during Cycle 1**, and for about 6 hours after the first dose of BI 891065 in Cycle 2**
Rationale for change		To reduce the patient burden of a surveillance period after BI 891065 administration with BI 754091 based on emerging data from Part B.
Section to be changed		Table 10.3:2 Time schedule for PK blood, biomarker, and immunogenicity sampling during Part B including food effect

Description of change		Removed ~~(C 3 only)~~ from mandatory biopsy during study treatment
Rationale for change		To allow flexibility for the timing of on-treatment biopsy collection in Part B
Section to be changed		Table 10.3:2 footnote c
Description of change		Biopsy for IAP degradation **to be taken as noted in Part B Flow Chart**
Rationale for change		To clarify the timing of biopsy collection in Part B

Number of global amendment		6
Date of CTP revision		12 February 2020
EudraCT number		2017-000465-74
BI Trial number		1379.1
BI Investigational Products		BI 891065 and BI 754091
Title of protocol		An open-label Phase I dose finding trial with BI 891065 alone and in combination with BI 754091 to characterise safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy in patients with advanced and/or metastatic malignancies
To be implemented only after approval of the IRB / IEC / Competent Authorities		X
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Additions to the text are **bolded** and deletions from the text are ~~crossed off~~. Only the parts of sections with changes are presented. Please note that formatting changes and minor changes to punctuation, spelling, and abbreviations that do not affect meaning are not noted in this summary.		

Section to be changed		Synopsis_Number of patients on each treatment and Section 7.7 Determination of Sample Size
Description of change		Part B (dose escalation BI 891065 in combination with BI 754091): approximately ~~30~~**31-37** patients
Rationale for change		The number of patients was updated to include additional patients to be enrolled in Part B.
Section to be changed		Flow Chart Part B
Description of change		Tumour biopsy was moved from Cycle 3 to Cycle 2 C2 | C3 **X** | ~~X~~
Rationale for change		To align the Flow Chart B table with the edits made to the footnotes in the previous amendment.
Section to be changed		Flow Chart Part B and Part C footnote c
Description of change		The safety laboratory assessments listed in footnote c was amended to: Troponin I/**Troponin T**
Rationale for change		To allow flexibility to sites for collection of Troponin at sites where local labs do not report Troponin I.
Section to be changed		Flow Chart Part B footnote j
Description of change		The effect of food will be tested in this part of the study **until sufficient data is obtained. Only q.d. patients enrolled in Part B will participate in the food effect study.**
Rationale for change		To clarify that food effects will only be tested on q.d. dosed patients.
Section to be changed		Flow Chart Part B footnote n
Description of change		Dosing amounts, **dosing frequency (e.g. b.i.d or q.d.)** and escalations…… Patients should not take BI 891065 prior to certain visits that require pre-dose blood sampling as detailed in Table 10.3: 2 **and Table 10.3: 3. For patients taking b.i.d. dosing, the evening dose should be skipped (Day 1 and Day 15 of Cycle 1). For all patients, the morning dose on Day 2 and Day 16 should be taken in the clinic (after pre-dose blood sampling is taken).**
Rationale for change		To clarify when doses should be skipped on PK analysis days.
Section to be changed		Flow Chart Part C
Description of change		Columns for Day 2 and Day 16 of Cycle 1 were added.
Rationale for change		To better indicate that patients have assessments to be collected on Days 2 and 16 of Cycle 1.
Section to be changed		Flow Chart Part C Blood sampling for BI 891064 pharmacokinetics
Description of change		X (C2 **only**)
Rationale for change		To clarify that the last blood sampling for BI 891064 pharmacokinetics will be at Cycle 2

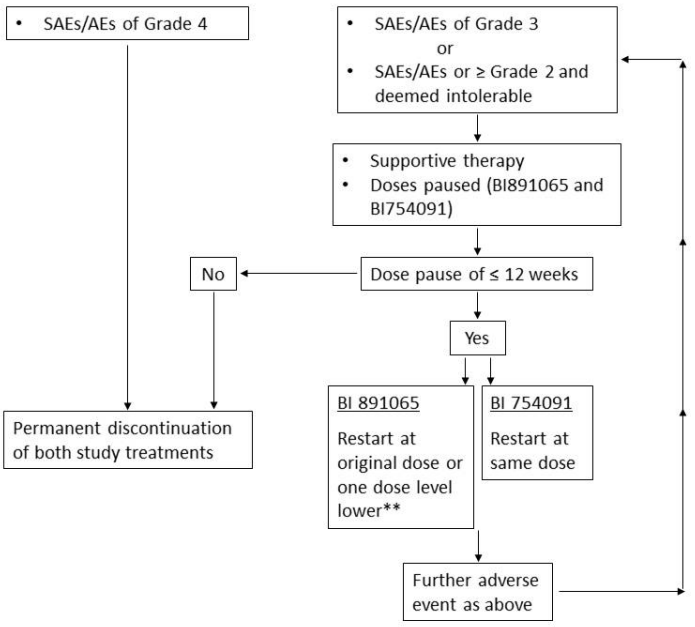
Section to be changed		Flow Chart Part C Blood sampling for biomarkers (cytokines) and footnote k and Table 10.3: 4 Time schedule for PK blood, biomarker, and immunogenicity sampling during Part C-NSCLC
Description of change		Blood sampling for biomarkers (cytokines) was added to Cycle 1 Day 2.
Rationale for change		To allow for collection of blood sampling for cytokines on Cycle 1 Day 2 for patients in Part C.
Section to be changed		Flow Chart Part C Blood sampling for biomarkers (PBMC/MDSC) and Blood sampling for biomarkers (cytokines) and Table 10.3: 4 Time schedule for PK blood, biomarker, and immunogenicity sampling during Part C-NSCLC
Description of change		<table><tr><td>C2+</td><td>EOT</td></tr><tr><td>X (C2**, 4 only**)</td><td>~~X~~</td></tr></table>
Rationale for change		To change the final biomarker blood sample collection from EOT to Cycle 4 Day 1.
Section to be changed		Flow Chart Part C footnote k
Description of change		Blood samples for biomarkers - samples for the quantification of cytokines will be taken pre-treatment during Cycle 1 on Days 1, 8, and 15, Cycle 2 on Day 1, and **Cycle 4 on Day 1** ~~at the EOT~~ visit (see Section 5.4.2 and Table 10.3: 3). Blood samples for biomarker peripheral blood mononuclear cells (PBMC)/ myeloid-derived suppressor cells (MDSCs) will be taken pre-treatment during Cycle 1 on Days 1, 8, and 15, Cycle 2 on Day 1, and **Cycle 4 on Day 1** ~~at the EOT~~ visit.
Rationale for change		
Section to be changed		Flow Chart Part C footnote m
Description of change		**Patients should not take BI 891065 prior to certain visits that require pre-dose blood sampling as detailed in Table 10.3: 4. Patients could be assigned q.d. or b.i.d. dosing. For patients taking b.i.d. dosing, the evening dose on infusion days should be skipped (Day 1 and Day 15 of Cycle 1). For all patients, the morning dose on Day 2 and Day 16 should be taken in the clinic (after pre-dose blood sampling is taken).** On BI 754091 infusion days, BI 891065 will be administered approximately 30 minutes after the end of the BI 754091 infusion.. Patients will be observed after their first dose of BI 891065 on Cycle 1 Day 1 ~~(for 8 hours)~~ and Cycle 2 Day 2 (for ~~64~~ hours) as outlined in Section 5.2.6.4.3.
Rationale for change		To clarify that in the regimen for patients in Part C could be q.d. or b.i.d. and that the evening dose on Cycle 1 Days 1 and 15 should be skipped and the morning dose on Cycle 1 Days 2 and 16 should be taken in the clinic after the pre-dose blood sampling

		is taken.
Section to be changed		Abbreviations
Description of change		b.i.d (twice a day) and q.d. (once a day) were added to the table.
Rationale for change		q.d. and b.i.d. abbreviations have been added to the table abbreviations since these have been added to the text in this amendment.
Section to be changed		Section 1.1 Medical Background
Description of change		The 2nd line treatment of NSCLC has also been markedly transformed by the introduction of PD-1/PD-L1 immune checkpoint inhibitor monoclonal antibodies (mAbs) (nivolumab, **durvalumab** and atezolizumab in addition to pembrolizumab).
Rationale for change		Durvalumab was added to the list of 2nd-line NSCLC PD-1/PD-L1 mAb treatments since it has been approved by the FDA.
Section to be changed		Section 1.4 Benefit-Risk Assessment
Description of change		For Part~~s~~ B ~~and C~~, patients will remain under surveillance after the administration of BI 891065 in combination with BI 754091 for 8 hours after the first dose of BI 891065 in Cycle 1, and then for 6 hours after the first dose of BI 891065 in Cycle 2. **For Part C, patients will remain under surveillance for 4 hours after the first dose of BI 891065 in both Cycle 1 and Cycle 2** (see Section 5.2.6.4.3).
Rationale for change		The surveillance time has been reduced for patients in Part C.
Section to be changed		Section 2.1.2.2 Part B
Description of change		**Q.D. and b.i.d. dosing schedules may be explored in Part B.**
Rationale for change		To identify that a b.i.d. cohort may be explored in Part B.
Section to be changed		Figure 3.1.: 1 Design of trial 1379.1 including 2 dose-escalation parts and 1 expansion cohort
Description of change		**Patients in Parts B and C may receive either q.d. or b.i.d. BI 891065**
Rationale for change		To identify that a b.i.d. cohort may be explored in Part B and Part C.
Section to be changed		Section 3.3.2 Inclusion criteria 4
Description of change		Eastern Cooperative Oncology Group (ECOG) score: 0 **to** ~~**or**~~ 1
Rationale for change		The inclusion criteria text was clarified.
Section to be changed		Section 3.3.3 Exclusion criteria 1, 14, 15
Description of change		(major according to the Investigator's **and/or Medical Monitor's assessment**)
Rationale for change		Medical monitor's input has been added to the exclusion criteria.
Section to be changed		Section 3.3.3 Exclusion criteria 6
Description of change		**At least 7 days must have elapsed between the last dose of such agent and the first dose of study drug.**
Rationale for change		The drug washout period has been clarified.

Section to be changed		Section 3.3.3 Exclusion criteria 7
Description of change		Persistent toxicity from previous treatments that has not resolved to ≤ Grade 1 (except for alopecia **and Grade 2 neuropathy due to prior platinum-based therapy**)
Rationale for change		The prior toxicity exclusion criteria has been clarified.
Section to be changed		Section 3.3.3 Exclusion criteria 10
Description of change		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 ~~to prolong the~~ **or possible risk of QT** interval ~~prolongation~~
Rationale for change		The cardiac risk exclusion criteria has been clarified
Section to be changed		Section 3.3.3 Exclusion criteria 18
Description of change		**Patients with asymptomatic CNS metastases may be enrolled following a 2-week washout period.**
Rationale for change		The CNS metastases exclusion criteria has been clarified.
Section to be changed		Table 4.1.1:1 BI 891065
Description of change		Once daily, **(q.d.) or twice daily (b.i.d.),** individual dose depending on dose escalation
Rationale for change		Both the q.d. and b.i.d. dosing schedule was added to the table.
Section to be changed		Section 4.1.2.1 Starting dose of BI 891065
Description of change		Based on the toxicities and exposures in the GLP-compliant dog study (the more sensitive species), a starting dose of 5 mg BI 891065 **once** daily has been chosen.
Rationale for change		To identify this text as describing the q.d. dosing.
Section to be changed		Section 4.1.3.2 Cohorts at dose levels ≥25 mg BI 891065 daily
Description of change		**Both q.d. and b.i.d. dose escalations may be performed in Part B.**
Rationale for change		To clarify both q.d. and b.i.d. dosing will used in Part B.
Section to be changed		Section 4.1.3.2 Cohorts at dose levels ≥25 mg BI 891065 daily
Description of change		The dose **and regimen** of BI 891065 in combination with BI 754091 to be used in Part C will be determined based on the safety and PK/PDc data of Parts A and B, including data of target engagement in tumour tissue.
Rationale for change		To clarify that both the dose and regimen of the drug combination to be used in Part C will be based on safety and PK/PDc data from Parts A and B.
Section to be changed		Section 4.1.4 Method of assigning patients to treatment groups
Description of change		Part B (combination therapy) will be assigned a **q.d. or b.i.d.** dose of BI 891065 and a dose of BI 754091, as determined by the SRC.

Rationale for change		To clarify both q.d. and b.i.d. dosing will used in Part B.
Section to be changed		Section 4.1.4 Method of assigning patients to treatment groups
Description of change		(maximum 400 mg **daily dose** of BI 891065)
Rationale for change		To identify this text as describing the q.d. dosing.
Section to be changed		4.1.5.1 Administration of BI 891065
Description of change		**BI 891065 may be taken in either a q.d. or b.i.d. dosing, depending on the assigned treatment regimen.** …… ~~The~~ **For applicable cohorts, the** fasting status and all meals on the PK days should be recorded in the patient diary…. BI 891065 doses should be taken orally at approximately the same time each morning **(and evening for patients** with **b.i.d. dosing). Exceptions are noted in** the ~~exception of prior to~~ **flowchart:** • Part A **patients will skip a dose on** Cycle 1 Day 2 ~~where study drug is not taken~~. • **Part B patients assigned to a b.i.d. regimen will skip the evening dose on Cycle 1 Day 1 and Day 15 (in preparation for PK testing on Cycle 1 Day 2 and Day 16).**
Rationale for change		To clarify both q.d. and b.i.d. dosing will used in Part B.
Section to be changed		Section 4.1.7 Dose reductions and dose delays
Description of change		**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 Medical Monitor and 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, and BI 754091 at the same fixed dose of BI 754091. 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 (see Section 5.2.6.4.2).** **As a general rule for Part B and Part C, 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. Up to two dose reductions are allowed per patient. For q.d. dosing regimens, dose reductions of BI 891065 are allowed only to doses previously explored in earlier cohorts. If a patient on a b.i.d. dosing regimen has a dose reduction, the dose should be reduced as follows: 200 mg b.i.d reduced to 100 mg b.i.d; 100 mg b.i.d reduced to 50 mg b.i.d.** **Criteria leading to permanent discontinuation of BI 891065 and BI 754091 are presented in Section 3.3.4.1.** A schematic of dose delays and reductions is presented in Figure 4.1.7: 1.



*See Appendix 10.2 for management of irAEs.

**The following caveat for restart of BI 891065:

- If at Cohort 1 dose, then restart at Cohort 1 dose
- Investigator to decide based on what is in the best interest of the patient. If dose is lowered, may escalate from lower dose to the maximum of the originally assigned dose when deemed clinically appropriate.
- If the AE/SAE prompting interruption is not drug related, BI 891065 may be re-introduced at the same dose level.

Figure 4.1.7: 1 Schematic of dose delays and reductions **for non-immune related AEs/SAEs***

~~As a general rule, related serious AEs/AEs of ≥ Grade 2 deemed intolerable by the patient or the treating physician and not responding to appropriate medical management and any SAEs/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 and C) until resolution to baseline or Grade 1.~~

~~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 the 5 mg monotherapy dose) and the same fixed dose of BI 754091 as long as the re-exposure is considered clinically indicated by the Investigator.~~

~~As a general rule (relevant for Part B and Part C), 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.~~

~~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 (see Section 5.2.6.4.2).~~ ~~Dose reductions of BI 891065 are allowed to doses previously explored in earlier cohorts if the Investigator anticipates a lower dose would be better tolerated. If a reduced dose is intolerable (as previously described), the treatment of that patient should be discontinued. Where deemed in the best interest of the patient, the investigator may restart at the originally assigned dose of BI 891065. If dose is lowered, the investigator may also escalate from the lower dose to the maximum of the originally assigned dose of BI 891065 as soon as deemed clinically appropriate (note: study treatment can be restarted during tapering of immunosuppressive medications. See Table 4.2.2.1:1 for more information).~~ ~~There will be no dose reductions or escalations of BI 754091 in any one patient.~~ ~~Criteria leading to permanent discontinuation of BI 891065 and BI 754091 are presented in Section 3.3.4.1.~~
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		Section 5.2.3 Safety laboratory parameters n
Description of change		The standard biochemistry panel will consist of glucose, sodium, potassium, chloride, calcium, phosphate, venous bicarbonate HCO3, ~~urea,~~ creatinine, AST, ALT, alkaline phosphatase, lactate dehydrogenase, total, direct and indirect bilirubin, total protein, albumin, urea nitrogen **(or urea in lieu of urea nitrogen)**, uric acid and creatinine kinase (CK). If CK is elevated, then CK-MB [cardiac], Troponin I/**Troponin T**, and myoglobin should be reactively tested.
Rationale for change		The collection parameters for blood urea and Troponin were clarified.
Section to be changed		Section 5.2.6.4.3 Cytokine release syndrome
Description of change		For Part~~s~~ B ~~and C~~: • Patients will remain under surveillance after the administration of BI 891065 [redacted] in combination with BI 754091 [redacted] during Cycles 1 and 2. • ~~Patients will remain under~~ **Duration of** surveillance **will be** for 8 hours after the first dose of BI 891065 during Cycle 1, and for 6 hours after the first dose of BI 891065 in Cycle 2 **For Part C:** • **Patients will remain under surveillance after the administration of BI 891065** [redacted] **in combination**

		with BI 754091 [redacted] during Cycles 1 and 2. **• Duration of surveillance will be for 4 hours after the first dose of BI 891065 during Cycles 1 and 2.**
Rationale for change		The surveillance time has been reduced for patients in Part C.
Section to be changed		Section 5.2.6.4.4 Immune-related adverse events (irAE) and Table 10.1: 1 Immune-related adverse events of special interest
Description of change		**Immune-related AEs should be reported as AESIs only for patients who received immunotherapy.**
Rationale for change		To clarify when irAEs are reported as AESIs.
Section to be changed		Section 5.3.2.4 Plasma sampling for coprophyrin
Description of change		**Section 5.3.2.4 Plasma sampling for coprophyrin** **Backup samples for PK analysis might be used for coproporphyrin analysis. Coproporphyrin is an exploratory plasma biomarker to investigate the potential of BI 891065 to inhibit OATP1B1/B3. Assays are under development. Measurement will be done when feasible assays have been developed and validated.**
Rationale for change		Coprophyrin analysis has been added to the trial protocol.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		Section 6.2.2.1 Food-interaction assessment
Description of change		At ~~all dose levels in Part B,~~ ~~a~~**A**n explorative food effect will be assessed **for q.d. patients in Part B**.
Rationale for change		To clarify that food analysis PK will conducted for only q.d. patients in Part B.
Section to be changed		Section 7.1.2 Part B
Description of change		They will take into account available data from Part A **of this trial and available data from the monotherapy dose escalation part of BI trial 1379.6** for the prior of BI 891065 and available data from the BI trial 1381.1 that aims to determine the MTD of BI 754091.
Rationale for change		To clarify data to be used for the baseline statistical analysis for Part B.
Section to be changed		Section 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 C_{max} at steady state. This conversion is based on the assumption that safety events are triggered by C_{max} at steady state. For example, based on Table 7.1.2: 1, the 200 mg b.i.d.**

regimen will be modelled as equivalent to a 300 mg q.d regimen. For any other b.i.d. doses considered, their conversions will be specified in the TSAP.

The posterior probabilities of over toxicity are evaluated based on historical data for BI 891065 in Tables 7.1.2: 2 and 7.1.2: 3, historical data for BI 754091 in Table 7.1.2: 4 and current data for the combination therapy of BI 891065 and BI 754091 in Table 7.1.2: 5. For example, as seen in Table 7.1.2: 6, the dose combination of 200 mg b.i.d. BI 891065 and 240 mg BI 754091 has a posterior probability of over toxicity below 25% and would therefore be suitable as a dose combination to select.

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.

Table 7.1.2: 1 Simulated Cmax at steady state with 95% confidence intervals.

Possible Regimen	Cmax (nmol/L)
200 mg q.d.	2457.12 (771.53 - 6835.05)
300 mg q.d.	3421.69 (1286.11 - 9653.55)
400 mg q.d.	4357.98 (1672.88 - 12541.8)
200 mg b.i.d.	3502.75 (1458.73 - 10986.75)

Table 7.1.2: 2 Historical data for BI 891065 from Part A (status as of 16 Dec 2019)

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

Table 7.1.2: 3 Historical data for BI 891065 from BI trial 1379.6 (status as of 16 Dec 2019)

Dose	N of patients with DLTs during MTD evaluation

	period / N of evaluable patients
100 mg q.d.	1/2

Table 7.1.2: 4 Historical data for BI 754091 from BI trial 1381.1 (status as of 30 Sep 2019)

Dose	N of patients with DLTs during MTD evaluation period / N of evaluable patients
80 mg	0/3
240 mg	0/71
400 mg	0/3

Table 7.1.2: 5 Data for combination of BI 891065 and BI 754091 from Part B (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

Table 7.1.2: 6 Posterior 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 %
50 mg q.d.	240 mg	0.977	0.023	0.000	0.071	0.036	0.0019	0.065	0.158
200 mg q.d.	240 mg	0.853	0.147	0.000	0.110	0.050	0.0035	0.102	0.229
200 mg b.i.d. [1]	240 mg	0.708	0.274	0.018	0.13	0.07	0.0	0.118	0.313

		<table><tr><td></td><td></td><td></td><td></td><td></td><td>2</td><td>3</td><td>31</td><td></td><td></td></tr><tr><td>400 mg q.d.</td><td>240 mg</td><td>0.615</td><td>0.313</td><td>0.072</td><td>0.154</td><td>0.105</td><td>0.023</td><td>0.130</td><td>0.423</td></tr></table> **[1] The 200 mg b.i.d. dose is modeled as equivalent to a 300 mg q.d. dose in terms of dose-toxicity relationship in the BLRM.**
Rationale for change		To revise clarify the BLRM statistical analysis for Part B.
Section to be changed		Section 9.1 Published References
Description of change		P19-00269 Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline.J Clin Oncol. Jun 10;36(17):1714-68.
Rationale for change		A new reference was added to the text.
Section to be changed		Section 10.2 Management of Immune-Related Adverse Events
Description of change		**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 and BI 891065 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 and BI 891065 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 and BI 891065 has to be withheld, and treatment with high-dose corticosteroids (1-2mg/kg/d 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 and BI 891065 may be considered for selected irAEs, but caution is advised, in particular in patients with early-onset irAEs. Expert consultancy and agreement with medical monitor is recommended prior to restart of therapy. - **Most Grade 4 irAEs warrant permanent discontinuation of BI 754091 and BI 891065.** - **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 andconsideration 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.** **BI 754091 and BI 891065 should be permanently discontinued for immune related** • **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**
- **<u>uveitis, iritis, episcleritis of</u> grade ≥3**
- **<u>autoimmune-hemolytic anemia</u> 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 and BI 891065 besides interrupting or permanently discontinuing BI 754091 and BI 891065 are not allowed.

In rare situations when benefit and risk assessment is considered positive for a patient to continue BI 754091 and BI 891065 treatment despite guidance to permanently discontinue (e.g. in case no alternative anti-cancer therapy is available), it should be discussed with the sponsor.

<u>Pneumonitis:</u>

- **For Grade 1 pneumonitis with radiographic evidence of worsening, withhold BI 754091 and BI 891065 until improvement or resolution; BI 754091 and BI 891065 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 and BI 891065 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 BI 891065 and immediately initiate treatment according to available guidelines.**

<u>Diarrhoea/Colitis:</u>

- **For Grade 1 diarrhoea/colitis, consider interruption of BI 754091 and BI 891065 therapy.**
- **For Grade 2 diarrhea/colitis, withhold BI 754091 and BI 891065 until patient's symptoms recovered to grade 1 or less. Consider initiating treatment with steroids.**
- **For Grade 3 diarrhoea/colitis, withhold BI 754091 and BI 891065 and immediately start treatment**

		(steroids, non-steroidal immunosuppressents) as per available guidelines. • **For Grade 4 diarrhoea/colitis, permanently discontinue BI 754091 and BI 891065 and immediately commence adequate therapy (e.g. i.v. corticosteroids).** • **For Grade 1-3 colitis, restart of BI 754091 and BI 891065 may be considered once symptoms improve to Grade 1 or less without need for continued steroids. After careful benefit risk assessment, BI 754091 and BI 891065 may also be restarted after recovery to grade 1 or less, and on corticosteroid ≤ 10 mg per day** • **BI 754091 and BI 891065 should be permanently discontinued for recurrent diarrhoea/colitis of any grade.** **<u>Diabetes</u>** • **Consider withholding BI 754091 and BI 891065 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)** o **Initiate insulin therapy** o **Evaluate subjects as appropriate per available guidelines regarding presence of type 1 diabetes** o **BI 754091 and BI 891065 should be withheld until glucose level is controlled with insulin with no sign of ketoacidosis.** • **BI 754091 and BI 891065 may be restarted once insulin therapy has established stable glycemic control** **<u>Thyroid disorders:</u>** **For diagnosed thyroid disorders, thyroid hormone supplementation and monitoring should occur as per available guidelines** • **Primary hypothyroidism:** o **For Grade 1 hypothyroidism, BI 754091 and BI 891065 may be continued, with regular monitoring of thyroid values.** o **For Grade 2 hypothyroidism, consider withholding BI 754091 and BI 891065** o **For Grade 3-4 hypothyroidism, withhold BI 754091 and BI 891065, consider admission and IV therapy, especially in case of myxedema** o **BI 754091 and BI 891065 may be restarted**

		once symptoms resolve to baseline with appropriate thyroid hormone supplementation • **Primary hyperthyroidism** o **For Grade 1 hyperthyroidism, BI 754091 and BI 891065 may be continued , with regular monitoring of thyroid values.** o **For Grade 2 hyperthyroidism, consider withholding BI 754091 and BI 891065, initiate therapy as per available guidelines.** o **For Grade 3-4 hyperthyroidism, withhold BI 754091 and BI 891065. Consider hospitalization, especially in case of thyreotoxicosis.** o **BI 754091 and BI 891065 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)** **<u>Adrenal insufficiency</u>** • **Interruption of BI 754091 and BI 891065 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 and BI 891065 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.** **<u>Hypophysitis:</u>** • **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 and BI 891065 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.** **<u>Hepatitis:</u>** • **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 and BI 891065 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 and BI 891065 should be suspended. Monitoring of liver values every 3 days is recommended. Initiate treatment according to available guidelines. Restarting of BI 754091 and BI 891065 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 and BI 891065 has to be permanently discontinued.** **<u>Nephritis:</u>** • **For Grade 1 nephritis, consider temporarily withholding BI 754091 and BI 891065.** • **For Grade 2 nephritis, withhold BI 754091 and BI 891065. Consult nephrology. Initiate treatment according to guidelines. In case of no improvement or worsening, permanently discontinue BI 754091 and BI 891065.BI 754091 and BI 891065 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 and BI 891065. 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 and BI 891065 should also be permanently discontinued for recurrent nephritis grade 2 or higher.** **<u>Rash</u>** • **For Grade 1 rash, continue BI 754091 and BI 891065. Initiate topical treatment.** • **For Grade 2 rash, BI 754091 and BI 891065 may be continued, in case of no improvement upon weekly monitoring, consider interruption of BI 754091 and BI 891065 therapy. Treat topically, add systemic corticosteroid therapies as clinically appropriate.** • **For Grade 3 rash, withhold BI 754091 and BI 891065. 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 and BI 891065 might be restarted, especially in case no alternative anti-neoplastic therapy is available.** • **For Grade 4 rash, BI 754091 and BI 891065 should be permanently discontinued.** • **BI 754091 and BI 891065 should also be discontinued for recurrent rash grade 3 or higher.**

		<u>Bullous dermatosis</u> • **For Grade 1 bullous dermatosis, use local wound care and observation. BI 754091 and BI 891065 can be continued.** • **For Grade 2 bullous dermatosis, withhold BI 754091 and BI 891065. Administer topical therapy, add systemic therapy as clinically adequate.** • **For Grade 3 bullous dermatosis, withhold BI 754091 and BI 891065, initiate topical and systemic therapy as per available guidelines. Restarting of BI 754091 and BI 891065 may be considered after dermatology consultation.** • **For Grade 4 bullous dermatosis, permanently discontinue BI 754091 and BI 891065.** **<u>Severe cutaneous adverse reaction (SCAR), Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN)</u>** • **For Grade 2 events, withhold BI 754091 and BI 891065, initiate treatment as per available guidelines. Closely monitor for improvement or worsening.** • **For Grade 3 events, withhold BI 754091 and BI 891065. 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 and BI 891065, 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 and BI 891065 may only be re-started upon event recovered to Grade 1 or less, on corticosteroid ≤ 10 mg per day, and after consultation with dermatology.** **<u>Encephalitis/Aseptic meningitis</u>** • **BI 754091 and BI 891065 should be permanently discontinued for any grade.** **<u>Myasthenia gravis</u>** • **For Grade 2 myasthenia gravis, withhold BI 754091 and BI 891065,** • **For Grade 3 or 4 myasthernia gravis, permanently discontinue BI 754091 and BI 891065** **<u>Guillain Barré Syndrome (GBS)</u>** • **Discontinue BI 754091 and BI 891065 permanently for any grade GBS.**

Transverse Myelitis

- **Discontinue BI 754091 and BI 891065 permanently for any grade transverse myelitis.**

Peripheral neuropathy, autonomic neuropathy

- **For Grade 1 events, may continue BI 754091 and BI 891065, but with low threshold to discontinue while monitoring closely for worsening.**
- **For Grade 2 events, withhold BI 754091 and BI 891065 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 and BI 891065.**

Inflammatory Arthritis

- **For Grade 1 arthritis, BI 754091 and BI 891065 can be continued. Administer analgetic treatment (acetaminophen, NSAID).**
- **For Grade 2-4 arthritis, withhold BI 754091 and BI 891065. Initiate treatment as per available guidelines, cave regarding reactivation of tuberculosis/opportunistic infections in case of prolonged immunosuppressive/DMARD therapy.**

BI 754091 and BI 891065 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 and BI 891065 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 and BI 891065, 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 and BI 891065 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 and BI 891065.**
- **BI 754091 and BI 891065 should be permanently discontinued if there is any evidence of myocardial involvement.**

Polymyalgia-like syndrome

- **For Grade 1 event, BI 754091 and BI 891065 can be continued.**
- **For Grade 2 event, withhold BI 754091 and BI 891065 and promptly initiate adequate therapy. If no improvement, treat as grade 3.**
- **For Grade 3 or G4 event, withhold BI 754091 and BI 891065, promptly initiate adequate therapy Rheumatology consultancy is highly recommended.**

BI 754091 and BI 891065 may be resumed after careful assessment of risks and benefits, rheumatology consultancy highly recommended prior to reinitiation. BI 754091 and BI 891065 may only be re-started upon recovery to grade 1 or less and on corticosteroid ≤ 10 mg per day.

<u>Myocarditis</u>
- **Discontinue BI 754091 and BI 891065 permanently for any grade of myocarditis.**

<u>Uveitis/Iritis, Episcleritis</u>
- **For Grade 1 events, treatment with BI 754091 and BI 891065 can continue. Treat topically as needed.**
- **For Gade 2 events, withhold therapy with BI 754091 and BI 891065, urgent ophthalomology referral is recommended. Initiate topical treatment, consider systemic therapy if needed. Restart of BI 754091 and BI 891065 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 and BI 891065 therapy.**
- **For Grade 3 or 4 events, permanently discontinue BI 754091 and BI 891065 therapy. Seek emergent ophthalmology consultation.. Initiate adequate local and systemic treatment.**

<u>Autoimmune-hemolytic anemia (AIHA)</u>
- **For Grade 1 AIHA, continue treatment with BI 754091 and BI 891065. Close follow-up of anemia and other lab values.**
- **For Grade 2-4 AIHA, discontinue BI 754091 and BI 891065 permanently. Initiate systemic therapy as per guideline. Consult Hermatology.**

<u>Acquired thrombotic thrombocytopenic purpura (TTP), haemolytic uremic syndrome.</u>
Timely recognition upon suggestive findings is essential, timely/immediate involvement of hematology consultancy may be beneficial.
- **For any grade TTP, permanently discontinue BI 754091 and BI 891065.**

- **For HUS (TTP excluded), withhold BI 754091 and BI 891065 for grade 1 and grade 2, provide supportive care. Upon full recovery, BI 754091 and BI 891065 may be restarted after carefuly weighing of risks and benefits.**
- **For Grade 3 or Grade 4 HUS, discontinue BI 754091 and BI 891065 permanently.**

Immune thrombocytopenia (ITP)
- **In case of Grade 1 ITP, BI 754091 and BI 891065 can be continued.**
- **For Grade 2 or Grade 3 ITP, withhold BI 754091 and BI 891065 and initiate systemic therapy. BI 754091 and BI 891065 may be restarted upon resolution to at least grade 1.**
- **For Grade 4 ITP, permanently discontinue BI 754091 and BI 891065.**

~~Management of immune-related event toxicities associated with anti-PD-1 mAbs are presented below. BI 754091 should be permanently discontinued for Grade 3-4 pneumonitis, Grade 3-4 adrenal insufficiency, Grade 4 diabetes mellitus, any grade encephalitis, Grade 4 hypophysitis, Grade 4 rash, Grade 3-4 or recurrent colitis of any grade, any recurrent Grade 3-4 AE, transaminase >5 times ULN or total bilirubin >3 times ULN, 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.~~

~~Pneumonitis:~~
- ~~For Grade 2 events, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days.~~
- ~~Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.~~
  - ~~For Grade 3-4 events immediately treat with i.v. steroids. Administer additional anti-inflammatory measures, as needed.~~
  - ~~BI 754091 should be permanently discontinued for Grade 3-4 pneumonitis, inability to taper steroids to 10 mg or less prednisone or equivalent within 12 weeks, or persistent Grade 2 AEs that do not recover to Grade 1 or less within 12 weeks.~~

~~Diarrhoea/Colitis:~~
~~Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhoea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).~~
- ~~All subjects who experience diarrhoea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should~~

		~~be substituted via i.v. infusion. For Grade 2 or higher diarrhoea, consider GI consultation and endoscopy to confirm or rule out colitis.~~
		• ~~For Grade 2 diarrhoea/colitis that persists greater than 3 days, administer oral corticosteroids.~~
		• ~~For Grade 3 or 4 diarrhoea that persists >1 week, treat with i.v. steroids followed by high-dose oral steroids.~~
		• ~~For Grade 3 or 4 colitis, or recurrent colitis of any grade, permanently discontinue BI 754091 and immediately treat with i.v. steroids followed by high-dose oral steroids.~~
		  • ~~When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days.~~
		• ~~BI 754091 should be permanently discontinued for Grade 3-4 or recurrent colitis of any grade, 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.~~
		
		~~Type I diabetes mellitus (if new onset, including diabetic ketoacidosis) Grade 3, or ≥ Grade 3 hyperglycaemia, if associated with ketosis (ketonuria) or metabolic acidosis~~
		• ~~For Type I diabetes mellitus Grade 3-4 or Grade 3-4 hyperglycaemia~~
		• ~~Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycaemia associated with metabolic acidosis or ketonuria.~~
		• ~~Evaluate subjects with serum glucose and a metabolic panel, urine ketones, glycosylated haemoglobin, and C-peptide.~~
		  – ~~BI 754091 should be permanently discontinued for Grade 4 diabetes mellitus, any recurrent Grade 3 AE or persistent Grade 2-3 AE that does not recover to Grade 1 or less within 12 weeks.~~
		
		~~Hypophysitis:~~
		• ~~For Grade 2 events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days. Replacement of appropriate hormones may be required as the steroid dose is tapered.~~
		• ~~For Grade 3 events, treat with an initial dose of i.v. corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days. Replacement of appropriate hormones may be required as the steroid dose is tapered.~~
		• ~~For Grade 4 events, permanently discontinue BI 754091, and treat with an initial dose of i.v. corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days. Replacement of appropriate hormones may~~

~~be required as the steroid dose is tapered.~~

- ~~BI 754091 should be permanently discontinued for Grade 4 hypophysitis, any recurrent Grade 3 AE, 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.~~

~~Hyperthyroidism or Hypothyroidism:~~

~~Thyroid disorders can occur at any time during treatment. Monitor subjects for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.~~

- ~~For Grade 2 hyperthyroidism events (and Grade 3 4 hypothyroidism):~~
- ~~In hyperthyroidism, nonselective beta blockers (e.g., propranolol) are suggested as initial therapy.~~
- ~~In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.~~
- ~~For Grade 3 4 hyperthyroidism~~
- ~~Treat with an initial dose of i.v. corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days. Replacement of appropriate hormones may be required as the steroid dose is tapered.~~
- ~~BI 754091 should be permanently discontinued for any recurrent Grade 3 4 AE, 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.~~

~~Hepatic:~~

- ~~For Grade 2 events, monitor liver function tests more frequently until returned to baseline values (consider weekly).~~
- ~~Treat with i.v. or oral corticosteroids~~
- ~~For Grade 3 4 events, treat with i.v. corticosteroids for 24 to 48 hours.~~
- ~~When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 28 days.~~
- ~~BI 754091 should be permanently discontinued for any recurrent Grade 3 4 AE, transaminase >5 times ULN or total bilirubin >3 times ULN, 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.~~

~~Renal failure or nephritis:~~

- ~~For Grade 2 events, treat with corticosteroids.~~
- ~~For Grade 3 4 events, treat with systemic corticosteroids.~~

		~~• When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 28 days.~~ ~~• BI 754091 should be permanently discontinued for any recurrent Grade 3-4 AE, 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.~~ ~~Adrenal insufficiency~~ ~~• BI 754091 should be permanently discontinued for Grade 3 to 4 adrenal insufficiency or persistent Grade 2 AEs that do not recover to Grade 1 or less within 12 weeks.~~ ~~Rash~~ ~~• BI 754091 should be permanently discontinued for Grade 4 rash, any recurrent Grade 3 AE or persistent Grade 2 to 3 AEs that do not recover to Grade 1 or less within 12 weeks.~~ ~~Encephalitis~~ ~~• BI 754091 should be permanently discontinued for any grade encephalitis.~~ ~~Infusion reactions:~~ ~~Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.~~
Rationale for change		To revise and clarify the management of immune-related adverse events based on more recent data.
Section to be changed		Table 10.3: 2 Time schedule for PK blood, [redacted] sampling during Part B including food effect
Description of change		Time schedule for PK blood, [redacted] during Part B including food effect **in q.d. treatment group**
Rationale for change		To identify that the PK, [redacted] sample collections described in the table are only for q.d. patients.
Section to be changed		Table 10.3: 2 Time schedule for PK blood, [redacted] sampling during Part B including food effect effect in q.d. treatment group and Table 10.3: 4 Time schedule for PK blood, [redacted] sampling during Part C-NSCLC
Description of change		b The following windows of time are allowed for PK **and ECG** sampling: **(ECGs should be performed PRIOR to PK sampling):**
Rationale for change		To clarify when ECGs should be collected relative to PK collections.
Section to be changed		Table 10.3:3 was added to the trial protocol
Description of change		Table 10.3: 3 Time schedule for PK blood, [redacted] sampling during Part B excluding food

effect in b.i.d. treatment group

						Samples				
Cycle	**Visit**	**Day**	**Time Point [hh:min]/ event**	**CRF Time /PTM**	**Triplicate ECG***	**Plasma[b] BI 891065**	**Plasma[b] BI 754091**	[redacted]	**Biopsy[c]**	[redacted]
1	2	1	Predose (between screening and C1D1 dosing)						X	
			-30 min (+/-15min)	-30 min	X					
1	2	1	Just before drug admin	Predose[a]	X		X	X		X
			BI 754091 admin	0:00						
			Just before infusion end	1:00			X			
			1:25	1:25	X**	X	X			
			BI 891065 admin	1:30						
			2:00	2:00		X	X			
			2:30	2:30	X**	X	X			
			3:30	3:30	X**	X	X			
			4:30	4:30	X**	X	X	X		
			6:30	6:30	X**	X	X			
			7:30	7:30	X	X	X			
			8:30	8:30	X**	X	X			
			9:30	9:30	X	X	X	X		
			11:30	11:30	X**	X	X			
			No drug intake	13:30						
	3	2	Just before drug intake	25:25	X	X	X	X		
			BI 891065 intake	25:30						
	4	8	Just before drug intake	167:55		X	X	X		
			BI 891065 intake	168:00						
	5	12	Just before drug intake	263:55		X	X			
			BI 891065 intake	264:00						

ADA = anti-drug antibodies; BI = Boehringer Ingelheim; CRF = Case Report Form; IAP = inhibitor of apoptosis; PTM = planned time
a PK to be taken following an overnight fast (minimum 10 hours) on this day
b The following windows of time are allowed for PK and ECG sampling (ECGs should be performed PRIOR to PK sampling):

- Predose samples (PTM -0:05, 25:25, 167:55, etc.): within 1 hour before drug intake
- One hour to 4:30 hours post first drug intake (PTM 1:00 through PTM

4:30): within ±10 minutes of designated time
- 6:30 to 11:30 hours post first drug intake (PTM 6:30 through 11:30): within ±15 minutes of designated time

Time windows are specified for procedural reasons; deviations do not automatically lead to exclusion of samples from data evaluation.
c Biopsy for IAP degradation to be taken as noted in Part B Flow Chart.
* In order not to confuse an ECG recording, all PK samples should be taken after performing the ECGs.
** ECGs will be taken throughout, as it is possible that time of maximum concentration is not accurately estimated; for safety, this is one of the most relevant time points, so should not be missed. As such, some ECGs may only be evaluated at later points or, if deemed unnecessary, not at all.

Table 10.3: 3 Time schedule for PK blood, [redacted] sampling during Part B excluding food effect in b.i.d. treatment group (continued)

						Samples				
Cycle	**Visit**	**Day**	**Time Point [hh:min]/ event**	**CRF Time /PTM**	**Triplicate ECGs***	**Plasma[b] BI 891065**	**Plasma[b] BI 754091**	**[redacted]**	**Biopsy[c]**	**[redacted]**
1	6	15	Just before drug admin	335:55[a]	X	X	X			
			BI 891065 intake	336:00						
			0:30	336:30	X	X				
			1:00	337:00	X**	X				
			2:00	338:00	X**	X				
			3:00	339:00	X**	X				
			5:00	341:00	X**	X				
			6:00	342:00	X	X				
			7:00	343:00	X**	X				
			8:00	344:00	X	X				
			10:00	346:00	X**	X				
			No drug intake	348:00						
	7	16	Just before drug intake	359:30***	X	X	X			
			BI 891065 intake	360:00						

		<table><tr><td rowspan="2">2-5, then every 2nd cycle</td><td rowspan="2">9-12 then every 2nd cycle</td><td rowspan="2">1</td><td>Just before drug admin</td><td>-0:05</td><td></td><td>X (C2 only)</td><td>X</td><td></td><td>X</td><td>X</td></tr><tr><td>Just before infusion end</td><td>1:00</td><td></td><td></td><td>X</td><td></td><td></td><td></td></tr><tr><td colspan="4">EOT</td><td></td><td></td><td>X</td><td>X</td><td></td><td>X</td></tr><tr><td colspan="4">30-Day FU</td><td></td><td></td><td>X</td><td></td><td></td><td>X</td></tr></table> ADA = anti-drug antibodies; BI = Boehringer Ingelheim; CRF = Case Report Form; ECG = electrocardiogram; EOT = end of treatment; FU = follow up; IAP = inhibitor of apoptosis; PTM = planned time a PK to be taken following an overnight fast (minimum 10 hours) on this day b The following windows of time are allowed for PK and ECG sampling (ECGs should be performed PRIOR to PK sampling): • Predose samples (PTM 335:55 [Day 15]): within 1 hour before drug intake • On Day 15 (PTM 336:30 through 339:00): within ±10 minutes of designated time • On Day 15 (PTM 341:00 through 346:00): within ±15 minutes of designated time • On Day16 (PTM 359:30): within 30 min before drug intake Time windows are specified for procedural reasons; deviations do not automatically lead to exclusion of samples from data evaluation. c Biopsy for IAP degradation to be taken as noted in Part B Flow Chart. * In order not to confuse an ECG recording, all PK samples should be taken after performing the ECGs. ** ECGs will be taken throughout, as it is possible that time of maximum concentration is not accurately estimated; for safety, this is one of the most relevant time points, so should not be missed. As such, some ECGs may only be evaluated at later points or, if deemed unnecessary, not at all. ***Central lab kits provided will contain extra tubes (for post-dose timepoints 360:30-370:00 on Day 16 and 383:55 on Day 17). These tubes should not be used for b.i.d patients.
Rationale for change		To describe the PK, [redacted] sample collections for Part B b.i.d. patients.
Section to be changed		Section 10.4 Pharmacokinect Analyses
Description of change		• C_{pre},N (pre-dose concentration of the analyte in plasma ~~after~~ **before** the Nth dose)
Rationale for change		To correct an error in the text for the C_{pre} N collection time.

APPROVAL / SIGNATURE PAGE

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Title: An open-label Phase I dose finding trial with BI 891065 alone and in combination with BI 754091 to characterise safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy in patients with advanced and/or metastatic malignancies

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Team Member Medicine	[redacted]	14 Feb 2020 17:12 CET
Approval-Translational Medicine Expert		14 Feb 2020 17:51 CET
Author-Clinical Trial Leader		14 Feb 2020 18:16 CET
Approval-Therapeutic Area [redacted]		14 Feb 2020 18:52 CET
Author-Trial Statistician		14 Feb 2020 21:57 CET
Author-Trial Clinical Pharmacokineticist		17 Feb 2020 02:10 CET
Verification-Paper Signature Completion		18 Feb 2020 19:48 CET

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Meaning of Signature	Signed by	Date Signed