Clinical Trial Protocol

	Document Number:	**c26016868-06**
EudraCT No.	2019-001082-32	
BI Trial No.	1426-0001	
BI Investigational Medicinal Product(s)	BI 1387446 Ezabenlimab (BI 754091)	
Title	Phase I, first in human trial evaluating BI 1387446 alone and in combination with ezabenlimab (BI 754091) in solid tumours	
Lay Title	A study to find the best dose of BI 1387446 alone or in combination with ezabenlimab (BI 754091) in patients with different types of advanced or metastatic cancer (solid tumours)	
Clinical Phase	Phase I	
Clinical Trial Leader	[redacted] Tel: Fax:	
Coordinating Investigator	[redacted] Phone: Fax:	
Status	Final Protocol (revised protocol [based on global Amendment 5])	
Version and Date	**Version: 6.0**	**Date: 18 Oct 2023**

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CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	30 May 2019
Revision date	18 Oct 2023
BI trial number	1426-0001
Title of trial	Phase I, first in human trial evaluating BI 1387446 alone and in combination with ezabenlimab (BI 754091) in solid tumours
Coordinating Investigator	[redacted] Phone: [redacted] Fax: [redacted]
Trial site(s)	Multi-center trial
Clinical phase	Phase I
Trial rationale	Immunotherapy with checkpoint inhibitors (CIs) may result in long term disease control and possibly cure, but still a significant portion of patients are primarily non-responsive to a CI or develop resistance on treatment. STING activation is considered a key mechanism in innate immune sensing of cancer. BI 1387446 is a STING agonist, which in animal models has led to shrinkage and complete disappearance of injected tumours, durable antitumour memory, and growth inhibitory effects on non-injected tumours. This trial will assess the safety and early signs of efficacy of intratumoural injection of BI 1387446 alone and in combination with intravenous infusion of ezabenlimab (BI 754091) (anti-PD-1) in patients with advanced malignant solid tumours.
Trial objective(s)	To characterize the safety and to determine the maximum tolerated dose (MTD) for BI 1387446 alone and in combination with ezabenlimab (BI 754091)
Trial endpoints	Primary endpoints: • MTD based on number of Dose-limiting toxicities (DLTs) • Number of patients with DLTs in the MTD evaluation period Time frame for all primary endpoints: Arms A, B from start of treatment until end of cycle 1 (3 weeks, MTD evaluation period) Secondary endpoints: • OR based on Response Criteria for Intratumoural Immunotherapy in Solid Tumours (itRECIST) • Best percentage change from baseline in size of non-injected target lesions • Best percentage change from baseline in size of injected target lesions

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	Time frame for all secondary endpoints: From start of treatment until the earliest of progression, death or end of trial (approximately 1 year).
Trial design	Open label trial with a dose finding phase
Total number of patients entered	Approximately 78 patients
Number of patients on each treatment	Approximately 78 patients • monotherapy superficial lesions: approximately 34 patients • combination therapy superficial lesions: approximately 44 patients
Diagnosis	Various malignant solid tumours
Main in- and exclusion criteria	*Main inclusion criteria:* • Adult male or female patients with diagnosis of an advanced, unresectable and/or metastatic malignant solid tumour and indication for treatment. • Patient must have exhausted established treatment options known to prolong survival for the malignant disease, or is not eligible for established treatment options. • Arms A, B: At least one tumour lesion which is suitable for injection, appropriate for the allocated treatment arm, and measurable. At least 1 discrete lesion, in addition to the lesion proposed for injection, which is amenable to biopsy. • ECOG 0 or 1 *Main exclusion criteria:* • Any investigational or antitumour treatment within 4 weeks or 5 half-life periods prior to the first treatment whichever is shorter • Persistent toxicity from previous treatments (including irAEs) that has not resolved to ≤ Grade 1, except for alopecia, xerostomia, and immunotherapy related endocrinopathies • History or evidence of active, non-treatment related autoimmune disease, except for endocrinopathies • History of pneumonitis related to prior immunotherapy • Presence of other active invasive cancers other than the one treated in this trial within 5 years prior to screening • Presence or history of uncontrolled or symptomatic brain or subdural metastases unless local therapy completed and metastases considered stable • Known history of HIV infection • Active infection requiring systemic therapy at the start of treatment in the trial • Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 2 weeks prior to the first treatment.

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Test product(s)	BI 1387446 Ezabenlimab (BI 754091)
dose	BI 1387446: [redacted] per day of administration Ezabenlimab (BI 754091): 240 mg every 3 weeks
mode of administration	BI 1387446: intratumoural injection (i.tu.) Ezabenlimab (BI 754091): intravenous infusion (i.v.)
Duration of treatment	Administration will continue until progressive disease (PD), unacceptable toxicity, other withdrawal criteria, or a maximum treatment duration of 34 cycles, whichever occurs first.
Statistical methods	Descriptive statistics will be used for all analyses. Dose escalation will be guided by a Bayesian logistic regression model (BLRM) with overdose control that will be fitted to binary toxicity outcomes using a hierarchical modelling approach to jointly model escalation arms A and B. The estimates of the model parameters will be updated as data are accumulating using the BLRM. At the end of the dose escalation the toxicity probability at each dose level in each arm will be calculated to determine an estimate of the MTD in each arm.

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FLOW CHART: OVERVIEW-ARM A AND ARM B

Trial Periods	Screening	Treatment period[1]												Post treatment period			
		Cycle 1			Cycle 2			Cycle 3			Cycle 4	Cycle 5	Cycle 6-34	End of treatment	30-Day Safety Follow-up	90-Day Safety Follow-up	Follow-up[2]
Visit	**Screening**	**C1 V1**	**C1 V2**	**C1 V3**	**C2 V1**	**C2 V2**	**C2 V3**	**C3 V1**	**C3 V2**	**C3 V3**	**C4V1**	**C5V1**	**C6V1 – C34V1**	**EoT[3]**	**30dFU[3]**	**90dFU[3]**	**EoTrial**
Days	[redacted]												**1**		**EoT+ 30 days**	**EoT+ 90 days**	
Time window for visits (day)						+1	+1	+1	+1	+1	+3	±3	±3	+ 7	+ 7	+ 14	
Overnight stay[4]		X			X												
Informed consent[5]	X																
Demographics[6]	X																
Medical history[6]	X																
Physical examination[6]	X	X	X[30]	X[30]	X	X[30]	X[30]	X	X[30]	X[30]	X	X	X[30]	X	X		
Vital signs[6]	X	X	X	X	X	X	X	X	X	X	X	X	X				
ECOG Performance Status[6]	X	X			X			X				X	X[31]	X	X		
Safety laboratory tests[6, 7, 8]	X[9]	X[32]	X[9]	X[9]	X	X[9]	X[9]	X	X[9]	X[9]	X	X	X	X			
12-lead ECG (single/triplicate)[10]	X	X			X			X				X	X[11]	X	X[12]		
Echocardiography (or MUGA)[37]	X				X[34]						X[34]		X[34]	X			
Review of in-/exclusion criteria	X	X															
Allocation to treatment		X															
[redacted]																	
[redacted]																	
PK blood sampling for BI 1387446[17]		X	X	X	X	X	X	X	X	X	X	X	X	X[16]			
PK blood sampling for ezabenlimab (BI 754091)[14, 17]		X	X	X	X	X	X	X			X	X	X	X[16]			
Anti-drug antibodies (ADAs) blood sampling[14, 17]		X			X			X					X[29]	X[16]			

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FLOW CHART: OVERVIEW-ARM A and ARM B (cont.)

Trial Periods	Screening	Treatment period[1]												Post treatment period			
		Cycle 1			Cycle 2			Cycle 3			Cycle 4	Cycle 5	Cycle 6-34	End of treatment	30-Day Safety Follow-up	90-Day Safety Follow-up	Follow-up[2]
Visit	Screening	C1 V1	C1 V2	C1 V3	C2 V1	C2 V2	C2 V3	C3 V1	C3 V2	C3 V3	C4V1	C5V1	C6V1 – C34V1	EoT[3]	30dFU[3]	90dFU[3]	EoTrial
Days	[redacted]	[redacted]									[redacted]	[redacted]	[redacted] 1		EoT+ 30 days	EoT+ 90 days	
FACS Immune cell panel blood sampling		X[18]	X[19]	X[19]	X[19]												
STING variants – blood	X																
Gene Expression Profile (GEP) - blood		X[20]		X[20]	X[20]												
Cytokine and chemokines sampling - blood		X[20]		X[20]	X[20]												
Archival tumour material (if available)	X																
Fresh tumour biopsy – injected lesion[28]	X[21]	X[22]			X[19]												
Fresh tumour biopsy – non-injected lesion[28]	X[21]				X[19, 27]							X[19,23, 27]					
Tumour assessment[24]	X				X						X		X	X[33]	X[35]		X[35]
Pregnancy testing for Women of Child-Bearing Potential[6] (serum)	X	X			X			X			X	X	X	X			
Assessment of lens opacity	X														X[36]		
All AEs/SAEs/AESIs[25]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[26]
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Completion of patient participation															X	X	X
Progression/ survival															X	X	X

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1. All cycles are 3 weeks [redacted] in duration. Patients will continue treatment with the study drugs until progressive disease (PD) by RECIST, withdrawal of patient consent, an unacceptable toxicity occurs, or the maximum number of cycles of treatment are reached, whichever occurs first. The maximum duration of treatment with BI 1387446 (Arms A and B) is 18 cycles, unless the patient has a partial response according to itRECIST, in which case treatment may continue for cycles 19-34 after consultation with the sponsor. BI 1387446 has to be paused if there is no lesion suitable for injection any more, but may be re-started in the absence of PD if any lesion becomes suitable for injection again. The maximum duration of treatment with ezabenlimab (BI 754091) (Arm B only) is 34 cycles. Patients will be allowed to stay on treatment in the case of initial radiological PD (iUPD by itRECIST), if the Investigator judges that it is in the patient's best interest and the patient has signed an informed consent describing this circumstance. Day 1 of Cycle 1 is defined as the day when BI 1387446 is first administered.
2. Applicable only to patients who did not experience PD on treatment. After the 90dFU, patients will have follow-up visits (in person or by telephone) for tumour progression and to monitor safety by collecting AEs/SAEs/AESIs every 3 months until PD, introduction of new anti-cancer treatment, death, loss to follow-up, withdrawal of consent or for a maximum of 6 months after EoT.
3. **EoT visit:** When a decision is taken to discontinue all treatment drugs, the EoT visit should be done instead of the scheduled visit. **30dFU visit:** To be performed in person 30 days after the EoT visit. At this visit, all AEs/SAEs/AESIs and other required information must be collected as specified in the Flow Chart. **90dFU visit:** To be performed by telephone (or in person if the investigator deems necessary) 90 days after the EoT visit. Only AEs/SAEs/AESIs and concomitant therapy need to be collected at the 90dFU visit.
4. At Cycle 2 Day 1, an overnight stay is recommended if logistically possible due to sampling planned at the visit.
5. The informed consent for trial participation should be signed prior to any trial procedure. Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions. A separate informed consent should be signed for biobanking if agreed by the patient. Per Section 4.1.2.3, a patient will be allowed to stay on treatment in the case of initial radiological PD (corresponding to iUPD by itRECIST/, if the Investigator judges that it is in the patient's best interest and the patient has signed a separate informed consent describing the circumstance.
6. The screening medical history and demographics, physical examination and Eastern Cooperative Oncology Group (ECOG) performance status, vital signs, electrocardiogram (ECG), echocardiography (or MUGA scan), safety laboratory, and screening pregnancy test (serum) should be done ≤28 days prior to initiation of treatment. 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, and vital signs (pre- and post-infusion) prior to first trial dose.
7. Measurements of vital signs should precede blood sampling.
8. Safety laboratory assessments including haematology, serum biochemistry, and urinalysis will be performed locally. The parameters to be assessed at each visit is listed in Section 5.2.3.
9. Focused/ limited parameters will be measured, refer to Section 5.2.3.
10. Triplicate 12-lead electrocardiograms (ECGs) will be obtained only at the timepoints outlined in Blood Sample Flow Chart for Arm A and Flow Chart for Arm B. At all other timepoints indicated in the Flow Chart and whenever the Investigator deems it necessary, single ECGs will be done prior to drug administration. ECG at screening must be done before blood work or other procedures after at least 5 minutes in resting position. ECG recording will be sent to a vendor for central evaluation.
11. A single ECG will be obtained as clinically indicated prior to drug administration, at least every two to three cycles (i.e. on Day 1 in Cycle 7, 9, 11, 13, 16, 19, 23,

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27, 31, and 34.

12. An ECG is optional at the 30-day safety follow-up visit if the EOT visit ECG was normal and no drug-related abnormalities were detected in on-trial ECGs.
13. All patients without disease progression may receive treatment with BI 1387446 for up to 18 cycles. For exception, refer to Section 4.1.2.3
14. Only Arm B. [redacted] In case one drug is administered on the planned treatment date and the other drug cannot be administered on the same day, this dose should be skipped and treatment be resumed as per schedule on the next planned administration.
15. All patients without disease progression may receive treatment with ezabenlimab (BI 754091) in Arm B for up to 34 cycles.
16. Measurement needs to be done at EoT only if the patients discontinue the trial before Cycle 4.
17. For detailed PK and ADA timepoints applied at different cycles and in different arms, refer to the respective blood sample Flow Chart.
18. To be taken predose and 24h after the first BI 1387446 injection.
19. To be taken predose.
20. To be taken at predose and 4h, 8h, 12h (preferred but any time between 9h and 24h post injection is acceptable) and 24h after the first BI 1387446 injection on Day 1 of Cycle 1 and 2 . On Cycle 1 [redacted] sampling should be at predose, 4h, and 8h post BI1387446 administration. For details, see Blood sample Flow Charts.
21. Baseline tumour-biopsy sample to be taken from the projected injected and one distinct non-injected lesion between screening and first administration of BI 1387446. Only patients considered eligible after assessment of inclusion/exclusion criteria will be subjected to the procedure. Refer to Section 4.1.4.1, 4.1.4.2 and 5.4.2.3 for lesion selection. In patients crossing over from Arm A to Arm B after completion of Cycle 1, new baseline biopsies from the injected and non-injected lesion should be taken. If biopsy at C2D1 was obtained without further treatment following the biopsy in Arm A, this new baseline biopsy is not needed.
22. Biopsy at Cycle1/Day 1 to be optionally taken 5-24h post BI 1387446 administration from the injected lesion only from patients enrolled into Arm A.
23. Optional biopsy.
24. Tumour assessments should be done according to itRECIST, 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 or magnetic resonance imaging [MRI]). The same radiographic procedure must be used throughout the trial. The baseline tumour assessments (CT/MRI) and should be performed ≤28 days prior to initiation of treatment. The first on-treatment tumour assessment will be done before treatment administration at Cycle 2 (a time window of -5 days is acceptable). Positron emission tomography (PET-CT) may be performed if clinically indicated based on tumour type, however, in this case a diagnostic-quality CT scan needs to be acquired as part of the PET-CT for RECIST measurements. The CT portion of a PET-CT can be used as the basis for RECIST measurements if the site has documented that a CT with appropriate radiation dose for diagnostic quality and IV/oral contrast was used (if not medically contraindicated).
Subsequent on-treatment tumour assessments will be performed before treatment administration (a time window of -7 days is acceptable) in C4, C6, C8, C10, C13, C16, C19, C23, C27, C31 and at EOT.
25. After the individual patient's end of the trial the Investigator should report only any cancers of new histology and exacerbations of existing cancer, study treatment related SAEs and study treatment related AESIs of which the Investigator may become aware of and only via the BI SAE form, refer to Section 5.2.7.2.1.

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26. AEs which were ongoing at the 30dFU will be followed.
27. Consecutive biopsies should be taken always from the same lesion if clinically feasible.
28. Biopsies are taken from the projected injected and one distinct non-injected lesion if not indicated differently in the Flow Chart. Mandatory timepoints are baseline and C2D1. At optional timepoints only, patients with lesions suitable for diagnostic biopsy associated with limited procedural risks should be included (refer to Section 5.4 for details).
29. Sampling for ADA only in Cycles 6, 9, 12, 18, 24, 30 and 34.
30. Abbreviated physical examination (focused on the specific disease, at the Investigator's discretion).
31. After Cycle 5, every other cycle (i.e. Cycle 7, 9, 11…33).
32. Safety laboratory does not need to be repeated if the result is available within 24h prior to the drug administration.
33. No need to perform tumour assessment if it has been done within the 3 weeks prior to EoT.
34. Echocardiography will be obtained prior to administration of trial drugs (if drug administration is applicable) on Day 1 in Cycle 4, C7, C11, C15, and at EOT (a time window of -7 days is acceptable). For Cycle 2 Day 1, echocardiography may be performed within 72 hours prior to drug administration.
35. If the patient stops trial treatment prior to completion of maximum number of cycles for a reason other than PD, the tumour assessment according to RECIST will be performed according to standard of care until the last follow-up needed according to protocol.
36. A slit-lamp examination will be performed by an ophthalmologist at screening, at the 30-day safety follow-up, and at any time during the treatment period, if clinically indicated. Opacities as seen on clinical slit-lamp examination will be graded according to LOCS III.
37. Although echocardiography is the preferred method, MUGA scans are permitted to quantify LVEF. The same method should be used in a single patient throughout the trial.

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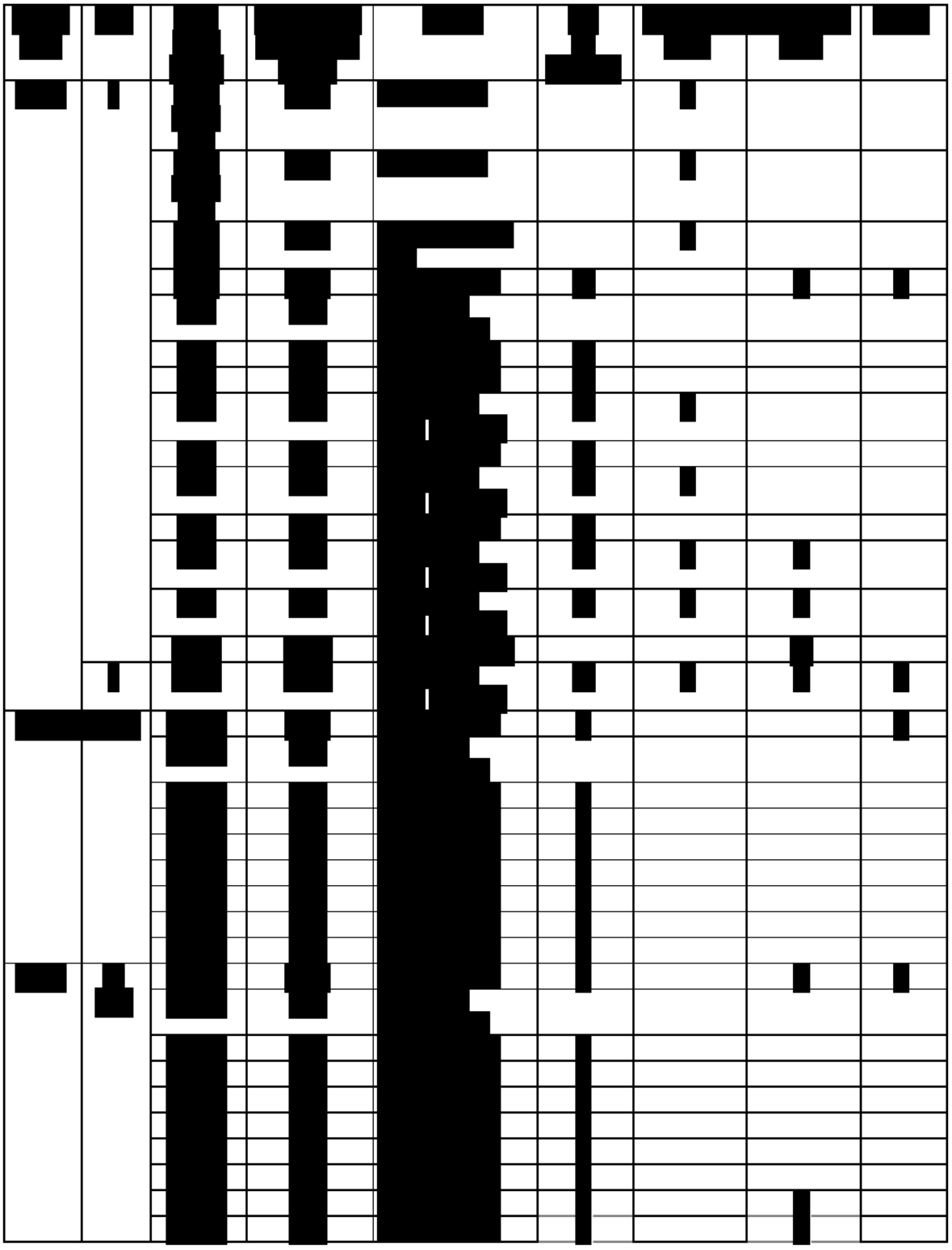
BLOOD SAMPLE FLOW CHART: ARM A



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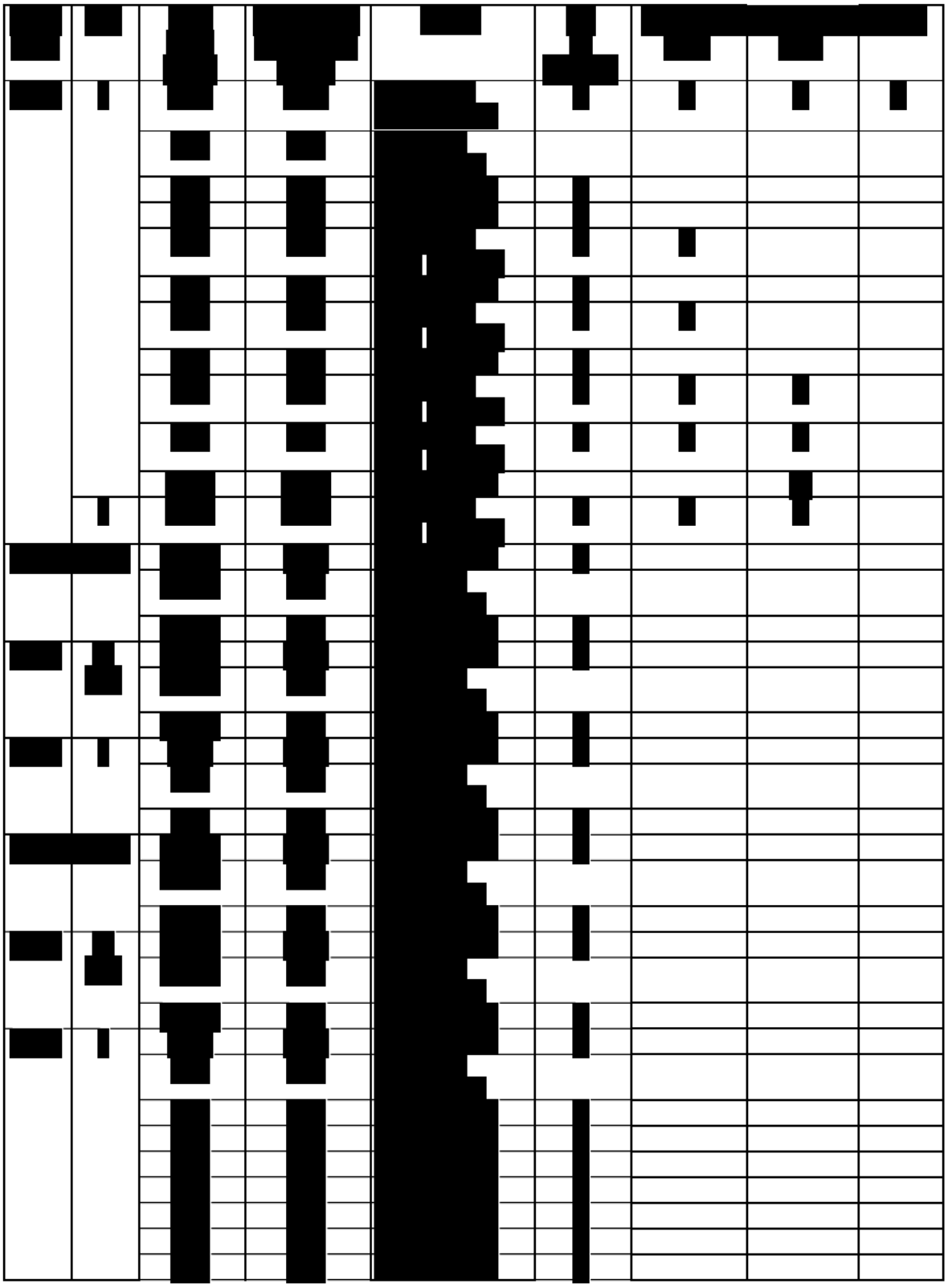
BLOOD SAMPLE FLOW CHART: ARM A (cont.)



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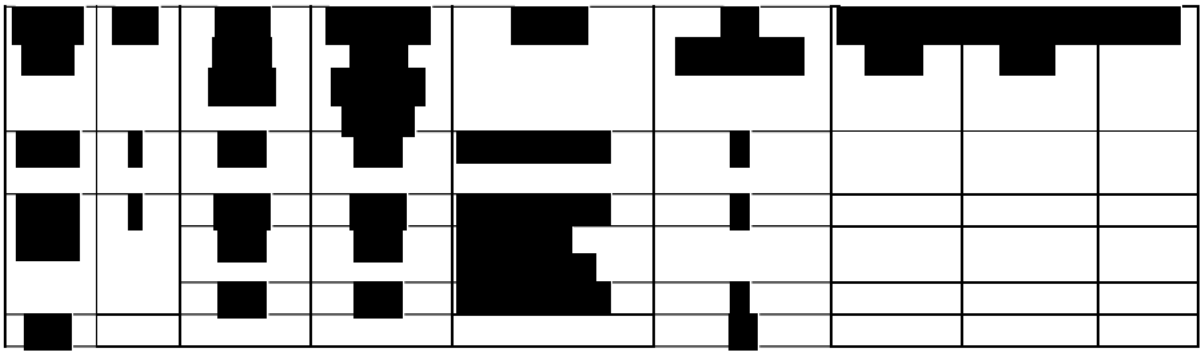
BLOOD SAMPLE FLOW CHART: ARM A (cont.)



1. Only if patient discontinues before Cycle 4
2. Time windows for blood sampling: +/-3min for 5min sample, +/- 5 minutes for samples until 1h, +/- 10 min for 2h and 4h samples, +/- 60 min for 8h and +/-2h for any timepoint later than 8h .
3. A blood sample should be taken for cytokine analysis and GEP if feasible preferably around 12 hours, but any time between 9h and 24h post injection in C1V1 and C2V1 is acceptable.
4. For C1V1 Day 1 and Day 2 for the [redacted] level only: include blood sample for metabolite identification (refer to Section 5.3.2).
5. When triplicate ECGs are scheduled prior to blood sampling, the 3 single ECG recordings should be performed within a maximum period of 5 minutes prior to blood sampling.

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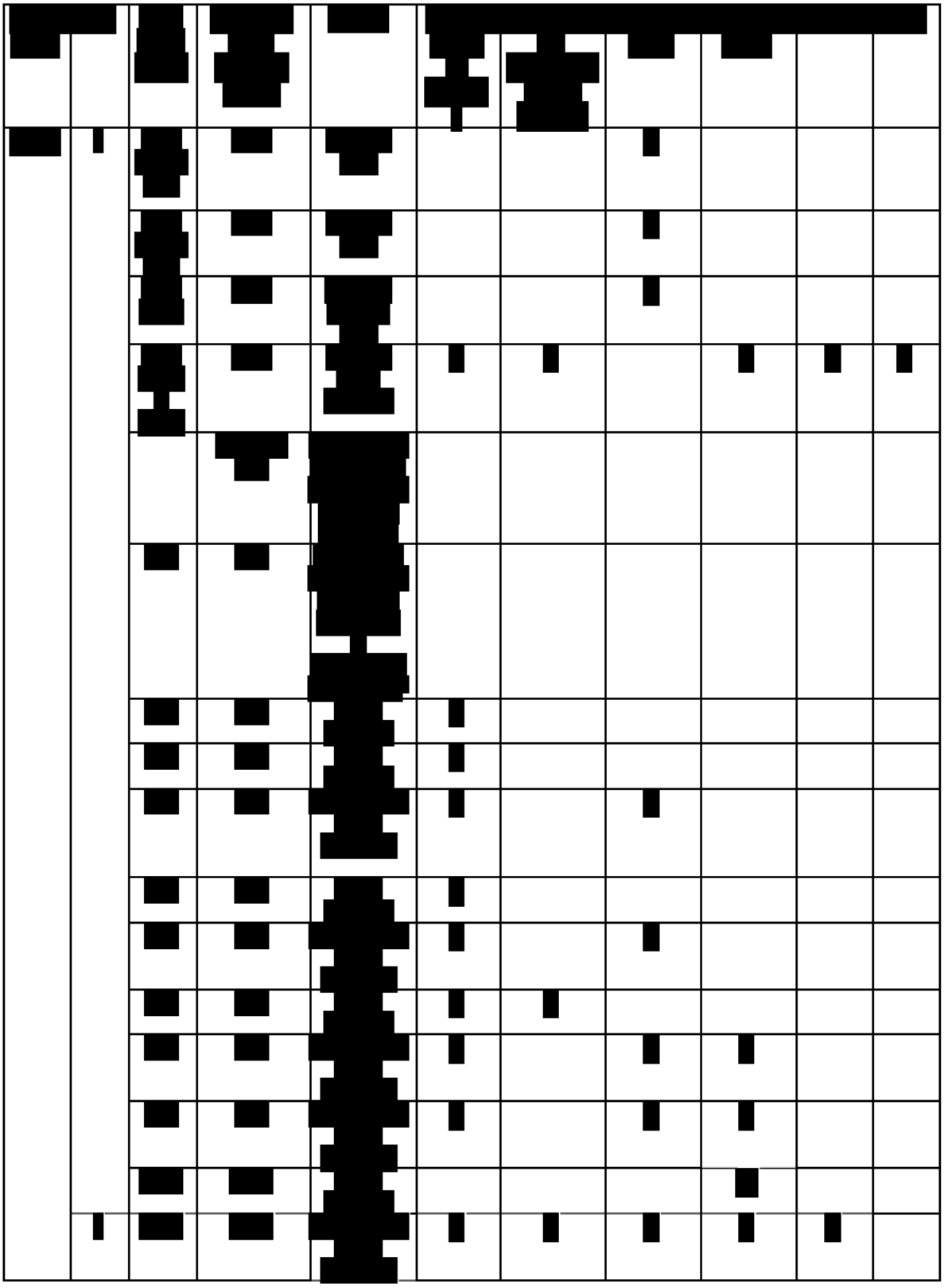
BLOOD SAMPLE FLOW CHART: ARM B



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BLOOD SAMPLE FLOW CHART: ARM B (cont.)

Cycle /Visit	Day	CRF Time /PTM	Time rel. to BI 1387446 admin	Event[3]	Analysed for BI 1387446	Analysed for ezabenlimab (BI 754091)	Triplicate ECG	Cytokine/ GEP	FACS	ADA

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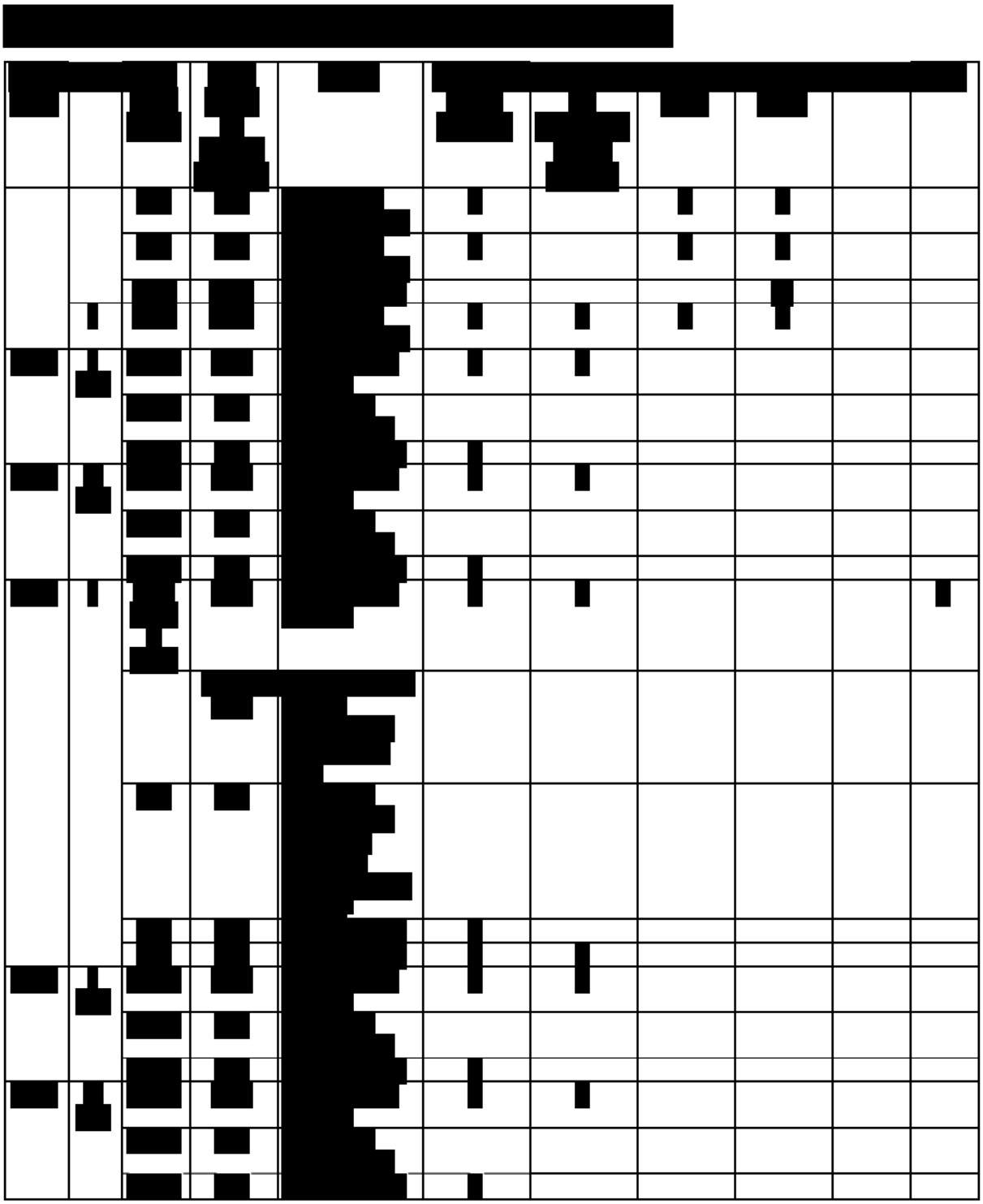

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BLOOD SAMPLE FLOW CHART: ARM B (cont.)

Cycle /Visit	Day	CRF Time /PTM	Time rel. to BI 1387446 admin	Event[3]	Analysed for BI 1387446	Analysed for ezabenlimab (BI 754091)	Triplicate ECG	Cytokine/ GEP	FACS	ADA
[redacted]										

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BLOOD SAMPLE FLOW CHART: ARM B (cont.)

Cycle/ Visit	Day	CRF Time /PTM	Time rel. to BI 1387446 admin	Event[3]	Analysed for BI 1387446	Analysed for ezabenlimab (BI 754091)	Triplicate ECG	Cytokine /GEP	FACS	ADA
[redacted]										
										[1]

1. Only if patient discontinues before Cycle 4
2. Only Cycle 6
3. Time windows for blood sampling: +/-3min for 5min sample, +/- 5 minutes for samples until 1h, +/- 10 min for 2h and 4h samples, +/- 60 min for 8h and +/-2h for any timepoint later than 8h.
4. For Cycle 19 and onwards, administration of BI 1387446 is applicable for patients with a partial response.
5. A blood sample should be taken for cytokine analysis and GEP if feasible preferably around 12 hours, but any time between 9h and 24h post injection in C1V1 and C2V1 is acceptable
6. When triplicate ECGs are scheduled prior to blood sampling, the 3 single ECG recordings should be performed within a maximum period of 5 minutes prior to blood sampling.
7. During visits where ezabenlimab (BI 754091) and BI 1387446 administration are planned, it is preferred the BI 1387446 administration [redacted]
8. The start of BI 1387446 administration will be considered time 0:00, even if its administration is [redacted]

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ABBREVIATIONS

ADA	Anti-drug antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original and Accurate
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	activated Partial Thromboplastin Time
ASBMT	American Society for Blood and Marrow Transplantation
AST	Aspartate Aminotransferase
$AUC_{0\text{-}tz}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point Area under the Curve
BHM	Bayesian Hierarchical Model
BI	Boehringer Ingelheim
BiPAP	Bilevel Positive Airway Pressure
BLQ	Below the Limit of Quantification
BLRM	Bayesian Logistic Regression Model
CA	Competent Authority
CDN	Cyclic dinucleotide
CI	Checkpoint inhibitor
CK	Creatine Kinase
CKD-EPI	Chronic Kidney Disease Epidemiology
C_{max}	Maximum measured concentration of the analyte in plasma
CPAP	Continuous Positive Airway Pressure
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organisation
CRS	Cytokine Release Syndrome
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events

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CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Database Lock
DHEA	Dehydroepiandrosterone
DILI	Drug Induced Liver Injury
DLT	Dose limiting Toxicity
DMARD	Disease modifying anti-rheumatic drugs
DNA	Deoxyribonucleic Acid
LV dp/dtmax	Decrease in contractility
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
EoT	End of Treatment
EoTrial	End of Trial
EudraCT	European Clinical Trials Database
EWOC	Escalation With Overdose Control
FC	Flow Chart
FFPE	Formalin-Fixed Paraffin-Embedded
FIH	First in Human
FUP	Follow-up
GCP	Good Clinical Practice
GEP	Gene Expression Profiling
GMP	Good Manufacturing Practice
HA	Health Authority
HCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HCO_3	Bicarbonate
i.v.	intravenous

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IB	Investigator's Brochure
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IFN	Interferon
IgG4	Immunoglobulin G4
IHC	Immunohistochemistry
IL-6	Interleukin-6
IL6R	Interleukin 6 Receptor
IL-8	Interleukin-8
INR	International Normalized Ratio
irAE	Immune-related Adverse Event
IRB	Institutional Review Board
iRECIST	Immunotherapy Response Evaluation Criteria in Solid Tumours
IRR	Infusion related reactions
IRT	Interactive Response Technology
ISF	Investigator Site File
itRECIST	Response Criteria for Intratumoural Immunotherapy in Solid Tumours
i.tu.	Intratumoural
LDH	Lactate Dehydrogenase
LOCS III	Lens Opacities Classification System III
LPLT	Last Patient Last Treatment
LPLV	Last Patient Last Visit
mAb	Monoclonal Antibodies
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
MUGA	Multigated Acquisition
NC	Not Calculated
NOA	Not Analysed
NOR	No Valid Result
NOS	No Sample Available

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NYHA	New York Heart Association
OD	Over Dose
OPU	Operative Unit
OR	Objective Response
ORR	Objective Response Rate
PD	Progressive Disease
PD-1	Programmed Cell Death-1
PD-L1	programmed Death-Ligand 1
PET	Positron emission tomography
p.o.	per os (oral)
PK	Pharmacokinetics
PT	Prothrombin time
PLT	Platelet
RA	Regulatory Authority
RBC	Red Blood Cell
RD-P2	Recommended Dose Part 2
RECIST	Response Evaluation Criteria in Solid Tumours
REP	Residual Effect Period
RNA	Ribonucleic Acid
RT	Radiotherapy
SAE	Serious Adverse Event
SC	Steering Committee
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
STING	Stimulator of Interferon Genes
SUSAR	Suspected Unexpected Serious Adverse Reactions
TD	Target Dose
TIL	Tumour-infiltrating Lymphocyte
t_{max}	Time from dosing to maximum measured concentration of the analyte in plasma
TMB	Tumour Mutational Burden
TMF	Trial Master File
TNM	Tumour, (lymph) Node, and Metastasis

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TSAP	Trial Statistical Analysis Plan
TSH	Thyroid Stimulating Hormone
UD	Under Dose
ULN	Upper Level of Normal
WBC	White Blood Cell
WHO	World Health Organisation
WOCBP	Woman of childbearing potential

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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 1,762,450 new cancer cases were expected to be diagnosed in 2019. The American Cancer Society estimated that there would be approximately 606,880 deaths due to cancer in the US during 2019 [R19-0312]. In particular if the disease is diagnosed in late, advanced stages, or after disease progression on available treatments, the prognosis of patients is poor and the vast majority succumb to their disease. Therefore, there is a substantial need for novel therapeutic agents and treatment strategies to improve the treatment outcome for cancer patients.

The STING pathway has been identified as a key innate immune sensing pathway to detect the presence of cytosolic cyclic dinucleotides derived from microbial invasion and self-DNA leakage. Mice deficient in the STING pathway show blunted type I IFN production, reduced anti-tumour T cell priming, and fail rejection of immunogenic tumours [R19-0315].

STING is an intracellular pattern recognition receptor expressed in various endothelial and epithelial cell types, as well as in hematopoietic cells such as T cells, macrophages and dendritic cells, including plasmacytoid dendritic cells. It stimulates the transcription of numerous genes involved in immune response, such as the type I interferons [R19-0314] and other proinflammatory cytokines, and through cross-priming by antigen presenting cells may lead to an adaptive antitumour immune response against tumour antigens, a concept which has previously been described as 'in-situ vaccination' [R19-0317].

The STING pathway plays a key role in spontaneous or treatment induced cancer immune response, and activation of this pathway is considered to induce or augment an anti-tumour immune response [R19-0506, R19-0674]. Intratumoural administration of STING agonists has resulted in remarkable therapeutic activity in animal models [R19-0316].
Activity of STING agonists was also observed in patients when used as single agent, and more pronounced when used in combination with a PD1-antibody [R19-0608, R19-0623].

1.2 DRUG PROFILE

1.2.1 BI 1387446

Mode of action
STING is a pattern recognition receptor that detects cytosolic nucleic acids and transmits signals that activate type I interferon (IFN) responses. It is localized in the endoplasmic reticulum. Double stranded DNA derived from either dying tumour cells or pathogens binds and activates the enzyme cyclic GMP-AMP Synthase (cGAS) which then generates cyclic di-nucleotides (CDNs) which bind to and activate STING. The naturally occurring CDN cGAMP and the synthetic CDN BI 1387446 induce a conformational change in STING homo-dimers that allows the binding and activation of the interaction partner tank binding

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kinase 1 (TBK1) which induces the downstream pathways IRF3 and NF-κB, ultimately leading to the expression and secretion of type 1 IFN and other inflammatory cytokines. Through IFN class I/II secretion, STING activation results in PD-L1 upregulation, and thus a therapeutic blockade of PD-1/PD-L1 signalling is considered to augment and sustain the adaptive antitumour immunity initially induced by STING signalling.

Key pharmacokinetic characteristics

[redacted]

Drug interactions with ezabenlimab (BI 754091)

[redacted]

Residual Effect Period

The Residual Effect Period (REP) of BI 1387446 is [redacted]

Data from non-clinical studies

In several syngeneic mouse tumour models (mouse cancer cell lines grafted in immunocompetent mice) poorly responding/refractory to anti-PD-1 treatment, the intratumoural injection of BI 1387446 given [redacted] resulted in a dose-dependent tumour eradication in injected lesions. Mice that experienced long term tumour regression (>40 days tumour free) did not to develop new tumours, when rechallenged with the same tumour cell line, indicating durable anti-tumour response and generation of immunological memory. A significant increase in tumour-specific CD8+ T cells was detected in responding mice.

In a bilateral tumour model setting (mouse cancer cell lines grafted in immunocompetent mice in the left and right flank), the intratumoural injection of BI 1387446 given [redacted] resulted in a dose-dependent tumour eradication in injected lesions and dose-dependent tumour growth control in the non-injected lesion indicating local and systemic efficacy.

The combination with a murine anti-PD-1 cross-reactive antibody in the bilateral tumour setting given [redacted] improved the tumour growth control of non-injected lesions.

In toxicology studies, BI 1387446 led to an increase in cytokines in blood from healthy human donors and both animal species tested in toxicology studies (mouse, Cynomolgus monkeys). Adverse effects induced by BI 1387446 were generally due to cytokine release and thus to the pharmacokinetic activity of the compound. In a telemetry study in Cynomolgus monkeys a negative inotropic effect of BI 1387446 was observed. The cytokine

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release profile for BI 1387446 in combination with tocilizumab was assessed in Cynomolgus monkeys. A marked increase in plasma levels of cytokines was observed when tocilizumab was administered 24 hours prior to BI 1387446 compared to BI 1387446 monotherapy, while no relevant effect was observed when animals were treated with tocilizumab 6h post BI 1387446. For details, refer to the Investigator's Brochure.

Data from clinical studies
This is the first trial in human and therefore no clinical data is available.

For a more detailed description of the BI 1387446 profile, refer to the current Investigator's Brochure (IB) [c26065921].

1.2.2 Ezabenlimab (BI 754091)

Mode of action
Ezabenlimab (BI 754091) is a humanised IgG4Pro isotype anti PD 1 mAb being developed as an i.v. infusion for the treatment of cancer. Ezabenlimab (BI 754091) has highly human frameworks and a low predicted immunogenicity score. The ezabenlimab (BI 754091) molecule has a molecular weight of approximately 148 kilodaltons.

Ezabenlimab (BI 754091) shows strong anti-tumour effects in several mouse tumour models. Single and repeat dosing studies showed that ezabenlimab (BI 754091) was well tolerated (as judged by body weight changes and clinical signs) and resulted in significant tumour growth inhibition (≥83%).

REP of ezabenlimab (BI 754091) is 30 days.

Data from clinical studies
Ezabenlimab (BI 754091) is currently being tested in patients in several BI-sponsored clinical trials, e.g. 1381-0001, 1381-0002. The dose of 240 mg ezabenlimab (BI 754091) once every 3 weeks was taken forward into the expansion portion of the Trial 1381-0001 trial and is considered the recommended phase II dose for ezabenlimab (BI 754091).

A total of 139 patients have been dosed with ezabenlimab (BI 754091) in clinical trials, 56 patients with monotherapy ezabenlimab (BI 754091), and 83 patients with ezabenlimab (BI 754091) plus BI 754111. At the data cut-off, there were no DLTs or Grade 5 AEs experienced by any patient on monotherapy treatment. The overall most common AEs for patients treated with monotherapy ezabenlimab (BI 754091) were fatigue, nausea, and decreased appetite. Thirteen of the 56 patients on monotherapy ezabenlimab (BI 754091) experienced immune related adverse events (irAEs) of rash, maculo-papular rash, colitis, diarrhoea, hypothyroidism, increased ALT, increased AST, arthralgia, pneumonitis, and pruritus. There were one ≥ Grade 3 irAE (Grade 3 increased AST) experienced by patients in the monotherapy population.

For a more detailed description of the ezabenlimab (BI 754091) profile, refer to the current IB [c07895879].

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1.2.3 Combination of BI 1387446 and ezabenlimab (BI 754091)

BI 1387446 and ezabenlimab (BI 754091) were tested as single agent and in combination in blood from healthy human donors to assess cytokine release and immune cell activation. Ezabenlimab (BI 754091) does not result in cytokine release. [redacted] second study was performed in Cynomolgus monkeys comparing cytokine levels following a single dose of BI 1387446 to cytokine levels following the combination of ezabenlimab (BI 754091) followed by BI 1387446 in the same animals. [redacted]
Both studies suggest that BI 1387446 treatment alone has potential for cytokine release and immune cell activation, but available data do not indicate that ezabenlimab (BI 754091) might potentiate these effects.
Combination of ezabenlimab (BI 754091) and BI 1387446 may lead to an increased rate and severity of irAEs compared to either drug alone, as is documented for combination of checkpoint inhibitors.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Treatment with cytotoxic drugs is an option for the majority of cancer types, but rarely leads to long term remissions in third or later line treatment settings. Immunotherapy with checkpoint inhibitors for the first time in oncology has raised the hope for long term disease control and possibly cure [R19-0313]. However, a significant portion of patients either have tumours which primarily are non-responsive to a checkpoint inhibitor or develop resistance on treatment. [R19-0318].

The STING pathway plays a key role in spontaneous or treatment induced cancer immune response, and activation of this pathway is considered to induce or augment an anti-tumour immune response.

The antitumour activity and safety profile observed in pre-clinical studies summarised in the previous section warrant clinical testing of BI 1387446.

This trial is the first in human study of intratumoural BI 1387446 as monotherapy and in combination with intravenous ezabenlimab (BI 754091) in patients with advanced malignant solid tumours. This trial will determine the maximum tolerated dose (MTD), as well as the safety, PK, pharmacodynamics, exploratory biomarkers, and early signs of efficacy of BI 1387446 intratumourally as monotherapy and in combination with intravenous administration of ezabenlimab (BI 754091) in patients with different advanced malignancies.

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In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking (refer to Section 5.5). If the patient agrees, banked samples may be used for future biomarker research and drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an adverse event (AE), or to gain a mechanistic or genetic understanding of drug effects and thereby better match patients with therapies. Banking will be limited to samples left over after primary analysis.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

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

BI 1387446 in preclinical studies has led to shrinkage and complete disappearance of injected tumours in mice, durable antitumour memory, and growth inhibitory effects on non-injected tumours. Intratumoural activation of the STING pathway is considered to induce a *de novo* anti-tumour immune response, leading to improved priming and activation of tumour-specific cytotoxic $CD8^+$ T cells and increased $CD8^+$ T cell infiltration into the tumour. Thus, STING agonists may be effective to treat tumours which are primarily non-responsive to checkpoint inhibitors as well as tumours with acquired resistance to checkpoint inhibitors.
Combination with an anti-PD1 antibody is considered indicated in relation to the mode of action, i.e. to counteract IFN-mediated PD-L1 expression and maintain CD8+T-cell activation.

1.4.2 Risks

BI 1387446 is a CDN targeting the STING receptor, which has not been tested in humans before. The risks of treatment have been evaluated based on the expected effects of [redacted] intratumoural STING pathway activation, the nonclinical *in vivo* and toxicology data, and available clinical data on other compounds targeting the STING pathway.

Based on the mode of action and available non-clinical data for BI 1387446, and considering the route of administration, the main potential risks associated with this drug are presumed to be:

- cytokine release syndrome
- procedural risks from intratumoural application
- immune-related adverse events
- decrease in cardiac contractility

Based on non-clinical data, a potential risk is supposed to be:

- eye lens toxicity

Published clinical data indicate that STING agonists are well tolerated when injected intratumourally into superficial lesions. MK-1454 demonstrated a manageable toxicity profile in patients with advanced malignant tumours as monotherapy and combination with

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pembrolizumab. The most common treatment-related AEs in ≥10% of patients included pyrexia, chills, fatigue, and injection site pain, which in most patients were grade 1 and 2 severity [R19-0609, R19-0623]. For ADU-S100 monotherapy, the most common AEs in ≥10% of patients were injection site pain, headache and pyrexia [R19-0608].

General safety measures for this FIH trial include:
- sequential enrolment of patients into a single cohort (Section 3.1.1)
- sequential start of cohorts at the same dose of BI 1387446 (Section 3.1.1)
- sequential start of backfill enrollment (Section 3.1.1)
- mandatory surveillance of patients (Sections 4.1.4.5 and 4.1.4.6)

The trial will be monitored by a Safety Monitoring Committee (SMC). The SMC will be chaired by an Investigator with experience in early clinical trials, and will be composed of Investigators/delegates from participating investigational sites and the sponsor. For details refer to the SMC charter and Section 8.7.

Cytokine release syndrome
Following intratumoural injection of BI 1387446 in animal models, a type I interferon response was elicited in the injected tumour and a transient increase in cytokines was detectable in plasma, with peak values around [redacted] post injection. The half life in plasma [redacted] In ongoing clinical trials with other STING agonists, fever was detected as a cytokine mediated symptom and may be classified as cytokine release syndrome (CRS) grade 1, but no CRS of higher grade with hypotension or hypoxia was reported. Risk mitigation measures include recommendations for prevention, early detection and treatment of CRS, e.g.
- guidance to avoid injection into lesions with high risk for accidental intravascular administration, e.g. lesions encasing or infiltrating major blood vessels, or subcapsular liver lesions (Section 4.1.4.2)
- mandatory patient surveillance (Section 4.1.4.5)
- recommendations for management of CRS (Section 4.1.4.6)
- assessment of adverse events, PK and blood cytokine data in regular intervals by the SMC

Immune-related adverse events
Immune-related AEs as defined in Appendix 10.1 will be captured as AESI and reviewed by the SMC in regular intervals throughout the trial. Recommendations for management are included in Appendix 10.1.2.

Procedural risks associated with intratumoural application and tumour biopsy
Injection of a drug using a needle is always associated with procedural risks. These include and are not limited to:
- infection
- bleeding
- injury to tissues in the needle track, e.g. nerves, vessels, organs
- reactions to local anesthesia if used, e.g. allergy, arrhythmia
- other events (e.g. possible ulcerations (scarring after biopsy) or compression due to swelling)

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Risk mitigation measures to address procedural risks are:

- selection of investigational sites with interventional radiology expertise and/or Investigators experienced in diagnostic biopsies and injection of drugs into tumour lesions
- risk adapted patient surveillance after intratumoural injection for early recognition of complications (Section 4.1.4.5)
- exclusion of patients in whom the designated lesion for injection has a high risk for local complications, e.g. bleeding related to encasement/infiltration of major blood vessels or contact with liver capsule, compression of vital structures in case of swelling of injected lesion (Section 4.1.4.2)

Decrease in cardiac contractility

In a telemetry study in Cynomolgus monkeys, a decline in contractility measured as LV dp/dtmax was observed at doses from [redacted] The decline in contractility was not associated with a decline in blood pressure or an increase in heart rate.

Risk mitigation measures include

- exclusion of patients with cardiac insufficiency NYHA grade III or IV or a left ventricular ejection fraction of < 50 % from the trial (Section 3.3.3).
- detailed instructions for monitoring of vital signs (heart rate, blood pressure, Sections 4.1.4.5 and 4.1.4.6).
- assessment of cardiac biomarkers (e.g. troponin, natriuretic peptide, Section 5.2.3)
- assessment of cardiac function by left ventricular ejection fraction (Section 5.2.4)

Eye lens toxicity

In a repeated dose toxicity study in C57Bl/6 mice, increased incidences of diffuse subcapsular opacities in the anterior lens region were observed in males at [redacted] cycle and in females at [redacted] cycle at the end of treatment. Due to the absence of any histopathological findings in the lenses of all treated animals, the fact that spontaneous ocular pathologies are well known for C57Bl/6 mice (R19-0517), and taking into account that cytokines may be secondarily elevated in various inflammatory ocular diseases, but have not been reported to induce direct lenticular changes, these lens opacities are not considered to be unequivocally test item-related.

Risk mitigation measures include

- Exclusion of patients with absolute contraindications for cataract surgery
- Assessment of lens opacity using slit-lamp by an ophthalmologist at screening, at the 30-day safety follow-up, and at any time during the treatment period, if clinically indicated (refer to Section 5.2.6).

BI 1387446 in combination with ezabenlimab (BI 754091)

Combination of ezabenlimab (BI 754091) and BI 1387446 may lead to an increased rate and severity of irAEs compared to either drug alone, as is documented for combination of checkpoint inhibitors.

Preclinical data suggest that ezabenlimab (BI 754091) does not potentiate BI 1387446 mediated cytokine release. CRS to BI 1387446 and IRRs to ezabenlimab (BI 754091) may be

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differentiated by the time of occurrence in relation to each drug administration, as IRRs to [redacted] overlap cannot be excluded. Details for surveillance and medical management of CRS are included in Section 4.1.4.6 and Appendix 10.2.

Tumour biopsy
To assess mode of action and pharmacodynamics biomarkers for dose selection, tumour biopsies are required in this trial. Tumour biopsies are associated with similar procedural risks as outlined before for intratumoural injection. To mitigate biopsy associated risks, selection of the distinct non injected lesion amenable for biopsy will be guided by the same principles as selection of lesions for injection. High risk locations should be avoided. Only in case non-significant risk sites are unavailable, lung biopsies will be permitted acknowledging the fact that many tumour types tend to metastasize to the lung (for further details refer to Section 5.4.2.3).

A risk-benefit assessment in the context of the COVID-19 pandemic for patients treated with BI 1387446 alone or in combination with ezabenlimab (BI 754091) has been performed. Based on the mode of action of activation of the STING pathway and PD-1 receptor blockade, BI 1387446 alone or in combination with ezabenlimab (BI 754091) is not expected to have a relevant impact on the susceptibility to or the course of a COVID-19 infection.

Published data provides preliminary evidence that CRS may play a role in severe cases of COVID-19 disease (R20-2735). Since, administration of BI 1387446 may also be associated with CRS, it cannot be fully excluded that patients with a COVID-19 infection may be at increased risk to develop a more severe course of illness during treatment with BI 1387446. Investigators should carefully consider on a case by case basis the prospect of delaying treatment for patients presenting with flu-like symptoms at the time of intended BI 1387446 treatment.

In case of a confirmed SARS-CoV-2 infection or COVID-19 disease, respectively, trial treatment will be discontinued immediately and appropriate measures for monitoring, treatment and quarantine will be implemented. The patient may resume trial treatment following recovery from a SARS-CoV-2 infection if the patient is expected to derive clinical benefit, as agreed between the investigator and sponsor.

Due to the underlying disease, exposure to intensive anti-cancer treatments and/or immunosuppressive therapies, patients in this trial may be immuno-compromised and at higher risk for infection and/or severe illness from COVID-19. In case of an increased risk of SARS-CoV-2 infection due to the physical visits to the sites, the visits should be avoided where the investigator judges that this is the safest course of action. These measures ensure the safety of the patients throughout the trial, maintain the integrity of the trial and will not affect the benefit-risk of BI 1387446.

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1.4.3 Discussion

A number of safety measures to mitigate possible risks are implemented in this trial. Patients with advanced and/or metastatic malignancies may possibly benefit from treatment with BI 1387446, and possibly even more from the combination of BI 1387446 and ezabenlimab (BI 754091). Possible benefit of trial treatments is expected to outweigh the risks in patients with advanced solid tumours who have exhausted treatment options.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

Characterize the safety and determine the maximum tolerated dose (MTD) for BI 1387446 as single agent and for BI 1387446 in combination with ezabenlimab (BI 754091). Obtain a preliminary efficacy signal.

2.1.2 Primary endpoint(s)

- MTD based on number of Dose-limiting toxicities (DLTs) (for definition of MTD refer to Section 7)
- Number of patients with DLT in the MTD evaluation period

Time frame: Arms A, B From start of treatment until end of cycle 1 (3 weeks, MTD evaluation period)

2.1.3 Secondary endpoint(s)

- Objective response based on Response Criteria for Intratumoural Immunotherapy in Solid Tumours (itRECIST)
- Best percentage change from baseline in size of injected target lesions
- Best percentage change from baseline in size of non-injected target lesions

Time frame for all secondary endpoints: From start of treatment until the earliest of progression, death or end of trial (approximately 1 year).

[redacted]

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[redacted]

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This study will consist of 3 arms, which will recruit patients in parallel with a clear predefined hierarchy for slot allocation (Section 3.1.2).

- Arm A: Dose escalation of BI 1387446 as single agent administered intratumourally into superficial lesions
- Arm B: Dose escalation of BI 1387446 administered intratumourally into superficial lesions, in combination with ezabenlimab (BI 754091) intravenously

Trial overview is shown in below Figure 3.1: 1.

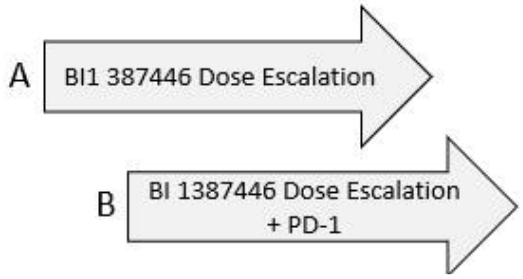

Figure 3.1: 1 Trial overview

This study will determine the MTD as well as the safety, PK, and pharmacodynamics of BI 1387446 as monotherapy and in combination with ezabenlimab (BI 754091).

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Arm A will determine the MTD for BI 1387446 intratumourally into superficial lesions as single agent. Patients with progressive disease may cross over to Arm B after completion of cycle 1, provided that Arm B is open for recruitment.

Arm B will determine the MTD for BI 1387446 intratumourally into superficial lesions in combination with ezabenlimab (BI 754091).

Arms A and B will investigate the safety, PK, and pharmacodynamics of BI 1387446 monotherapy (Arm A) or BI 1387446 in combination with ezabenlimab (BI 754091) (Arm B).

Arms A and B will start in a staggered manner (refer to Section 3.1.1).

To acquire additional data to more fully inform dose selection, additional patients may be enrolled to backfill cohorts at dose levels that have been previously cleared (refer to Section 3.1.1).

Dose escalation will be guided by Bayesian logistic regression modelling with overdose control: In Arm A and B, dose escalation will be guided by a BLRM using a hierarchical modelling approach to jointly model both arms. The data obtained from both arms will determine the MTD estimate per arm 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 including echocardiographic/MUGA scan measurements acquired on Day 1 of Cycle 2 and related findings) 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).

The trial will be monitored by a SMC which will convene for each dose escalation decision. The SMC will assess for each dose cohort if dose escalation to the next dose level is possible based on DLTs in the MTD evaluation period, AEs, and safety laboratory data. DLTs and AEs reported in later cycles of patients enrolled in previous dose cohorts will be considered in addition. After the patients in a dose cohort have either experienced a DLT or have been observed for at least the MTD evaluation period without experiencing a DLT, the BLRM will be updated with the newly accumulated data. In particular, during dose escalation, the BLRM will be evaluated after the occurrence of each DLT before enrolling any further patients.

The SMC may recommend stopping the dose escalation after the criterion for MTD (refer to Section 7) is fulfilled. The RP2D will not exceed the MTD and will not exceed the highest dose investigated during dose escalation.

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3.1.1 Sequence of treatment arms and cohorts

A dose level of BI 1387446 will always be explored as single agent first. Only once determined to be safe as single agent, this dose of BI 1387446 will be used in combination with ezabenlimab (BI 754091), always lagging at least one dose level behind when administered in combination with BI 754091.

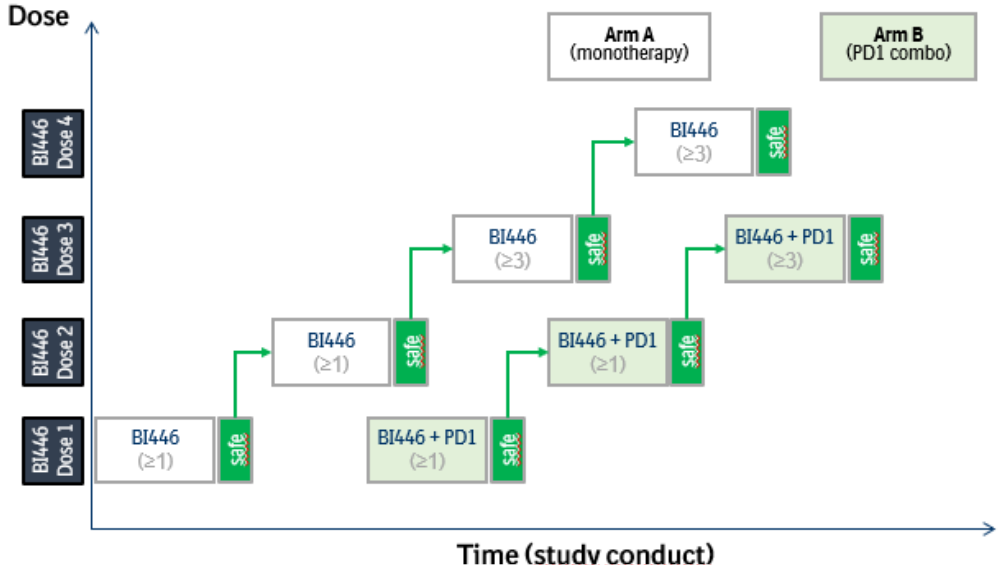

Figure 3.1.1: 1 Sequence of cohorts. BI446: BI 1387446, PD1: ezabenlimab (BI 754091).

Patients with progressive disease on BI 1387446 monotherapy (Arm A) may cross over to the combination (Arm B) after completion of cycle 1 and will be treated at the highest dose level declared to be safe by the SMC at this time. These patients will continue treatment in combination by re-starting treatment at Cycle 1 Day 1 in Arm B. These patients will be analysed in Arm A as long as treated with monotherapy. Instead of completing the REP after monotherapy, patients may cross over to Arm B without repetition of all screening procedures, but will have to undergo a limited set of assessments as specified in Section 6.2.1. A minimum interval of 7 days must have elapsed between last dose of BI 1387446 in Arm A and first dose of ezabenlimab (BI 754091) or BI 1387446 in Arm B. Cross-over patients will be included together with other 'backfill patients' (patients enrolled to backfill cohorts at dose levels that do not exceed the MTD, see Section 3.1.2 for details) in the safety and efficacy assessment in Arm B, but will not be considered for the main analysis of the MTD. For the main analysis of the MTD, cross-over patients will only be included while being treated with BI 1387446 monotherapy in Arm A. However, cross-over patients will be included in the sensitivity analyses of the MTD and thus be considered in addition (refer to Section 7 for details).

Arm B will open at the starting dose level once the starting dose level in Arm A is considered safe by the SMC.

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3.1.2 Method of assigning patients to individual treatment cohorts

Treatment Arms A and B will be started sequentially. Arm A will start first. Once the first dose level in Arm A has been determined to be safe, Arm B may be initiated.

Minimum number of patients for each dose level within a treatment arm
Dose escalation decisions will be based on occurrence of DLTs. [redacted] Following the occurrence of a drug related Grade 2 or greater AE, excluding asymptomatic Grade 2 laboratory abnormalities that resolve without medical intervention within 48 hours and transient Grade 2 local injection site reactions that resolve within 48 hours (whereby supportive treatment is allowed), a minimum of 3 patients will be required per dose cohort. The SMC will decide on further trial conduct based on data from the minimum number of patients or can recommend to enroll additional patients at a given dose level.

Maximum number of patients for each dose level within a treatment arm
Once a dose cohort in a treatment arm has been determined to be safe and patient allocation to the next higher dose level is completed, additional patients may be enrolled into the same treatment arm at lower dose levels previously determined to be safe. This so called 'backfill' is intended to enlarge the safety and activity dataset, and to serve as a basis for selection of the RD-P2 in case of a non-linear dose-response relationship. A dose level in a treatment arm will not recruit more than 8 patients which have completed at least one treatment cycle, unless the SMC decides that more patients are needed to perform an adequate safety assessment or to account for patients who have crossed over from Arm A to Arm B. That is, each dose level in a treatment arm will enroll in the lower doses at least 1 patient, unless a Grade 2 or greater AE occurred (with the above exceptions), then at least 3 patients will be enrolled, and an intended maximum of 8 patients, and in the higher doses at least 3 patients and an intended maximum of 8 patients.

Data from 'backfill' patients will be reviewed during the SMC meetings as well. That is, ‘backfill' patients who have either experienced a DLT or have been observed for at least the MTD evaluation period without experiencing a DLT will be included into the main BLRM analysis at the next subsequent SMC meeting. Particularly, in case DLTs are observed in 'backfill' patients, this information may affect the magnitude of dose escalation or even result in dose de-escalation. Refer to Section 7.2.2 for details.

Patient assignment rules
1. Treatment slots for dose escalation have priority over 'backfill' slots
Slots which are required for dose escalation decisions of the highest recruiting dose level will be allocated prior to 'backfill' slots.

2. Arm A has priority over Arm B
In case slots of the same priority (i.e. dose escalation or 'backfill') are open in arms A and B, and criteria 2 is met, patients will be recruited into Arm A prior to Arm B, unless Arm A is more than 2 dose levels ahead of Arm B.

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Treatment start of individual patients within the same cohort
For all patients enrolled into a cohort required for DLT assessment, a minimum time period has to be elapsed between first treatment days of subsequent patients. In the first dose level in each arm, the second patient can receive the first dose of trial drug the earliest 7 days after the first patient has been dosed. For the second and all subsequent dose levels in a single treatment arm, a minimum of 3 days is required between the first dose to the first and second patient. For all subsequent patients prior to dose escalation in this arm, a 2 day interval is required. Only once a dose level has been determined safe by the SMC, subsequent patients ('backfill') may be dosed at the same day on this dose level in the respective treatment arm.

In case of the occurrence of DLTs, the SMC may decide about intervals between enrollment of patients, if applicable.

Table 3.1.2: 1 Minimum intervals between first dose of trial drug given to subsequent patients within the same cohort.

Dose	Patient 2	subsequent pts (prior to SMC/cohort safe)	subsequent pts ('backfill', post SMC/cohort safe)
Level 1	+7 days	+2 days	any time
Level ≥2	+3 days	+2 days	any time

3.1.3 Definition of superficial lesions

During screening, a projected lesion for injection needs to be selected.

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Table 3.1.3: 1 Definition of superficial lesions

Definition	injected lesion outside of a body cavity
Location	skin subcutaneous intramuscular chest wall (without infiltration of visceral pleura) abdominal wall (without infiltration of intraabdominal structures)
Location	superficial lymph nodes (cervical, supra-/infraclavicular, axillary/pectoral, epitrochlear/ brachial, inguinal, femoral, popliteal) superficial organs (salivary glands, thyroid, parathyroid, breast)
Dose escalation arm	A, B

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

Ezabenlimab (BI 754091) is expected to be required for efficacy due to the upregulation of PD-L1 following STING activation. This expectation is supported by internal and published preclinical data as well as clinical data on MK-1454 as monotherapy and in combination with pembrolizumab. Preclinical data for ADU-S100 indicate that the dose response relationship may be non-linear, possibly resulting in a decline in efficacy on non-injected lesions at higher doses. Thus, early combination with ezabenlimab (BI 754091) during dose finding is considered important for selection of a recommended dose for further development of BI 1387446.

In addition, a flexible enlargement of cohorts which have been confirmed to be safe by the SMC, the so called ‘backfill’ concept will be used to generate sufficient data at lower dose levels which appear relevant for dose selection and may only be identified during trial conduct.

BI 1387446 by its mode of action will increase cytokines, and thus has a potential risk to lead to cytokine release syndrome. Although there has been no increase of cytokines in preclinical

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models for combination of BI 1387446 and ezabenlimab (BI 754091) compared to BI 1387446 alone, the trial design will ensure that a dose of BI 1387446 can only be tested in combination with ezabenlimab (BI 754091) if the same or a higher dose has been confirmed safe as monotherapy.

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

3.3 SELECTION OF TRIAL POPULATION

A total of approximately 78 patients may be treated in this trial, which will be conducted at about 6 sites in Europe, the United Kingdom, and the United States. Each site is expected to enrol on average approximately 10-20 patients.

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

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

3.3.1 Main diagnosis for trial entry

Patients with malignant solid tumours will be eligible for this trial.

Refer to Section 8.3.1 for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

1. At least 18 years of age at the time of consent or over the legal age of consent in countries where that is greater than 18 years.
2. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.
   If a patient declines to participate in the voluntary pharmacogenetics component of the trial, he/she will not be excluded from other aspects of the trial.
3. Male or female patients. Women of childbearing potential (WOCBP) [defined as a woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation

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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] and men able to father a child must be ready and able to use highly effective methods of birth control per ICH M3 (R2), that result in a low failure rate of less than 1% per year when used consistently and correctly, 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 Section 4.2.2.3.

4. Eastern Cooperative Oncology Group score of 0 or 1 [R01-0787].
5. Life expectancy of at least 12 weeks after the start of the treatment according to the Investigator's judgement.
6. Histologically or cytologically confirmed diagnosis of an advanced, unresectable and/or metastatic malignant solid tumour and indication for treatment
7. Patient must have exhausted established treatment options known to prolong survival for the malignant disease, or is not eligible for established treatment options.
8. Medically fit and willing to undergo all mandatory trial procedures.
9. At least one tumour lesion which is suitable for injection (Section 4.1.4.1, Screening/initial administration), appropriate for the allocated treatment arm (Section 3.1.3), and measurable as defined in Section 10.3.
10. At least 1 discrete lesion, in addition to the lesion proposed for injection, which is amenable to biopsy and is not located in the brain, mediastinum or pancreas.
11. Adequate organ function or bone marrow reserve as demonstrated at screening by the following laboratory values:
    a. absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (≥ 1.5 x 10^3/µL, ≥ 1,500/mm^3)
    b. platelet count ≥ 100 x 10^9/L (≥ 100 x 10^3/µL, ≥ 100 x 10^3/mm^3)
    c. haemoglobin ≥ 90 g/L (≥ 9.0 g/dL, ≥ 5.6 mmol/L)
    d. total bilirubin ≤ 1.5 times the upper limit of normal (ULN), except for patients with Gilbert's syndrome: total bilirubin ≤ 3 x ULN or direct bilirubin ≤ 1.5 x ULN.
    e. alanine aminotransferase (ALT)/Aspartate aminotransferase (AST):
        - patients without liver metastases: ALT/AST ≤2.5 x ULN
        - patients with liver metastases with planned injection into liver lesion: ALT/AST ≤2.5 x ULN
        - patients with liver metastases without planned injection into liver lesions: ALT/AST ≤ 5 x ULN
    f. Creatinine ≤ 1.5 x ULN. If creatinine is > 1.5 x ULN, patient is eligible if concurrent creatinine clearance ≥ 45 ml/min (≥ 0.045 L/min) (measured or calculated by CKD-EPI formula). [1]
    g. prothrombin time (PT) ≤ 1.5 x ULN
    h. activated partial thromboplastin time (aPTT) ≤1.5 x ULN

3.3.3 Exclusion criteria

1. Any investigational or antitumour treatment (including antibodies targeting PD1- or PD-L1) within 4 weeks or 5 half-life periods (whichever is shorter) prior to the initial administration of BI 1387446 or ezabenlimab (BI 754091).

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2. Persistent toxicity from previous treatments (including irAEs) that has not resolved to ≤ Grade 1, except for alopecia, xerostomia, and immunotherapy related endocrinopathies which may be included if clinically stable on hormone supplements or antidiabetic drugs as per Investigator judgement
3. History or evidence of active, non-treatment related autoimmune disease, except for endocrinopathies which may be included if clinically stable on hormone supplements or antidiabetic drugs.
4. History or evidence of pneumonitis related to prior immunotherapy
5. Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 2 weeks prior to the first dose of BI 1387446 or ezabenlimab (BI 754091).
6. The tumour at the projected injection site has a high risk for local complications, e.g. bleeding related to encasement/infiltration of major blood vessels or contact with liver capsule, compression of vital structures in case of swelling of injected lesion, in the opinion of the Investigator (see Section 4.1.4.2).
7. Presence or history of uncontrolled or symptomatic brain or subdural metastases, unless local therapy was completed and metastases considered stable by the Investigator
8. Presence of other active invasive cancers other than the one treated in this trial within 5 years prior to screening, with the exception of appropriately treated basal-cell carcinoma of the skin, in situ carcinoma of the uterine cervix, or other local tumours considered cured by local treatment.
9. Known history of human immunodeficiency virus (HIV) infection.
10. Active infection requiring systemic therapy at the start of treatment in the trial, including active viral hepatitis infection or active tuberculosis infection.
11. Has received a live vaccine within 30 days prior to first dose of BI 1387446.
12. Cardiac insufficiency NYHA III or IV
13. Left ventricular ejection fraction < 50% measured by echocardiography or MUGA scan
14. Significant resting ECG abnormalities defined as ventricular tachyarrhythmias, presence of unstable atrial fibrillation (defined as ventricular response >100 bpm), significant bradycardia (defined as a heart rate of <50 bpm), complete left bundle branch block, right bundle branch block and left anterior hemiblock, third degree AV block, or a mean resting corrected QT interval (QTc) >470 msec
15. History of severe hypersensitivity reactions to mAbs
16. 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 in the opinion of the Investigators.
17. a. Arm C: Patients on therapeutic doses of anticoagulants (see section 4.2.2.1). This criterion was effective through Clinical Trial Protocol Version 3.0 (26-May-2021) only.
    b. For Arm C, radiation therapy of the lesion proposed for injection within 6 months of initial administration of BI 1387446. This criterion is effective starting with Protocol Amendment, Clinical Trial Protocol Version 4.0.
    c. Starting with this Protocol Amendment, Clinical Trial Protocol Version 5.0, Arm C has been removed and this criterion is no longer applicable.
18. Chronic alcohol or drug abuse
19. Major surgery (major according to the Investigator's assessment) performed within 4 weeks prior to first trial treatment.

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20. Any pre-existing or concurrent disease or condition that, in the Investigator's opinion, would compromise patient safety, poses an undue risk to the patient, makes him/her an unreliable trial subject, unlikely to complete the trial, or unable to comply with the protocol procedures.
21. Women who are pregnant, nursing, or who plan to become pregnant or nurse during the trial or within 6 months after the last dose of study treatment.
22. Presence of any absolute contraindications to cataract surgery
23. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events including congenital long QT syndrome, family history of sudden unexpected death from cardiac related causes, myocardial infarction or major cardiac surgery within 3 months prior to enrollment, history or presence of uncontrolled hypertension (>150 mmHg systolic or >100 mmHg diastolic bp)

3.3.4 Withdrawal of patients from treatment or assessments

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

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

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

The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and CRF. If applicable, consider the requirements for Adverse Event collection reporting (refer to Sections 5.2.7.2.1 and 5.2.7.2.2).

3.3.4.1 Discontinuation of trial treatment

An individual patient will discontinue trial treatment if:

- The patient wants to discontinue trial treatment, without the need to justify the decision.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the Investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
- The patient needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment (Refer to Section 4.2.2.1).
- The patient can no longer receive trial treatment for medical reasons (such as surgery, adverse events, other diseases, or pregnancy). Recurring radiologic disease progression (Refer to Section 4.1.2.3).

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- Adverse events requiring a permanent discontinuation of trial drugs, e.g.Cytokine release syndrome Grade ≥3Infusion-related reaction to ezabenlimab (BI 754091) Grade ≥3Drug-related AE not recovering to G1/baseline within 12 weeks
    - More than 2 dose reductions of BI 1387446 would be required for management of AEs
    - Immune-related AEs requiring permanent treatment discontinuation as per Section 10.1.2.
- If the patient experiences an infection with SARS-CoV-2 (as confirmed in accordance with local practice/accepted guidelines, see Section 5.2.3), the patient may resume trial treatment following recovery from SARS-CoV-2 infection if the patient is expected to derive clinical benefit, as agreed between the investigator and sponsor.

Patients in a dose cohort needed to make a dose escalation decision will be replaced in case they discontinued early during Cycle 1 for non-safety related reasons (e.g. unable to attend the protocol defined visits for to personal reason, refer to Section 3.3.4.4 below), or trial disruption e.g., measures to control the spreading of COVID-19. These patients will be replaced until the minimum number of patients required for evaluation is reached.

In case of a temporary reason for trial disruption, trial treatment should be restarted if medically justified, refer to see Section 4.1.4.3.

Even if the trial treatment is discontinued, the patient without disease progression remains in the trial and, given his/her agreement, will undergo the procedures for early treatment discontinuation and follow-up as outlined in the Flow Chart and Section 6.2.3.

If a patient should become pregnant during the trial, the treatment with BI 1387446 and ezabenlimab (BI 754091) (where applicable) must immediately be stopped. The patient will be followed up until delivery or termination of pregnancy (see Section 5.2.7.2.3 for information on pregnancy forms). The data of the patient will be collected and reported in the eCRF until the last patient's last visit and any events occurring thereafter will be reported in the BI drug safety database.

3.3.4.2 Withdrawal of consent to trial participation

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

1. Failure to meet expected enrolment goals overall or at a particular trial site.

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2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial.
3. Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

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

3.3.4.4 Replacement of patients

In Arms A and B, patients withdrawn during the MTD evaluation period for a reason other than having a DLT, or who miss any dose of study medication during the MTD evaluation period, or who miss the echocardiography/MUGA scan measurements acquired on Day 1 of Cycle 2), are not evaluable for the MTD determination. These patients will be replaced if not decided otherwise by the SMC (e.g. because the number of evaluable patients for the current dose cohort is considered high enough for a dose escalation decision). Patients who experience a DLT will not be replaced.

3.3.5 Discontinuation of trial enrolment by the sponsor

Boehringer Ingelheim reserves the right to discontinue enrolment of new patients in the trial at any time if the development of the compound is terminated. All patients that have signed the ICF by the time of development termination will continue with the treatment plan as originally specified in the clinical trial protocol.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

The characteristic of test products are given in below.

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Table 4.1.1:1 BI 1387446

Substance:	BI 1387446
Pharmaceutical formulation:	[redacted]
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	[redacted]
Posology:	Administration of the assigned doses on specific treatment days within treatment cycles of [redacted] duration (see Section 4.1.2.3 for details)
Mode of administration:	intratumoural injection (i.tu.)

Guidance for pharmacists and site staff [redacted] is included in ISF. Refer to instructions for the preparation and handling of BI 1387446 and ezabenlimab (BI 754091) in the ISF.

Table 4.1.1:2 Ezabenlimab (BI 754091)

Substance:	Ezabenlimab (BI 754091)
Pharmaceutical formulation:	[redacted]
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	[redacted]
Posology:	Administration of the assigned doses on specific treatment days within treatment cycles of [redacted] duration (see Section 4.1.2.3 for details)
Mode of administration:	intravenous infusion (i.v.)

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Table 4.1.1:3 Ezabenlimab (BI 754091)

Substance:	Ezabenlimab (BI 754091)
Pharmaceutical formulation:	[redacted]
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	[redacted]
Posology:	Administration of the assigned doses on specific treatment days within treatment cycles of [redacted] duration (see Section 4.1.2.3 for details)
Mode of administration:	intravenous infusion (i.v.)

4.1.2 Selection of doses in the trial and dose modifications

4.1.2.1 BI 1387446

BI 1387446 will be administered intratumourally under visual inspection for visible skin tumours, or under imaging guidance, e.g. ultrasound, CT.

Starting dose

Based on toxicology studies, a starting dose of [redacted] day has been chosen for Arms A and B. For details, refer to the IB [c26065921].

Maximum dose

The maximum dose for BI 1387446 being tested in this trial will be [redacted]

4.1.2.1.1 Dose escalation scheme

The starting dose for BI 1387446 in Arms A and B is [redacted] Dose escalation steps will be guided by a BLRM. Dose increments between subsequent dose levels in a dose escalation arm will not exceed 100%.

The provisionally planned dose levels to be assigned to separate cohorts of patients are listed in Table 4.1.2.1.1: 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 SMC.

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Table 4.1.2.1.1: 1 Provisional dose levels for dose escalation of BI 1387446 in Arms A, B

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

* from previous dose

4.1.2.1.2 Determination of injection volume for BI 1387446

All cycle 1 doses will be injected in a [redacted] regardless of tumour size. In subsequent cycles the injection volume will be adapted according to tumour size. Table 4.1.2.1.2: 1 should be used as guidance. In case the volume recommended is considered too large, e.g. for flat or patchy lesions by the Investigator, a smaller volume than recommended per longest diameter may be selected, but [redacted] The injection volume of a single dose may be [redacted] The concentration of the [redacted] will be [redacted]

Table 4.1.2.1.2: 1 Determination of injection volume in relation to size of injected tumour

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Suitable syringes and needles for injection are specified in instructions included in the ISF. Injected lesion, dose, injection volume, needle type, needle diameter and needle length have to be captured for each injection in the eCRF.

4.1.2.2 Ezabenlimab (BI 754091)

BI 754091 will be administered at the recommended phase II dose of 240 mg i.v. [redacted] to all patients enrolled in combination treatment cohorts [c07895879].

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4.1.2.3 Treatment schedule

Patients will receive either BI 1387446 as single agent (Arm A) or BI 1387446 in combination with BI 754091 (Arms B and C) as described in Table 4.1.2.3: 1 for Arm A, Table 4.1.2.3: 2 for Arm B.

All treatments will be administered in cycles of [redacted] duration.

Patients will continue treatment with the study drugs until progressive disease (PD) by RECIST, withdrawal of patient consent, an unacceptable toxicity occurs, or the maximum number of cycles of treatment are reached, whichever occurs first.

PD assessment will be based on itRECIST and refers to the overall response assessment including all injected and non-injected lesions. Overall PD assessment after initial progression is comparable to iUPD with iRECIST (the possibility of iTPD will not be considered in this study).

Treatment beyond initial radiological progression can only be administered if there is

- objective evidence of clinical benefit,
- absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease,
- absence of decline in ECOG performance status that can be attributed to disease progression,
- absence of tumour progression at critical anatomical sites (e.g., leptomeningeal disease) requiring urgent alternative medical intervention, and
- absence of significant, unacceptable or irreversible toxicities related to study treatment.

The maximum duration of treatment with BI 1387446 is 18 cycles, unless the patient has a partial response, in which case treatment may continue for cycles 19-34 after consultation with the sponsor. BI 1387446 has to be paused if there is no lesion suitable for injection any more, but may be re-started in the absence of PD if any lesion becomes suitable for injection again.

The maximum duration of treatment with ezabenlimab (BI 754091) (arm B only) is 34 cycles.

Patients will be allowed to stay on treatment in the case of initial radiological PD, if the Investigator judges that it is in the patient's best interest and the patient has signed an informed consent describing this circumstance.

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Table 4.1.2.3: 1 Treatment schedule Arm A

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

*optional for patients with a partial response

[redacted]

4.1.3 Method of assigning patients to treatment groups

Treatment arms A and B will be started sequentially. Patients will be assigned to treatment arms and cohorts through an Interactive Response Technology (IRT) system. For patient allocation rules, refer to Section 3.1.

Note that the medication number is different from the patient number (the latter is generated via the IRT System).

4.1.4 Drug assignment and administration of doses for each patient

[redacted]

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[redacted]

BI 1387446 is available in [redacted] (Table 4.1.1: 1) [redacted]

Ezabenlimab (BI 754091) will be administered intravenously. The recommended Phase II dose of ezabenlimab (BI 754091) to be used in combination with BI 754111 is 240 mg [redacted]

Both trial medication will be administered by authorised site staff in a specialised unit where emergency care can be provided (e.g. intensive care unit available, medical personnel trained in advanced life support).

Guidance for Investigators on materials for administration of drug is included in ISF. Refer to instructions for the preparation and handling of BI 1387446 and ezabenlimab (BI 754091) in the ISF.

In the event of force majeure or other disrupting circumstances (e.g. pandemic, war, please see Section 6), physical patient visits to the sites may not be feasible or may need to be restricted to ensure patient safety. Based on a thorough assessment of the benefits and risks, the investigator may still decide to continue trial treatment.

4.1.4.1 Lesion selection – BI 1387446

Lesions will be selected between screening and C1V1 and subsequent injections based on location and diameter. Patients may receive injections only into superficial lesions (see Section 3.1.3).

Lesions selected for injection should be measurable on cross sectional imaging or measurable by calliper and suitable to photodocumentation. Lesions have to be unequivocally identified in the CRF, in conjunction with all relevant BI 1387446 administration data. If possible, lesions selected for injection on cross sectional imaging studies should be captured on the image and provided to the CRO. Photodocumentation of lesions has to distinguish as well between injected and non-injected lesions, respective information has to be submitted together with the image.

Screening / initial administration

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The longest diameter of the proposed tumour lesion for injection (including lymph nodes) for a superficial lesion has to be ≥1 cm.

Repeat administration
Upon repeat administration, BI 1387446 should be administered preferably into the same lesion, as long as the lesion is suitable for injection (independent of size). In case other lesions than the primarily projected or selected lesion appear more suitable for injection than the previously selected lesion, BI 1387446 may be injected into a different lesion, as long as the new lesion is in line with the criteria as outlined above for screening/initial administration.
If no lesion is suitable for injection, BI 1387446 may be paused and restarted as considered indicated if a lesion suitable for injection becomes available in the absence of progression. As long as patients continue receiving ezabenlimab (BI 754091), BI 1387446 may be re-started independent of the duration of the interruption. In case both trial drugs need to be paused, the treatment may only be resumed if the treatment interruption is ≤12 weeks.

Initial and repeat administration
If more than one lesion qualify for injection, the lesion which is safest to inject should be selected first. In case two or more lesions are considered equally safe by the Investigator, the largest lesion should be selected for injection first. Lesions considered high risk for local complications should not be selected for injection (Section 4.1.4.2).

A single dose should preferably be injected into one lesion. The injection volume (Section 4.1.2.1.2) should be distributed across the tumour volume as much as possible by moving the needle within the tumour. In case the smallest possible volume as per Table 4.1.2.1.2: 1 cannot be injected into a single lesion and a second lesion qualifying for injection in the respective treatment arm is available, the dose may be distributed into up to two lesions.

4.1.4.2 Restrictions for lesion selection – BI 1387446

Lesions considered high risk for local complications should not be selected for injection. This includes tumours with

- encasement or suspected infiltration of major blood vessels,
- lesions located adjacent to vital structures which would be functionally impaired by swelling of injected lesion, e.g. trachea, carotid artery

4.1.4.3 Dose reductions and dose delays

As a general rule, any SAEs/AEs of ≥ Grade 3 will result in a pause of treatment with BI 1387446 and/or ezabenlimab (BI 754091) until resolution to baseline or Grade 1.

In combination treatment arms, both drugs (BI 1387446 and ezabenlimab (BI 754091)) will be stopped, paused, or re-exposed together unless an AE can be attributed to either BI 1387446 or ezabenlimab (BI 754091). Only if a causal relationship to one trial drug can be unequivocally established, the other trial drug may be continued.

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BI 1387446
Up to 2 dose reductions of BI 1387446 are allowed if the treatment pause due to an AE is ≤12 weeks and the re exposure is considered clinically indicated by the Investigator.

Dose reductions will be only permitted to doses previously explored in lower dose levels. In case of re-occurrence or worsening of the same AE upon re-start of BI 1387446 at a lower dose, a second dose reduction of BI 1387446 is not permitted and BI 1387446 has to be permanently discontinued. Re-escalation to higher doses is not permitted. In case a third dose reduction would be required, treatment of that patient should be permanently discontinued. Treatment interruptions >12 weeks are only permitted for AEs not considered drug related and may be agreed on a case by case basis with the Sponsor.

Ezabenlimab (BI 754091)
Dose reductions or escalations of ezabenlimab (BI 754091) are not permitted. In case of adverse events, administration of ezabenlimab (BI 754091) should be delayed for up to 12 weeks to permit recovery from adverse events. Treatment interruptions >12 weeks are only permitted for AEs not considered drug related and may be agreed on a case by case basis with the Sponsor.

Infusion-related reactions
In the event of an infusion-related reaction ≤ Grade 2, the infusion rate of ezabenlimab (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 ezabenlimab (BI 754091) has to be permanently discontinued.

4.1.4.4 Dose limiting toxicity

DLTs will be recorded throughout the trial. Only DLTs starting in the first cycle of monotherapy (Arm A), or during the first cycle of BI 1387446 in combination with ezabenlimab (BI 754091) (Arm B) are required for dose-escalation decisions made by the SMC. DLT information from later cycles will be taken into consideration if applicable.

Any of the following AEs will be classified as DLTs unless unequivocally due to underlying malignancy or an extraneous cause:

A) Hematologic toxicity
   1) any grade 5 toxicity
   2) neutropenia grade 4 lasting for >5 days
   3) neutropenia grade ≥3 with documented infection
   4) febrile neutropenia
   5) thrombocytopenia grade 4
   6) thrombocytopenia grade 3 with concomitant bleeding grade ≥2 (i.e. bleeding requiring intervention)

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B) Grade 4 anaemia

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C) Non-haematological toxicity
   1) 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)
   2) AST or ALT elevation grade ≥ 4
   3) CRS grade ≥3
   4) Any other ≥Grade 3 non-haematologic toxicity with the following exceptions:
      a. Grade 3 irAE that resolves to ≤ Grade 1 or to baseline with immunosuppressive therapy within 2 weeks
      b. Grade 3 fatigue that persists <7 days
      c. Grade 3 rash that resolves to ≤ Grade 1 within 2 weeks
      d. Grade 3 or 4 elevation in serum amylase and/or lipase that is not associated with clinical or radiographic evidence of pancreatitis
      e. Grade 3 electrolyte abnormality that lasts <72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical intervention
      f. Grade 3 nausea or vomiting that lasts <48 hours, and resolves to ≤ Grade 1 either spontaneously or with conventional medical intervention
      g. Alopecia
      h. 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.
      i. Grade 3 tumour flare syndrome
   5) Pneumonitis Grade 2
   6) 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
   7) Any Grade ≥2 toxicity that persists and results in a delay of >14 days of 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 not listed above should be considered a DLT for dose escalation purposes.

Late DLTs are AEs that meet the DLT criteria but occur on treatment after the completion of the initial MTD evaluation period (Arm A and B: Cycle 1, including echocardiographic/MUGA scan measurements acquired on Day 1 of Cycle 2 and related findings). If any late DLT is reported during dose escalation, the BLRM will be rerun using all DLTs, and updated results will be reviewed in the SMC meeting to recommend the next dose level and cohort size.

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4.1.4.5 Precautions and surveillance for procedural risks from intratumoural application

Needle insertion into a tumour lesion is associated with procedural risks known from diagnostic biopsy, e.g. infection, bleeding, injury to tissues in the needle track (e.g. nerves, vessels, organs), adverse reactions to local anesthesia if used.

BI 1387446 may only be administered by a physician who is experienced in diagnostic biopsy or intratumoural injection of immunotherapy drugs (physician, radiologist/interventional radiologist, or surgeon).

In case patient develops symptoms potentially indicating local complications, adequate surveillance and additional diagnostic measures need to be implemented as medically appropriate. A decline in Hgb by ≥2.0 g/dL (≥ 20 g/L, ≥ 1.24 mmol/L) must result in prolongation of surveillance by at least 4h including repetition of all assessments as per Table 4.1.4.5: 1. Imaging should be performed as medically indicated for diagnosis of a bleed.

Table 4.1.4.5: 1 Duration of in-hospital patient surveillance needs to be adapted for procedural risks

Lesion location	Minimum duration of surveillance	Mandatory assessments
Superficial lesion	30 minutes	vital signs (depending on surveillance period, at least at 30 +/- 15 mins or 60 +/- 15 mins) visual inspection of injection site

In case longer surveillance is mandated on selected visits for other reasons, e.g. risk mitigation of cytokine release syndrome (Section 4.1.4.6), the longest duration as defined per protocol at a given timepoint will apply.

4.1.4.6 Cytokine release syndrome

Patients will be closely monitored for CRS and, in case of suspected or confirmed CRS, have to receive appropriate and immediate treatment. All trial sites will have emergency resuscitation services and access to intensive care available.

Mandatory surveillance for CRS

- Patients will remain under surveillance for 24 hours after the first administration of BI 1387446 (STING agonist) on Cycle 1 Day 1.
- Patients will remain under surveillance for at least 8 hours after the second and third administration of BI 1387446 on Cycle 1 [redacted]
- Patients will remain under surveillance for at least 8 hours on Cycle 2 Day 1.
- Patient will remain under surveillance for at least 8 hours in Cycle 5 Day 1 of Arms A and B.

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- Patient surveillance may be shortened on subsequent administrations as medically appropriate, considering the minimum duration as defined in Section 4.1.4.5, provided that no cytokine release syndrome was observed in the previous administration.
- In case a patient suffered from cytokine related symptoms at the previous BI 1387446 injection, the surveillance at the subsequent administration needs to be prolonged to at least 8 hours.
- Patients requiring steroids as premedication or requiring medication for symptoms of any kind (including any signs/symptoms concerning CRS) for any reason during the CRS surveillance periods will stay for observation and continue to be monitored for CRS for at least 24 hours after administration of BI 1387446

Monitoring of asymptomatic patients will include measurement of body temperature, heart rate, and blood pressure, at least every 2 hours. Parameters have to be captured in CRF. Those parameters will not only be used to capture the symptoms of CRS, but also be evaluated for signs of cardiac insufficiency. If more frequent assessments are chosen due to clinical symptoms, a representative selection of these additional assessments need to be captured in the CRF as well. Patients will be assessed for signs or symptoms of CRS (e.g. fever, hypotension, tachycardia, hypoxia, 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, or in case of urgency to another, closer hospital.

CRS grading should be performed according to American Society for Blood and Marrow Transplantation (ASBMT) consensus grading [R19-0309], organ toxicities in the context of CRS should be reported according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0. AEs of CRS Grade ≥2 are defined as AESIs.

Treatment of CRS should be based on published recommendations and guidelines [R19-0310, R19-0311], the recommendations for treatment of CRS in Appendix 10.2 should be considered by the investigator as guidance. In general, in case more than symptomatic treatment is required, corticosteroids should be administered first. IL-6 targeting drugs should be used only once appropriate doses of corticosteroids did not result in adequate improvement or resolution. Pre-emptive administration of anti-IL6-therapy, e.g. use of tocilizumab or siltuximab prior to BI 1387446 injection or immediately thereafter without presence of clinical symptoms of CRS, is not permitted.

In patients with clinically manifested CRS, it is recommended to measure cytokines in the local laboratory at onset of symptoms, approximately 24 hours, and 48 hours thereafter or upon discharge from hospitalization (whichever occurs earlier).

A patient with CRS grade 1 or 2 may be re-exposed to BI 1387446 and ezabenlimab (BI 754091) at the subsequent planned administration timepoint provided that all symptoms have completely resolved for at least 48 hours.
Following a CRS grade 3 or 4, patients must not be re-exposed to the drug which is considered associated with the event. In case of uncertain causality assessment, both trial

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drugs must be permanently discontinued. For details on management of trial drugs refer to Appendix 10.2.

4.1.4.7 Management of immune-related AEs

Immune related AEs are expected with the use of ezabenlimab (BI 754091) and/or BI 1387446, and need to be documented and managed according to Appendix 10.1 and published guidelines [P19-00269].

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This trial will be conducted as an open-label fashion.

4.1.5.2 Unblinding and breaking the code

Not applicable.

4.1.6 Packaging, labelling, and re-supply

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

4.1.7 Storage conditions

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

4.1.8 Drug accountability

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

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

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- Availability of FDA Form 1572 (if applicable).

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

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

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Anticancer therapy
No other investigational therapy or anticancer agent should be given to patients. If such agents are required for a patient, then the patient must first be withdrawn from the trial.

Immunosuppressive medications
Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor-alpha blockers are prohibited. Use of immunosuppressive medications for the management of investigational product-related AEs or in patients with contrast allergies is acceptable, and does not necessarily warrant immediate treatment discontinuation. In addition, use of inhaled, topical, intranasal corticosteroids or local steroid injections (e.g. intra-articular injection) is permitted. Temporary uses of corticosteroids for concurrent illnesses (e.g. food allergies, computed tomography (CT) scan contrast hypersensitivity) are acceptable upon discussion with the Sponsor.
For the treatment of CRS, supportive therapy including steroids, interleukin 6 receptor (IL6R) antagonists and IL6 antagonists may be used as clinically indicated.

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Vaccines
In Arm A, live attenuated vaccines are prohibited during the trial through 30 days after the last dose of BI 1387446. In Arm B, the use of live attenuated viruses has to be delayed until 70 days after the last dose of ezabenlimab (BI 754091) or 30 days after the last dose of BI 1387446, whichever comes later.

The decision on COVID-19 vaccination of a BI study patient must be taken based on an individual Benefit-Risk Assessment by the investigator after thorough discussion with the patient. This assessment should consider the approved labels of the respective vaccine as well as the provisions given in the Clinical Trial Protocol. Furthermore, there should be a time window of at least 3 days between administration of the vaccine and study medication. COVID-19 vaccination or BI 1387446 may be postponed considering the patients individual risk. COVID-19 vaccination should be considered as concomitant medication and reported as such in the CRF.

Considering the mechanism of action of activation of the STING pathway and PD-1 receptor blockade, attenuation of vaccine-induced protective immunity by BI 1387446 and/or BI 754091, respectively, is not assumed.

The package insert for approved COVID-19 vaccinations should be carefully reviewed for local guidance considering acute moderate/severe febrile illness, and the risk of an anaphylactic reaction to the vaccine. A diminished response to the vaccine needs to be considered for immunocompromised conditions which may be observed in patients with advanced or metastatic solid tumour after prior anti-cancer therapies.

It is important to encourage a patient to continue taking precautions such as wearing a mask, maintaining social distancing and washing hands frequently, even after a patient receives a COVID-19 vaccine. These precautions will be necessary until public health experts advise otherwise.

Herbal medications
Herbal preparations/medications are not allowed throughout the trial unless agreed to by the Principal Investigator. 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. If instructed by the Principal Investigator, patients should stop using these herbal medications 7 days prior to first dose of study treatment.

Palliative radiotherapy
For symptom control, palliative radiotherapy of a single lesion is permitted in the dose escalation part of the trial, except during the first cycle as it could interfere with the DLT evaluation for MTD determination. Palliative radiotherapy is allowed only for lesions which are not previously injected with BI 1387446, provided that the reason for radiotherapy does not reflect PD and does not interfere with response assessment. Lesions that have been exposed to radiotherapy are no longer evaluable, and may not be included in the imaging based response assessment of target/ non-target lesions and the overall assessment. The

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Sponsor should be informed prior to the administration of palliative radiotherapy, except for emergency situations.

IL-6 antagonists
In case tocilizumab or other IL-6 antagonists are required for management of severe adverse events, BI 1387446 and ezabenlimab (BI 754091) have to be permanently discontinued.

4.2.2.2 Restrictions on diet and life style

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

4.2.2.3 Contraception requirements

Due to the advanced stage of disease of Phase I trial patient populations and the high medical need, females of childbearing potential can be included in this trial provided that they agree to use a highly-effective contraception method.

Females *not of childbearing potential* must have evidence of such by fulfilling one of the following criteria at screening:

- Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy
- Post-menopausal: defined as more than 50 years-of-age and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments
- Women under 50 years-of-age would be considered postmenopausal if they have been amenorrhoeic for at least 12 months following the cessation of exogenous hormonal treatments, and have serum follicle-stimulating hormone and luteinizing hormone levels in the postmenopausal range for the institution.

WOCBP (trial participant or partner of a trial participant) must use a highly effective method of birth control per ICH M3 (R2) that results in a low failure rate of less than 1% per year when used consistently and correctly if their sexual partner is a man able to father a child. These methods include:

- Total sexual abstinence when this is in line with the preferred and usual lifestyle of the study participant (periodic abstinence such as calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable methods of contraception), or
- Bilateral tubal ligation, or
- vasectomised partner (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate and provided that partner is the sole sexual partner of the female clinical trial participant), or
- Intrauterine device or intrauterine hormone-releasing system.

Women of childbearing potential must follow these methods during the trial and for at least 6 months after the end of the trial treatment.

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Note: although hormonal contraception is considered a highly effective method of birth control, women of childbearing potential using a contraceptive pill must use an additional barrier method.

Men (trial participant or partner of a trial participant) must agree to use a condom, unless vasectomised with documented absence of sperm, and ensure that their female partner of childbearing potential is using an additional highly-effective method of birth control, during the trial and until at least 6 months after the end of the trial treatment.

Details of contraception methods may be adapted according to local requirements and are described in the patient information in the ICF.

4.3 TREATMENT COMPLIANCE

BI 1387446 and ezabenlimab (BI 754091) will be administered at the sites by the Investigator and/or trained site personnel, and dosing will be recorded in the eCRF. Therefore, actual dosing is expected to precisely follow the prescribed drug regimen. Missed or interrupted doses will be recorded in the eCRF with the associated reasons. The method of collecting dosing information assures that total exposure can be calculated programmatically taking into account any missing doses.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

The tumour response will be evaluated according to Response Criteria for Intratumoural Immunotherapy in Solid Tumours (itRECIST) (R20-2734). itRECIST criteria have been introduced recently and are tailored for solid tumours and intratumoural therapy trials. itRECIST criteria incorporate features of RECIST 1.1 (R09-0262) and iRECIST (R17-0923) with the intent to capture both systemic and local effects of intratumoural therapy. Thus, injected lesions remain evaluable for overall response assessment as long as these are integral to the intratumoural treatment regimen. As with RECIST 1.1, the classification algorithm follows the quantitative and qualitative assessment of tumour burden and defines the maximal number of target lesion (TL) tumours using the same measuring criteria as with RECIST 1.1. Importantly, the new criteria further categorize the target and nontarget tumour categories into injected and noninjected tumours (i.e., target injected (T-I), target noninjected (T-NI), nontarget injected (NT-I), and nontarget noninjected (NT-NI)). For details please refer to Section 10.3 and the recently published paper by Goldmacher et al (R20-2734).

The assessment by the Investigator and/or the local radiologist will be the basis for continuation or discontinuation of the trial in an individual patient (in addition to safety). The baseline imaging must have been performed within 4 weeks prior to treatment with the trial medication and the Investigator will record the target and non-target lesions in the eCRF. Target lesions will be classified as target injected (T-I) or target non-injected (T-NI). The same method of assessment and the same technique must be used to characterise each

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reported lesion at baseline and during treatment. Lesions in previously irradiated areas may not be considered measurable at baseline unless the lesions appeared after irradiation.
Tumour assessments will be performed as indicated in the Flow Chart

- at screening (as close as possible to the treatment start and no more than 28 days before the start of BI 1387446 in Arms A and B).
- before treatment administration at Cycle 2 Day 1 (a time window of -5 days is acceptable) in all treatment arms.
- before treatment administration (a time window of -7 days is acceptable) in C4, C6, C8, C10, C13, C16, C19, C23, C27, C31 and at EOT.

Copies of the scans will be collected by the sponsor or designee.
Additional imaging may be obtained at the discretion of the Investigator.

If the patient stops trial treatment prior to completion of maximum number administrations for a reason other than PD, the tumour assessment according to itRECIST will be performed according to standard of care until the last follow-up needed according to protocol.

All tumour imaging data acquired in this trial will be centrally collected by a CRO and centrally assessed by a designated core lab. Based on the centrally collected imaging data further integrated assessments of treatment-induced changes in imaging metrics, e.g. in tumour volume(s), shape(s), texture(s), will be performed. This so-called radiomics analysis is exploratory and will be performed by a service provider (CRO or academic) nominated by the Sponsor. Furthermore, centrally collected imaging data may be evaluated on an exploratory basis by a designated core lab to explore the impact of itRECIST on assessing efficacy outcomes over iRECIST/RECIST 1.1.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

Physical examinations will be performed at screening, prior to trial medication administration on Day 1 of each cycle, at the EOT visit, and at the 30-day safety follow-up visit. However, patients will have an additional abbreviated physical examination (focused on the specific disease, at the Investigator's discretion) as indicated in the Flow Chart.
The physical examination will include measurement of height (screening only) and of body weight, and the evaluation of the ECOG performance score. Weight will be measured during screening and at each full physical examination (not during abbreviated physical examinations).

The ECOG score will be assessed at screening, on Day 1 of Cycles 1, 2 and 3, on Day 1 of every other cycle beginning with Cycle 5 prior to trial medication intake, at the EOT visit, and at the 30-day safety follow-up visit.

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

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5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the Flow Chart, prior to blood sampling.
This includes systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest. The results must be included in the source documents available at the site.
Vital signs will be monitored after drug administration as specified in Section 4.1.4.5 and Section 4.1.4.6.

5.2.3 Safety laboratory parameters

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

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Table 5.2.3: 1 Safety laboratory tests

Category	**Parameters**	**Screen.**	**CxD1 EOT**	**other**
Haematology	white blood cell count (WBC), haemoglobin, platelet count (PLT)	x	x	x
	haematocrit, red blood cell count (RBC), white blood cell differentiation preferably expressed in absolute values (neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils, other if applicable)	x	x	
Coagulation	International Normalized Ratio (INR), activated Partial Thromboplastin Time (aPTT), Prothrombin Time (PT)	x	x	x
Biochemistry	Glucose, sodium, potassium, creatinine, AST, ALT, alkaline phosphatase, lactate dehydrogenase (LDH), creatine kinase (CK), total bilirubin. If total bilirubin is elevated: direct bilirubin. If CK is elevated: CK-MB (cardiac), Troponin I and myoglobin.	x	x	x
	calcium, phosphate, magnesium, chloride, bicarbonate (HCO_3), urea, total protein, albumin, C-reactive protein	x	x	
	Troponin I or Troponin T[1]	x	C4	
	N-terminal pro BNP (brain natriuretic peptide)[2]	x	C2 C4 C7	
	Cholesterol, triglycerides, c-peptide	x	x[3]	

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Table 5.2.3: 1 Safety laboratory tests (cont.)

Category	Parameters	Screen.	CxD1 EOT	other
	Creatinine clearance if creatinine is >1.5xULN	x		
Hormones	TSH, free T4		x	
Immunoglobulins	Serum immunoglobulin levels (IgG, IgM, IgA, IgE).	x	x[4]	
Urinalysis	Dipstick analysis of pH, protein, glucose, blood, leucocytes, nitrite. In case of pathological findings further evaluation should be performed and results documented	x	x	
Pregnancy test	β-HCG testing in serum in females of childbearing potential	x	x	

1. One test to be selected per investigational site and patient and to be reported throughout
2. If Nt proBNP not available, it may be replaced with a decline in preference by mid-regional pro-ANP, total BNP or ANP. One test to be selected per investigational site and patient and to be reported throughout.
3. If clinically indicated
4. Obtained at all timepoints where lymphocyte typing is done (refer to the assessment of immune cell subsets (via FACS) in Section 5.4.2 and in the Flow Chart)

Cardiac markers (Troponin I or Troponin T, NTproBNP or listed substitutes) have to be obtained at screening, in the respective treatment cycle indicated in Table 5.2.3:1, and as clinically indicated in other cycles. In case the patient develops clinical symptoms of cardiac insufficiency, cardiac markers should be obtained as appropriate in addition to the mandatory timepoints. The same markers as listed for mandatory timepoints should be obtained.

Unequivocal clinical symptoms of cardiac insufficiency should always trigger an unscheduled echocardiography. In the absence of unequivocal clinical symptoms, the following cut-offs for cardiac markers should be considered as guidance to trigger further diagnostic workup including assessment of left ventricular ejection fraction (Section 5.2.5):

- Troponin T: increase to more than 3x baseline/ULN or absolute value > 100 ng/L (> 0.1 ng/mL, > 0.10 µg/L)
- NTproBNP: increase to more than 2 x baseline/ULN or absolute value >600 pg/mL (> 600 ng/L)

Patients do not have to be fasted for the blood sampling for the safety laboratory.

Screening laboratory assessments performed within 72 hours of the first trial treatment administration are not required to be repeated on Cycle 1 Day 1. Other safety laboratory should be performed within 24 hours of the visits.

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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 (refer to Section 5.2.7).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (refer to Section 5.2.7.1.4 and the DILI Checklist provided in the eDC system). The amount of blood taken from the patient concerned will be increased due to this additional sampling.

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 Flow Chart outlines which visits will require ECGs, and Blood sampling Flow Chart outlines which time points require triplicate ECGs to be done along with certain PK samples (Arm A and B).

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

Electrocardiogram machines will be provided for the trial to facilitate central readings. Before study start, the study sites will be trained for the proper use of the equipment and transfer of the electronic data to the vendor. All ECGs will be transmitted to the central vendor for analysis.

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

The ECG recordings must also be analysed and checked for abnormality by the Investigator (or designated physician) who will also calculate the QTcF value for each time point as the mean of the 3 ECGs. Particular attention must be paid to T wave inversions. It is not mandatory to wait for central evaluation of ECGs to make clinical decisions. 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 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

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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.

At timepoints when ECG and blood sampling for PK are planned at the same time, ECG should be performed prior to PK sampling. Triplicate ECGs should be performed within a maximum period of 5 minutes prior to blood sampling.

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 for assessment of all ECGs.

Central morphological analyses of the ECGs (cardiologic assessments) will be performed by a board-certified cardiologist or equivalent. 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 Echocardiography / MUGA scan

Echocardiography to assess left ventricular (LV) function needs to be performed at screening and in regular intervals as indicated in the Flow Chart. In case trial drugs are administered at the respective visit, echocardiography should be obtained prior to trial drug administration.

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LV ejection fraction (LVEF) has to be measured and reported in the eCRF, additional relevant abnormal findings may be reported as baseline conditions/adverse events. Although echocardiography is the preferred method, MUGA scans are permitted to quantify LVEF. The same method should be used in a single patient throughout the trial.

In case the patient develops clinical symptoms of cardiac insufficiency, unscheduled echocardiography should be obtained as soon as possible to quantify LV ejection fraction and additional parameters as clinically indicated.

A clinically relevant decline in LVEF, defined as an absolute decrease by at least 10 percentage points, should be confirmed by a subsequent assessment after 1-2 weeks. A confirmed LVEF decline should be reported as adverse event. Upon detection of a clinically relevant decline in LVEF, BI 1387446 should be paused until LVEF returns to baseline, and should only be resumed at a reduced dose. In case of a recurrent decline upon re-exposure at a reduced dose of BI 1387446, treatment should be permanently discontinued.
In case a clinically relevant decline in LVEF is observed, patients should be closely followed for signs of cardiac disease throughout the trial. Results from additional imaging studies should be captured in the eCRF.

5.2.6 Other safety parameters

Assessment of lens opacity
Ocular history as part of the medical history will be reviewed at screening. Examination of patients for the presence and extent of lens opacities using slit-lamp examination will be performed by an ophthalmologist at screening, at the 30-day safety follow and at any time during the treatment period, if clinically indicated. Lens opacities as seen on clinical slit-lamp examination will be graded and documented according to the Lens Opacities Classification System III (LOCS III) (R99-2093).

5.2.7 Assessment of adverse events

5.2.7.1 Definitions of AEs

5.2.7.1.1 Adverse event

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

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

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

- Worsening pre-existing conditions, excluding disease progression.

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- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the Investigator.

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

5.2.7.1.2 Serious adverse event

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

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

5.2.7.1.3 AEs considered “Always Serious”

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

The latest list of “Always Serious AEs” can be found in the eDC system. A copy of the latest list of “Always Serious AEs” will be provided upon request. These events should always be reported as SAEs as described above.

5.2.7.1.4 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor’s Pharmacovigilance Department within the same timeframe that applies to SAEs, please see Section 5.2.7.2.2.

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The following are considered as AESIs:

Dose limiting Toxicities (DLTs)
All DLTs are considered to be AESIs, and must be reported as such. The definition of DLT is presented in Section 4.1.4.4.

Hepatic injury and drug-induced liver injury (DILI)
During the course of the trial the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets the hepatic injury definition or potential Hy´s law criteria at any point during the trial.

The Investigator participates, together with the Medical Monitor and clinical project representatives, in review and assessment of cases meeting potential hepatic injury and Hy´s law criteria. Hy´s law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than a DILI caused by the investigational product.
The Investigator is responsible for recoding data pertaining to these cases and for reporting them as AEs and/or SAE according to the outcome of the review and assessment in line with standard safety reporting processes.

Hepatic injury definition:
A hepatic injury is defined by the following alterations of hepatic laboratory parameters in patients with normal liver parameters at baseline (ALT, AST, and bilirubin within normal limits):

- 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, or in samples drawn within 30 days of each other, or
- aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

For patients with abnormal aminotransaminase levels between >1 and <3 x ULN at baseline:

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

For patients with abnormal aminotransaminase levels between ≥3 x ULN and <5 x ULN at baseline:

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

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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.

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

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

Lab values meeting the hepatic injury definition will need to be reported as AESI. Please follow the flowchart below for reporting hepatic injury / potential DILI cases

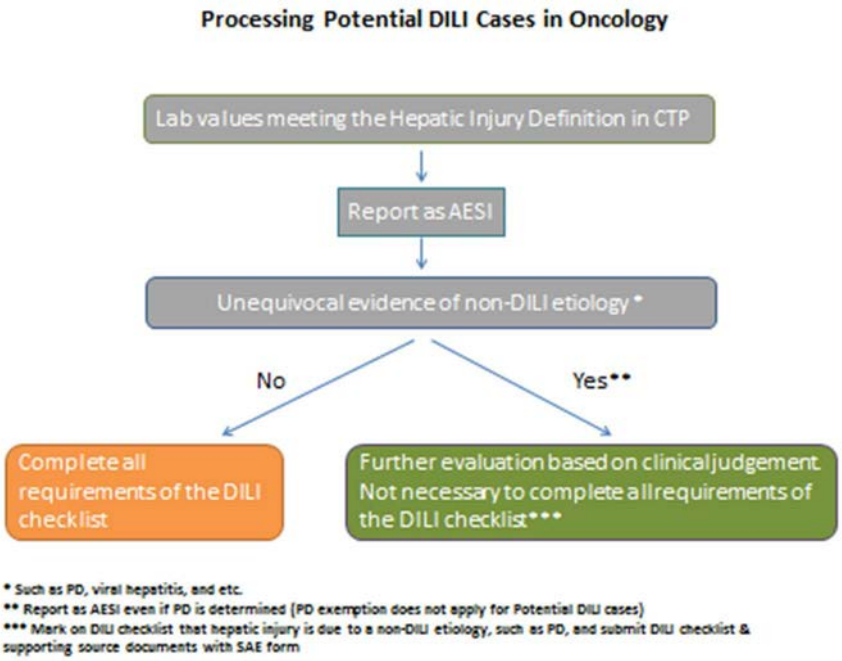

Figure 5.2.7.1.4: 1 Processing Potential DILI Cases in Oncology

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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. All immune-relate events are to be reported as AEs. Some irAEs also need to be reported as AESIs as defined by the sponsor in Table 10.1.1: 1. If an Investigator determines a grade 3 event (not on the list) to be immune-related, the Investigator should also report that event as an AESI.

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

5.2.7.1.5 Intensity (severity) of AEs

The severity of adverse events should be classified and recorded in the CRF according to the CTCAE v5.0.

5.2.7.1.6 Causal relationship of AEs

Medical judgement should be used to determine whether there is a reasonable possibility of a causal relationship between the adverse event and the given study treatment, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

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

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

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).

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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.

5.2.7.2 Adverse event collection and reporting

5.2.7.2.1 AE Collection

The Investigator shall maintain and keep detailed records of all AEs in the patient files.

The following must be collected and documented on the appropriate CRF(s) by the Investigator:
- From signing the informed consent onwards until the individual patient's end of trial: all AEs (serious and non-serious) and all AESIs.
- After the individual patient's end of trial:
  the Investigator does not need to actively monitor the patient for new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the Investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see Section 5.2.7.2.2), but not on the CRF.

5.2.7.2.2 AE reporting to the sponsor and timelines

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

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

5.2.7.2.3 Pregnancy

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

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Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires a written consent of the pregnant partner; in the event that consent cannot be obtained, information will be collected and reported in accordance with regulatory requirements. The ISF will contain the trial specific information and consent for the pregnant partner.

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

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

5.2.7.2.4 Exemptions to AE/SAE reporting

The occurrence of disease progression is recorded as part of the assessment of trial endpoints for the analysis of efficacy. The following rules will be followed for reporting disease progression and associated signs and symptoms for the analysis of safety;

- If the disease progression, or any associated signs and symptoms, meet standard seriousness criteria (see Section 5.2.7.1.2), 'disease progression' must be reported as an SAE.
- If the disease progression and any associated signs and symptoms do not meet standard seriousness criteria, 'disease progression' is not reported as an AE.
- Clinical signs and symptoms of disease progression which do not meet standard seriousness criteria will be recorded on the AE page of the eCRF. If a sign or symptom is on the 'Always Serious AE' list, it will also be reported as an SAE. If signs and symptoms are attributable to a diagnosis (other than 'disease progression'), reporting the diagnostic term is preferable e.g. pulmonary embolism rather than dyspnoea, intestinal obstruction rather than abdominal pain.
- If there is evidence suggesting a causal relationship between the investigational drug(s) and the progression of the underlying malignancy, the event must be reported as an SAE.
- Lab values meeting the potential severe DILI definition in Section 5.2.7.1.4 must always be reported as AESI, even if the most likely cause is disease progression. No exemption to AE reporting applies.

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

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5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Pharmacokinetic profiles of BI 1387446 and ezabenlimab (BI 754091) will be investigated. Exact date and clock time of drug administration and pharmacokinetic sampling will be recorded in the CRFs. Planned sampling times should be adhered to as close as possible. However, these sampling times only represent guidance; thus, deviations which may occur are not regarded as protocol violations. PK sampling times and periods may be adapted during the trial based on information obtained during trial conduct including addition of samples and visits as long as the total blood volume taken per subject does not exceed 500 mL. Such changes would be implemented via non-substantial CTP amendments.

5.3.1 Assessment of pharmacokinetics

BI 1387446
If feasible, the following PK parameters may be determined for BI 1387446 after single and multiple doses of BI 1387446 (as single agent and in combination), as measured during the first and subsequent cycles (administration q1w) and evaluated as further exploratory parameters:

- $C_{max(,N)}$ (maximum measured concentration of the analyte in plasma [after Nth dose])
- $T_{max(,N)}$ (time from dosing to maximum measured concentration of the analyte in plasma [after Nth dose])
- $AUC_{0\text{-}tz(,N)}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point [after Nth dose])

Additional PK parameters may be determined after single and multiple doses of BI 1387446, if considered appropriate.

[redacted]

Ezabenlimab (BI 754091)
Descriptive statistics of plasma concentrations at timepoints indicated in the Flow Chart.

5.3.2 Plasma sampling for metabolism analysis

Additional K2-EDTA plasma samples for the optional identification of drug metabolites will be investigated in the [redacted] in Arm A Cycle 1 Day 1 and Day 2. Based on the knowledge gained during the trial conduct, e.g. from preliminary PK results, the dose group may be modified to a different one. The change will be implemented via a non-substantial CTP amendment.

For sampling times for metabolism, refer to the Blood sampling Flow Charts. The blood samples will be drawn at the same time points as PK samples on Day 1 and Day 2 of Cycle 1

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(see Blood sampling Flow Charts). At each of these times, 4.9 mL blood will be needed for metabolite analysis. The blood samples will be processed in the same way as the PK samples (see Section 5.3.3). However, the plasma obtained (approximately 2 mL) will be transferred into polypropylene tubes (each containing approximately 1 mL, labelled MIST1 and MIST2). Samples will be stored at approximately -20°C or below until transfer to the metabolism laboratory. At a minimum, the sample tube labels should list BI trial number, subject number, visit, planned sampling time and 'MetID'.

Plasma samples dedicated to metabolism investigation are transferred to:

[redacted]

Only data related to the parent compound and its metabolites will be acquired. Evaluation of drug metabolism will be reported separately and will not be included in the Clinical Trial Report (CTR). The study samples will be discarded after completion of the experiments but not later than 5 years after the CTR has been archived.

5.3.3 Methods of sample collection

Blood samples should not be obtained from the arm used for ezabenlimab (BI 754091) infusion. In case a central venous access is used for infusion, the blood sample can be collected from either forearm or central line. Blood sampling for BI 1387446 should be performed in anatomical distance from the injection site, e.g. if the right arm is the injection site for the tumour, the left arm should be used for PK blood sampling. The actual sampling date and time (24-hour time clock) for each sample has to be recorded accurately.

For quantification of analyte concentrations, blood will be drawn for BI 1387446 and ezabenlimab (BI 754091) at the time points specified in the PK time schedule in Blood sample Flow Charts.

Samples may be used for further methodological investigations, however only data related to this trial, the analyte or bioanalytical assay will be generated by these additional investigations (e.g. using the sample for ADA or biomarker for PK if sample volume allows). 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.
Details on sample collection for BI 1387446 and ezabenlimab (BI 754091) characteristics, processing, handling and shipment are provided in the Laboratory Manual.

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[redacted]

5.4 ASSESSMENT OF BIOMARKER(S)

This section refers to exploratory biomarkers.

The study of biomarkers will be hypothesis-generating and will substantially contribute to the understanding of the BI 1387446 mode of action. Where possible biomarkers will be used to retrospectively identify patient subgroups with differential prognoses and/or responses to treatment. The following exploratory biomarkers may be examined in this trial:

- Immunohistochemical analysis of immune-oncology –related markers on tumour cells and Immune cell infiltrates
- Peripheral cytokine secretion
- Flow analysis of different immune cell subsets in blood
- Gene expression analysis of immune-oncology-related panel of genes in blood and tissue.
- Genomic profiling to determine tumour mutational burden (TMB) and microsatellite status.
- Germline STING variants.

Should other tissue/blood biomarkers become relevant, these may also be explored. The list of biomarkers planned to be studied during the trial may change based on new information in the literature or early analyses.

In the case of premature trial discontinuation due to the reasons specified under section 3.3.4 or 3.3.5, the sponsor reserves the right to discontinue selected analyses. Respective samples may be used for further investigations as described in 5.4.1, or if a separate informed consent has been given, samples may be used for biobanking (section 5.5).

5.4.1 Methods of sample collection

Fresh pre- and on-treatment tumour biopsy collections for biomarker analyses will be mandatory from all patients (according to the Flow Chart). All samples must be adequately labelled by the trial site personnel. For fresh biopsies always use the equivalent of no less than two core needle biopsies (18 gauge or greater).

If available additional archival tumour tissue from the most recent time point before study entry will be collected during screening (see Flow Chart) for all patients. Archival tumour tissue sample should be provided as FFPE-preserved tissue, preferably as an embedded block and less preferably as mounted tissue sections (at least 8 up to 20 sections of 5 µm thickness) prepared under RNase free conditions.

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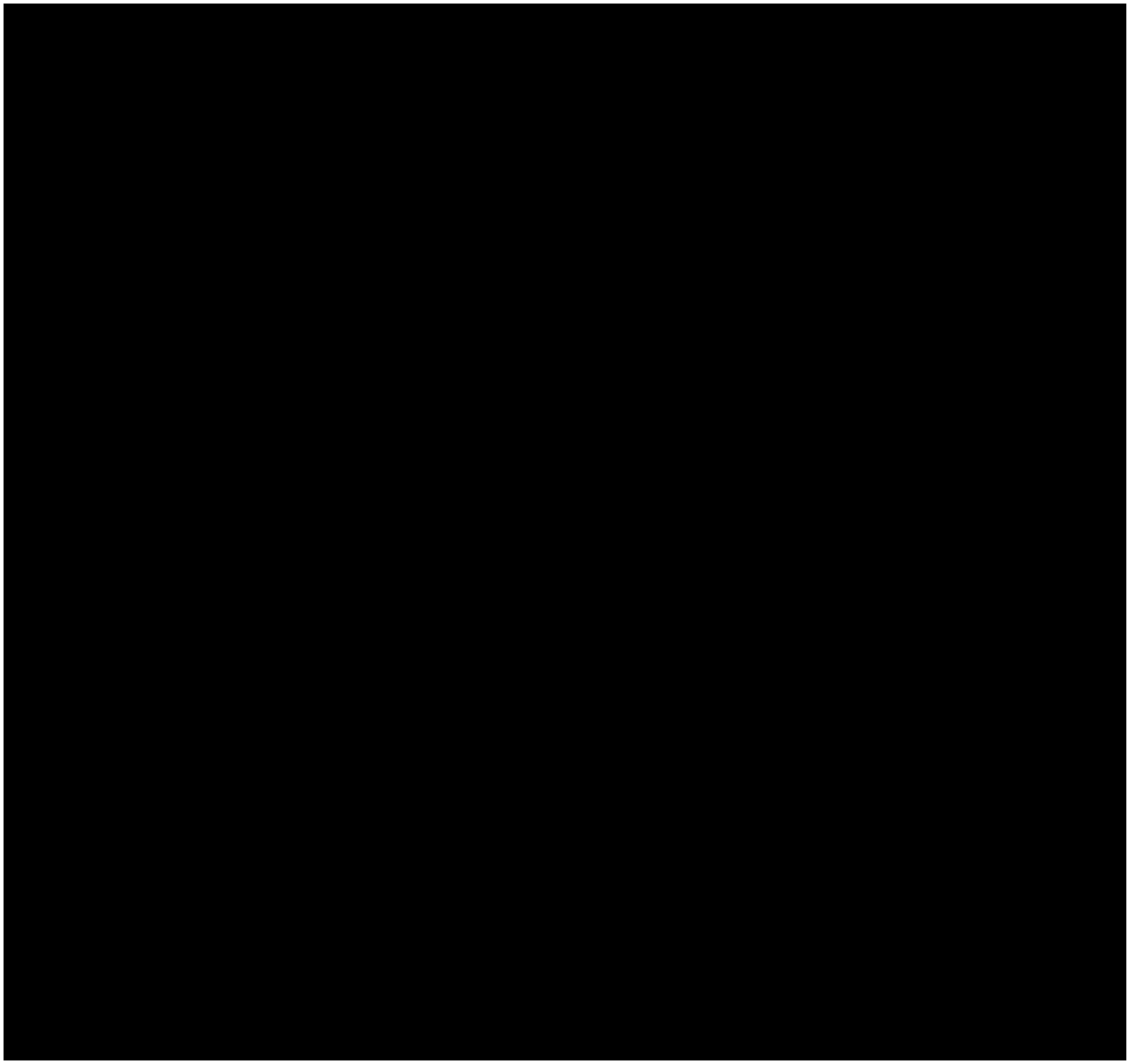
Details about tumour tissue and blood sample collection, plasma/serum preparation, required tubes, labelling of tubes, storage and shipment (frequency and addresses) will be provided in the ISF and the respective lab manual.
Samples may be used for further methodological investigations, however only data related to this trial, the analyte or an analytical assay will be generated by these additional investigations. If the patient has not consented to optional biobanking (see Section 5.5) trial samples left over after primary analysis will be discarded after completion of these additional investigations but not later than 5 years after the final trial report has been signed.



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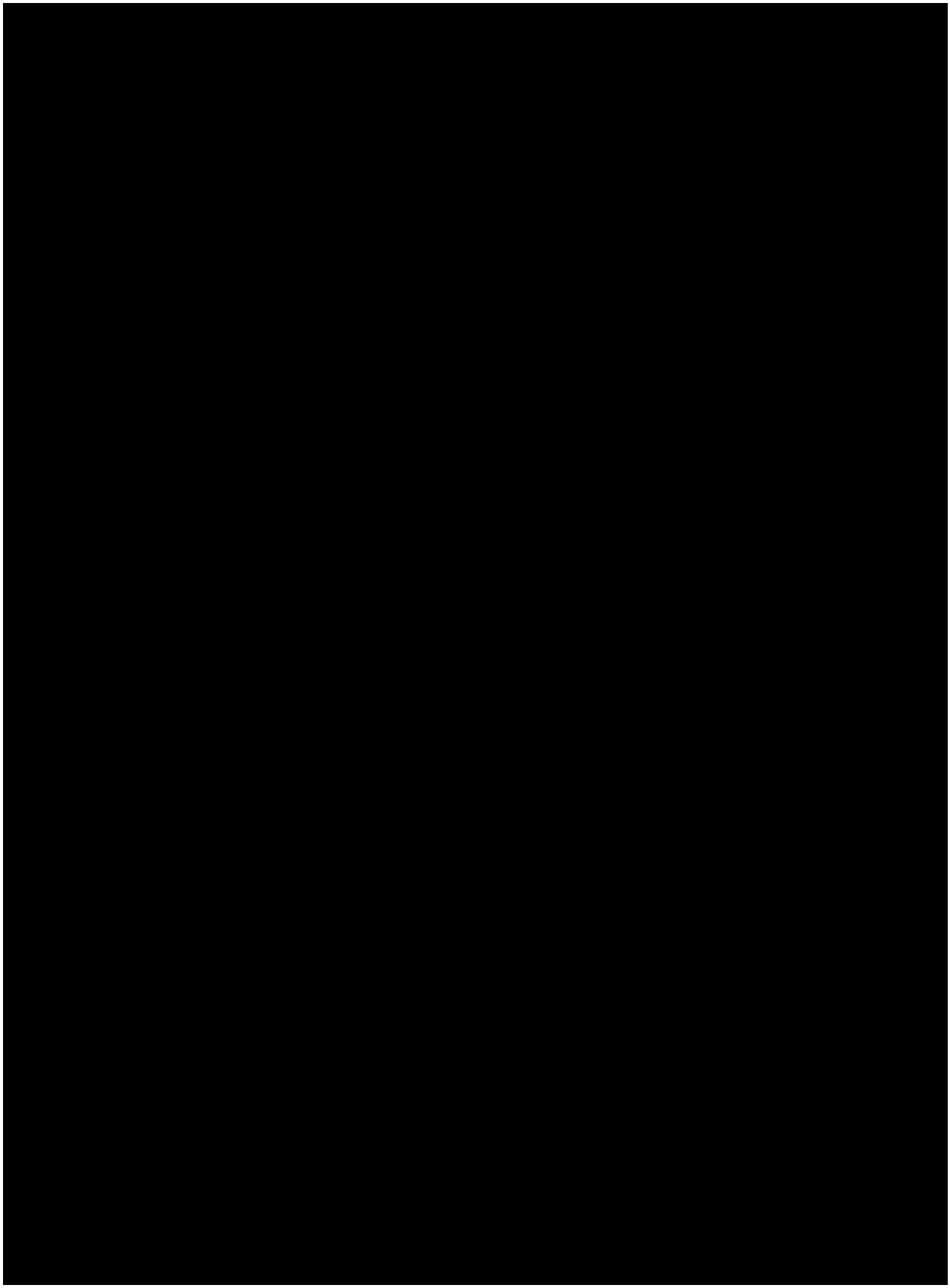

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5.5 BIOBANKING

Participation in biobanking is voluntary and not a prerequisite for participation in the trial. Biobanking will only occur after a separate biobanking informed consent has been given in accordance with local ethical and regulatory requirements. Banked samples may be used for further unspecified explorative investigations.

5.5.1 Methods and timing of sample collection

Detailed instructions on sampling, preparation, processing, shipment and storage are provided in the laboratory manual. For sampling timepoints see Flow Chart.
Banking will be limited to samples left over after primary analysis as specified in Section 5.4.
The following samples may be banked:

- Plasma samples
- FFPE tissue
- DNA and RNA

5.6 OTHER ASSESSMENTS

Assessment of anti-drug antibodies (ADAs)
For ADA assessments (ezabenlimab (BI 754091)), the specified blood volume will be drawn into blood-drawing tubes at the time points listed in Blood sampling Flow Charts.

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

Samples may be used for further methodological investigations, however only data related to this trial, the analyte or bioanalytical assay will be generated by these additional investigations (i.e. using the sample for ADA or biomarker for PK if sample volume allows).

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The trial samples will be discarded after completion of the additional investigations but not later than 5 years after the final trial report has been signed.

Note that for some disease indications, it may be necessary to use samples collected prior to administration of study treatments in order to assess the performance of the ADA assay.

[redacted]

5.7 APPROPRIATENESS OF MEASUREMENTS

All assessments have been planned in accordance with traditional oncology Phase I trial methodology except the itRECIST that is a new guideline for response assessment in trial testing intratumoural immunotherapeutics. itRECIST criteria were recently introduced (R20-2734) and incorporate features of RECIST Version 1.1 (R09-0262) and iRECIST (R17-0923), aiming at assessing response differences between injected and non-injected lesions. itRECIST is still to be validated as a predictor of outcome in trials of intratumoural immunotherapy. Considering that the FIH trial of BI 1387446 will evaluate the preliminary anti-tumour activity on an exploratory basis, it is deemed appropriate to use itRECIST. Centrally collected imaging data may be re-evaluated using RECIST 1.1/iRECIST on an exploratory basis by a designated core lab to further explore the impact of the novel itRECIST criteria on efficacy outcomes.

The pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used for assessments of drug exposure.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients should adhere to the visit schedule as specified in the Flow Chart.

Each cycle has duration of [redacted] Cycle 1, 2, and 3 requires 3 visits on [redacted] If treatment administration is delayed at any time (e.g. missed visit), the schedule of all subsequent visits/cycles will be recalculated based on the actual date of treatment. 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.

At Cycle 1 and Cycle 2, some visits require overnight stay driven by PK sampling. This overnight at the site for administrative reasons to allow treatment and PK sampling will not be considered an SAE, unless any other criteria for an SAE are fulfilled.

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

In the event of force majeure or other disruptive circumstances (e.g. pandemic, war) the investigational plan as per this clinical trial protocol may not be feasible at a site. With the consent of the patient, sponsor and investigator may agree on alternative, back-up or rescue methodology which may include but will not be limited to virtual patient visits and assessments, and home healthcare nurse visits. The implementation of these measures will depend on patient's consent, operational feasibility, local law and regulations. If alternative methodology is implemented, the deviations from the original plan will be precisely documented.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in period(s)

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

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

Patients who cross over from Arm A to Arm B do not have to repeat all screening procedures, but a limited set of assessments should be available, i.e.

- Imaging for response assessment (unless available between last dose of BI 1387446 in Arm A and first dose of ezabenlimab (BI 754091) or BI 1387446 in Arm B, and not older than 28 days).
- Biopsy from injected and non-injected lesion (unless performed in Arm A and no subsequent treatment with trial drugs in Arm A following the biopsy)
- Echocardiography, unless performed within the last 4 weeks

These patients will start treatment in Arm B at Cycle 1 Day 1.

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

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

Medical History:
Medical history of cancer:

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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 (TNM Classification of Malignant Tumours) will be provided as obtained at diagnosis and at trial screening. Previous surgeries will be reported. The patient's reason(s) for not being eligible for established treatment options should be documented in the patient record and will be recorded in the eCRF.

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.

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

Molecular characteristics of the tumour:
Microsatellite status, Tumour mutational burden (TMB), Expression levels of PD-L1, ER, PR, HER2, HPV status and any available information on tumour mutations will be recorded in the eCRF.

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

6.2.2 Treatment period(s)

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

6.2.3 Follow-up period and trial completion

The EOT visit will be performed as soon as possible but no later than 7 days after permanent discontinuation of the trial medications (BI 1387446 and/or ezabenlimab (BI 754091)) for any reason or e.g. when the Investigator decided with the patient to permanently discontinue the trial medications or became aware that the trial medications 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 EOT, unless it has been done within the past 3 weeks.

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6.2.3.1 30-day and 90-day safety follow-up visits

The 30-day safety follow-up visit is performed in person 30 (+7) days after the EOT visit. At this visit, all AEs/SAEs/AESIs and other required information must be collected as specified in the Arm A/B Flow Chart. The 90-day safety follow-up visit is performed by telephone (or in person if the investigator deems necessary) 90 (+14) days after the EOT visit. At this visit, only AEs/SAEs/AESIs and concomitant therapy need to be collected.

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 90 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.

6.2.3.2 Follow-up visit

Additional follow-up visits after the 90-day safety follow-up visit will only be performed for patients who did not progress on treatment to monitor tumour progression and safety. These will be performed once every 12 weeks at least (by telephone or in person) until PD, introduction of a new anti-cancer treatment, death, loss to follow-up, withdrawal of consent, or for a maximum of 6 months after EoT.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

This trial will be performed as an open-label trial. The primary objectives of this trial are to determine the MTD and/or the RD-P2 of BI 1387446 as monotherapy in superficial lesions (Arm A) and to determine the MTD and/or the RD-P2 of BI 1387446 in combination with ezabenlimab (BI 754091) in superficial lesions (Arm B). To determine the MTDs, patients are entered sequentially into escalating dose cohorts (see Section 3).

The dose escalation will be guided by a Bayesian 5-parameter logistic regression model with overdose control [R15-4233] using a hierarchical modelling approach to jointly model both arms and taking into account data available for ezabenlimab (BI 754091) from the ongoing trial 1381-0001. Trial 1381-0001 is also an oncology dose finding trial which comprises a similarly heterogeneous population of patients with solid tumours. A comparison between trial 1426-0001 and 1381-0001 regarding study population, DLT definition and treatment schedule is presented in Appendix Table 10. 5: 3. A visualisation of the joint-modelling approach is given in Figure 7: 1.

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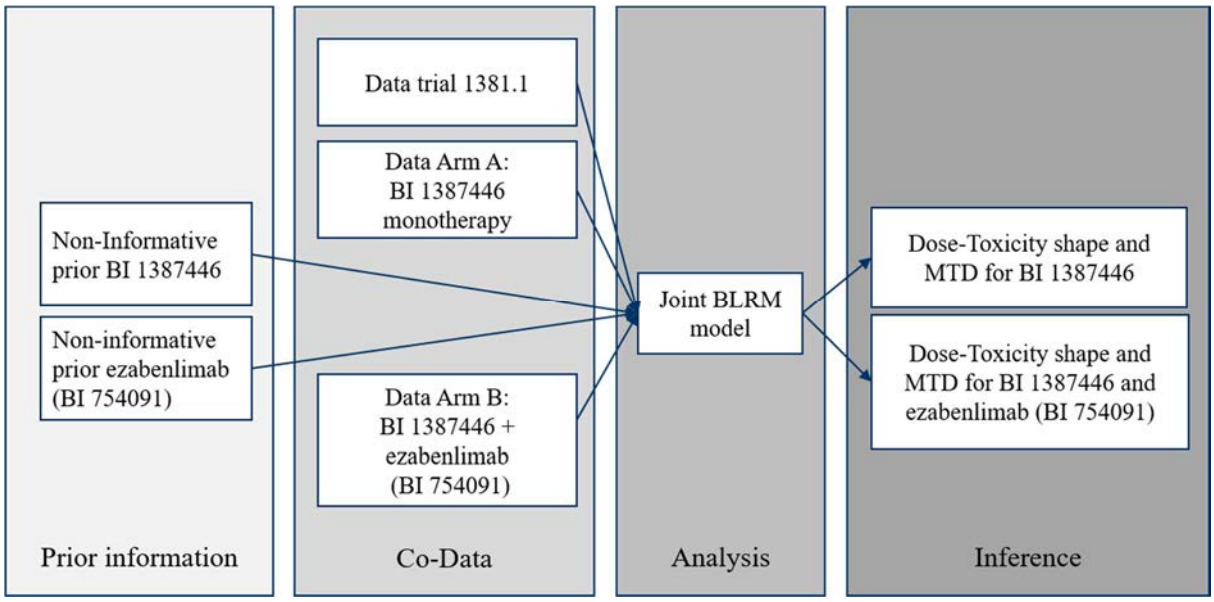

Figure 7: 1 Joint BLRM modelling approach for Arms A and B

The logistic regression model for Arm A and B is defined as follows. Let $\pi_{1,d1}$ be the probability of having a DLT when giving dose d_1 of BI 1387446 as monotherapy, and $\pi_{2,d2}$ the probability of having a DLT when giving dose d_2 of the combination partner ezabenlimab (BI 754091) as monotherapy, respectively. A logistic regression is used to model the dose-toxicity relationship for each of these drugs individually:

BI 1387446: $\text{logit}(\pi_{1,d1}) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$
Ezabenlimab (BI 754091): $\text{logit}(\pi_{2,d2}) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*)$
Here, the doses [redacted] and $d_2^* = 240$ mg represent the reference doses for BI 1387446 and ezabenlimab (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 1387446 and ezabenlimab (BI 754091), a dose-dependent interaction term $-\infty < \eta < \infty$ is introduced in the model by the following definition:
$\text{odds}(\pi_{12,d1,d2}) = \text{odds}(\pi^0_{12,d1,d2}) \exp(\eta\, d_1/d_1^*\, d_2/d_2^*)$
and $\pi_{12,d1,d2}$ is used in the likelihood
$r_{d1,d2} \sim \text{Binomial}(n_{d1,d2}, \pi_{12,d1,d2})$

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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.

The joint analysis of the dose escalation Arms A and B of this trial and the information available from trial 1381-0001 follows a normal-normal hierarchical model with 3 parameter models:

1) A multi-variate normal distribution for BI 1387446 as single agent:
   $\theta_{1,j} = \left(\log\left(\alpha_{1,j}\right), \log\left(\beta_{1,j}\right)\right) \sim N\left((\mu_{\alpha_1}, \mu_{\beta_1}), \Psi_1\right), j = 1, \ldots, 3$
2) A multi-variate normal distribution for ezabenlimab (BI 754091) as single agent:$\theta_{2,j} = \left(\log\left(\alpha_{2,j}\right), \log\left(\beta_{2,j}\right)\right) \sim N\left((\mu_{\alpha_2}, \mu_{\beta_2}), \Psi_2\right), j = 1, \ldots, 3$
3) A normal distribution for the interaction parameters η_j:
   $\eta_j \sim N\left(\mu_\eta, \tau_\eta^2\right), j = 1, \ldots, 3$

The parameters $\theta_{1,j}$, $\theta_{2,j}$, and η_j are the corresponding trial-specific parameters of each trial-specific BLRM (for trials j=1,2,3). The covariance matrices Ψ_i (i=1,2) are assumed to be of the form

$$\Psi_i = \begin{pmatrix} \tau_{\alpha_i}^2 & \rho_i \tau_{\alpha_i} \tau_{\beta_i} \\ \rho_i \tau_{\alpha_i} \tau_{\beta_i} & \tau_{\beta_i}^2 \end{pmatrix}$$

For this hierarchical model, the monotherapy dose-finding in Arm A and the double combination therapy dose-finding in Arm B, and trial 1381-0001 are assumed to be separate trials, with different inter-study random effects $\tau_{\alpha_1}, \tau_{\beta_1}, \tau_{\alpha_2}, \tau_{\beta_2}, \tau_\eta$ for the involved parameters. The parameters $\log\left(\alpha_{i,j}\right)$ and $\log\left(\beta_{i,j}\right)$ (i=1,2; j=1,2,3) are assumed to be potentially correlated with correlation coefficients ρ_i, i=1, 2, while the remaining parameters are assumed to be uncorrelated. Refer to [R18-3210] for details.

Since a Bayesian approach is applied, prior distributions f for each of the parameters $\mu_{\alpha_1}, \mu_{\beta_1}, \mu_{\alpha_2}, \mu_{\beta_2}, \mu_\eta, \tau_{\alpha_1}, \tau_{\beta_1}, \tau_{\alpha_2}, \tau_{\beta_2}, \tau_\eta$ and for ρ_1, and ρ_2 need to be specified. Weakly informative prior distributions were chosen for the μ- and ρ-parameters, prior distributions for the τ-parameters are chosen to represent a small to moderate between-trial heterogeneity (see Table 7: 1).

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Table 7: 1 Prior parameters of the joint model for Arms A and B

Parameter	Prior distribution
μ_{α_1}	N(log(0.5),2)
μ_{β_1}	N(0,1)
μ_{α_2}	N(log(0.5),2)
μ_{β_2}	N(0,1)
μ_{η}	N(0,1)
τ_{α_1}	logN(log(0.25),log(2)/1.96)
τ_{β_1}	logN(log(0.125),log(2)/1.96)
τ_{α_2}	logN(log(0.25),log(2)/1.96)
τ_{β_2}	logN(log(0.125),log(2)/1.96)
τ_{η}	logN(log(0.125),log(2)/1.96)
ρ_1	U(-1,1)
ρ_2	U(-1,1)

The toxicity probabilities $\pi_{1,d1}$, and $\pi_{12,d1,d2}$, of a DLT at each dose/dose combination will be calculated directly from the posterior samples regarding the arm-specific parameters, i.e. including the respective arm-specific random effects per parameter. They will be summarized per arm using the following intervals:

Under toxicity: [0.00, 0.16)
Targeted toxicity: [0.16, 0.33)

Overtoxicity: [0.33, 1.00]

Prior probabilities of DLTs at different dose levels/dose combinations, as well as the corresponding probability of under-, targeted and overtoxicity, are shown in Table 7: 2 and Table 7: 3 for the initial weakly informative priors of the joint model for Arms A and B. As can be seen from these tables, the prior medians of the DLT probabilities represent reasonable assumptions on toxicity, and the uncertainty around the medians is large, showing the low amount of information this prior provides.

Prior probabilities in Arm A show that [redacted] fulfils the EWOC criterion and is therefore a suitable starting dose for the monotherapy dose finding in superficial lesions. Prior probabilities for Arm B do not allow to start combination dose finding at [redacted] without additional data. However, from the data scenarios provided in Section 10.5 and from

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Tables 7: 4 and 7: 5, it can be seen that with some additional data from the monotherapy dose finding trials, the overdose probabilities decrease [redacted] becomes a suitable starting dose. Of note: At time of amending the CTP to version 5.0, Arm B was already started at this dose level.

Table 7: 2 Prior probabilities of DLTs in Arm A

[redacted]

Table 7: 3 Prior probabilities of DLTs in Arm B

[redacted]

In addition, Tables 7: 4 and 7: 5 show the prior probabilities for Arm A and B taking into account data from 1381-0001 that has already been obtained by the time of the CTP writing of this trial. The following data from 1381-0001 has been included in the calculations for the tables given below: [redacted]

Since this data will be included in all BLRM analyses, the prior probabilities given in Table 7: 2 and Table 7: 3 are not used in practice but only the ones shown in the below tables.

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Table 7: 4 Prior probabilities of DLTs in Arm A (taking into account data from 1381-0001)

[redacted]

Table 7: 5 Prior probabilities of DLTs in Arm B (taking into account data from 1381-0001)

[redacted]

The BLRM-recommended dose combination for the next cohort is the level with the highest posterior probability of the DLT rate falling in the target interval [0.16, 0.33) among the doses or dose combinations fulfilling the EWOC principle. Per EWOC it should be unlikely (<25% posterior probability) that the DLT rate at the dose combination will exceed 0.33. However, the maximum allowable dose increment for the subsequent cohort will be no more than 100% for each drug.

The MTD may be considered reached in each arm separately if all of the following criteria are fulfilled:

- Next recommended dose by the BLRM = current dose.

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- At least 12 patients have been treated in the specific arm.

And at least one of the following criteria is fulfilled:

- The posterior probability of the true DLT rate in the target interval [0.16 – 0.33) of the MTD is above 0.50, OR
- At least 6 patients have been treated at the MTD.

A detailed evaluation of the model using hypothetical data scenarios and operating characteristics is provided in the statistical appendix (Section 10.5).

The dose finding part of the trial will be analysed once using the hierarchical model described above. A sensitivity analysis of the dose finding part will consist of separate analyses of each dose finding arm using weakly informative priors for each arm.

7.1 NULL AND ALTERNATIVE HYPOTHESES

No confirmatory testing is performed and hence no null and alternative hypotheses are defined. A justification of the sample size is provided in Section 7.5.

7.2 PLANNED ANALYSES

7.2.1 General considerations

For the determination of the MTD, only MTD evaluable patients will be considered. For the analysis of all other endpoints, all patients in the treated set (i.e. patients treated with at least one dose of trial medication) will be included in the analysis. Analyses will in general be performed by initial treatment, with the exception of patients who cross over from Arm A to Arm B. These patients will be analysed as part of Arm A as long as they are treated with monotherapy and as part of Arm B when they are treated with combination therapy.

More details and all other patient analysis sets will be defined in the Trial Statistical Analysis Plan (TSAP).

No per protocol set will be used in the analysis. However, important protocol deviations will be summarized.

7.2.2 Primary endpoint analyses

In order to identify the MTD, the number of evaluable patients with DLTs during the MTD evaluation period at each dose level in each arm must be presented. Replaced patients will be excluded from the determination of MTD.

For Arm A and B, the main analysis of the MTD will use the joint 5-parameter BLRM model described above using DLT data from the MTD evaluation period. For this analysis, cross-over patients will only be included while being treated with BI 1387446 monotherapy in Arm A.

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The following sensitivity analyses for the analysis of the MTD will be performed to support the determination of the RD-P2:

- Separate BLRMs will be used for each escalation arm using all DLT data, not only DLT data from the MTD evaluation period
- The joint BRLM will be evaluated using all DLT data, not only DLT data from the MTD evaluation period

The sensitivity analyses will include all treated patients, including 'backfill' patients and cross-over patients. More details on sensitivity analyses will be specified in the TSAP.

7.2.3 Secondary endpoint analyses

The OR based on itRECIST criteria (i.e. including injected and non-injected lesions) will be analysed descriptively in terms of OR rate, defined as the proportion of patients with best overall response of CR or PR. Best percentage change from baseline in size of non-injected target lesions and Best percentage change from baseline in size of injected target lesions will be analysed using descriptive statistics as well as waterfall plots.

The secondary endpoints will be displayed for each escalation arm separately.

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[redacted]

7.2.5 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and 90 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 90 days after the last dose of trial medication. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA) at database lock.

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

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

Other safety analyses (AESIs, centrally evaluated ECG, etc.) will be specified in detail in the TSAP.

[redacted]

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7.2.7 Interim Analyses

No formal interim analysis is planned. The Sponsor will continuously monitor the safety. The dose escalation design foresees that the sponsor and the SMC perform regular safety evaluations. These evaluations will be unblinded to dose.

Pharmacokinetics:
No formal interim analysis is planned. Exploratory PK analysis of BI 1387446 and ezabenlimab (BI 754091) and PK - biomarker analysis might be performed at appropriate time points. The Trial Pharmacokineticist will receive the bioanalytical results from the Trial Bioanalyst. The exploratory analysis will provide individual and geometric mean plasma concentration-time profiles and might include PK parameters of drug exposure such as an appropriate AUC and C_{max}. No inferential statistical analysis will be performed on these data. No formal report(s) will be written.

7.3 HANDLING OF MISSING DATA

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

For details of handling of missing PK data refer to Appendix 10.4.

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7.4 RANDOMISATION

No randomisation will be performed in this trial. Patients will be assigned to escalation arms as described in Section 3.1.1.

7.5 DETERMINATION OF SAMPLE SIZE

No formal statistical power calculations to determine the sample size were performed for this trial.

For the dose escalation part, in Arm A and B, approximately 78 patients are expected to be enrolled based on the number of dose levels that are planned to be tested. That is, the planned number of patients for the individual treatment arms is approximately: 34 patients for Arm A and 44 patients for Arm B.

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 Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU directive 2001/20/EC / EU regulation 536/2014 and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as “protocol deviation”.

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

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

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

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB / Independent Ethics Committee

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(IEC and CA according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the Investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative."
The patient must be given sufficient time to consider participation in the trial. The Investigator or delegate obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The Investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.
The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

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

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

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

8.3 RECORDS

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

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8.3.1 Source documents

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

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

Copies of tumour assessment scans will be collected by the sponsor for later Radiomics assessment. This could include CT/MRI 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. Before sending or uploading those copies, the Investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents before sending them to the sponsor.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.
For the CRF, data must be derived from source documents, for example:

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

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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 eCRF and are considered Part of the ISF.

8.3.2 Direct access to source data and documents

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

In the event of force majeure or other disrupting circumstances (e.g. pandemic, war, please see Section 6), site access may be restricted thus limiting the ability to perform standard site monitoring activities on site such as on-site source data review and source data verification. Therefore, some of these activities may be performed remotely or replaced by centralized monitoring to the extent possible, based on a documented risk assessment and in alignment with local regulations.

8.3.3 Storage period of records

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

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

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

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

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

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

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

8.6 TRIAL MILESTONES

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

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

The "**Last patient last visit primary endpoint**" (LPLVPE) date is defined as the date on which the last patient finalised the first cycle and underwent echocardiogram/MUGA scan on Day 1 of Cycle 2 for MTD assessment in Arm A or Arm B.
The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual Investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site.
Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

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

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Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.
The IEC / CA in each participating EU member state will be notified about the trial milestones according to the respective laws.
A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.
The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

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

Safety Monitoring Committee
The Safety Monitoring Committee (SMC) will be composed of Investigators from participating investigational sites and representatives from the Sponsor:

- BI Clinical Program Lead
- BI Clinical Trial Lead
- BI Statistician
- BI Pharmacovigilance Representative
- All Investigators participating in the clinical trial
- Guests may be invited as appropriate, e.g. interventional radiologists from participating investigational sites

The SMC will convene for all dose escalation decisions. For decision making during dose escalation, the following members need to attend the meeting:

- BI CPL or appropriately qualified delegate
- Investigators or appropriately qualified delegate involved in the treatment of patients in the respective dose cohort

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

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

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

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

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

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

Vendors for IRT and central ECG will be used in this trial. Details will be provided in the IRT Manual and ECG manual, available in the ISF.

External laboratory services will be used in this trial. Details will be provided in the Laboratory Manuals, available in the ISF.

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10. APPENDICES

10.1 IMMUNE-RELATED ADVERSE EVENTS

10.1.1 Immune related adverse events of special interest

Table 10.1.1: 1 Immune-related adverse events of special interest

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

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Table 10.1.1: 1 Immune-related adverse events of special interest (cont.)

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

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Table 10.1.1: 1 Immune-related adverse events of special interest (cont.)

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

10.1.2 Management of immune-related adverse events

Regarding 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,

- For irAEs listed below, the guidance from Section 4.1.4.3 is not considered applicable stating that only if a causal relationship to one trial drug can be unequivocally established, the other trial drug may be continued. On combination treatment both

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drugs (BI 1387446 and ezabenlimab (BI 754091)) will be stopped, paused, or re-exposed together.

- Ezabenlimab (BI 754091) and BI 1387446 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). A dose reduction of BI 1387446 may be considered, but is not required for the first occurrence of an irAE grade 1.
- For most Grade 2 irAEs, ezabenlimab (BI 754091) and BI 1387446 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. A dose reduction of BI 1387446 should be considered, but is not required for the first occurrence of an irAE, but is mandatory if the same irAE recurs upon rechallenge with BI 1387446.
- For Grade 3 irAEs, ezabenlimab (BI 754091) and BI 1387446 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 ezabenlimab (BI 754091) and BI 1387446 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. BI 1387446 should be administered at a reduced dose.
- Most Grade 4 irAEs warrant permanent discontinuation of ezabenlimab (BI 754091) and BI 1387446.
- 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. A dose reduction of BI 1387446 may be considered, but is not required for the first occurrence of an endocrine irAE.

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

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

Ezabenlimab (BI 754091) and BI 1387446 should be permanently discontinued for immune related

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- 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 >10x ULN if baseline was >2.5-5x ULN] or total bilirubin >3x ULN [or >5x ULN if baseline was >1.5-3x 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-haemolytic anaemia 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.

For BI 1387446, up to 2 dose reductions are allowed if the treatment pause due to an AE is ≤12 weeks and the re exposure is considered clinically indicated by the Investigator. Dose adjustment of ezabenlimab (BI 754091) besides interrupting or permanently discontinuing ezabenlimab (BI 754091) are not allowed (see Section 4.1.4.3).

In rare situations when benefit and risk assessment is considered positive for a patient to continue ezabenlimab (BI 754091) and/or BI 1387446 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 ezabenlimab (BI 754091) and BI 1387446 until improvement or resolution; ezabenlimab (BI 754091) and BI 1387446 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 ezabenlimab (BI 754091) and BI 1387446 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 ezabenlimab (BI 754091) and BI 1387446 and immediately initiate treatment according to available guidelines.

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Diarrhoea/Colitis:

- For Grade 1 diarrhoea/colitis, consider interruption of ezabenlimab (BI 754091) and BI 1387446 therapy.
- For Grade 2 diarrhoea/colitis, withhold ezabenlimab (BI 754091) and BI 1387446 until patient's symptoms recovered to grade 1 or less. Consider initiating treatment with steroids.
- For Grade 3 diarrhoea/colitis, withhold ezabenlimab (BI 754091) and BI 1387446 and immediately start treatment (steroids, non-steroidal immunosuppressants) as per available guidelines.
- For Grade 4 diarrhoea/colitis, permanently discontinue ezabenlimab (BI 754091) and BI 1387446 and immediately commence adequate therapy (e.g. i.v. corticosteroids).
- For Grade 1-3 colitis, restart of ezabenlimab (BI 754091) and BI 1387446 may be considered once symptoms improve to Grade 1 or less without need for continued steroids. After careful benefit risk assessment, ezabenlimab (BI 754091) and BI 1387446 may also be restarted after recovery to grade 1 or less, and on corticosteroid ≤ 10 mg per day
- Ezabenlimab (BI 754091) and BI 1387446 should be permanently discontinued for recurrent diarrhoea/colitis of any grade.

Diabetes

- Consider withholding ezabenlimab (BI 754091) and BI 1387446 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
  - Ezabenlimab (BI 754091) and BI 1387446 should be withheld until glucose level is controlled with insulin with no sign of ketoacidosis.
- Ezabenlimab (BI 754091) and BI 1387446 may be restarted once insulin therapy has established stable glycemic control

Thyroid disorders:

Thyroid disorders can occur at any time during treatment. Monitor subjects for changes in thyroid function (at screening and in regular intervals during treatment as indicated in Flow Chart and Section 5.2.3, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. For diagnosed thyroid disorders, thyroid hormone supplementation and monitoring should occur as per available guidelines

- Primary hypothyroidism:
  - For Grade 1 hypothyroidism, ezabenlimab (BI 754091) and BI 1387446 may be continued, with regular monitoring of thyroid values.
  - For Grade 2 hypothyroidism, consider withholding ezabenlimab (BI 754091) and BI 1387446
  - For Grade 3-4 hypothyroidism, withhold ezabenlimab (BI 754091) and BI 1387446, consider admission and IV therapy, especially in case of myxedema

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- Ezabenlimab (BI 754091) and BI 1387446 may be restarted once symptoms resolve to baseline with appropriate thyroid hormone supplementation

- Primary hyperthyroidism
  - For Grade 1 hyperthyroidism, ezabenlimab (BI 754091) and BI 1387446 may be continued, with regular monitoring of thyroid values.
  - For Grade 2 hyperthyroidism, consider withholding ezabenlimab (BI 754091) and BI 1387446, initiate therapy as per available guidelines.
  - For Grade 3-4 hyperthyroidism, withhold ezabenlimab (BI 754091) and BI 1387446. Consider hospitalization, especially in case of thyrotoxicosis.
  - Ezabenlimab (BI 754091) and BI 1387446 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 ezabenlimab (BI 754091) and BI 1387446 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 ezabenlimab (BI 754091) and BI 1387446 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 ezabenlimab (BI 754091) and BI 1387446 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 (Section 5.2.7.1.4).
- For Grade 1 hepatitis (elevated AST/ALT < 3x ULN and/or total bilirubin <1.5x ULN), ezabenlimab (BI 754091) and BI 1387446 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), ezabenlimab (BI 754091) and BI 1387446 should be suspended. Monitoring of liver values every 3 days is recommended. Initiate treatment according to available guidelines. Restarting of ezabenlimab (BI 754091) and BI 1387446 may be considered upon recovery to grade 1 or less, and on corticosteroid ≤ 10 mg per day.

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- For Grade 3 or higher hepatitis, ezabenlimab (BI 754091) and BI 1387446 have to be permanently discontinued.

For eligible patients with elevated screening/baseline AST/ALT (>2.5-5x ULN or bilirubin >1.5-3x ULN):

- Carefully monitor patients for signs of autoimmune hepatitis.
- In case of increased levels of AST/ALT >2x baseline to ≤10x ULN and/or bilirubin >2x baseline to ≤5x ULN, ezabenlimab (BI 754091) and BI 1387446 should be suspended. Monitoring of liver values every 3 days or more frequently, if clinically indicated, is recommended. Restarting of ezabenlimab (BI 754091) and BI 1387446 may be considered upon recovery to baseline or less, and on corticosteroid ≤ 10 mg per day.
- In case of increased AST/ALT >10x ULN and/or bilirubin >5x ULN, ezabenlimab (BI 754091) and BI 1387446 have to be permanently discontinued. Initiate treatment as per guidelines

Nephritis:

- For Grade 1 nephritis, consider temporarily withholding ezabenlimab (BI 754091) and BI 1387446.
- For Grade 2 nephritis, withhold ezabenlimab (BI 754091) and BI 1387446. Consult nephrology. Initiate treatment according to guidelines. In case of no improvement or worsening, permanently discontinue ezabenlimab (BI 754091) and BI 1387446. Ezabenlimab (BI 754091) and BI 1387446 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 ezabenlimab (BI 754091) and BI 1387446. 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.
- Ezabenlimab (BI 754091) and BI 1387446should also be permanently discontinued for recurrent nephritis grade 2 or higher.

Rash

- For Grade 1 rash, continue ezabenlimab (BI 754091) and BI 1387446. Initiate topical treatment.
- For Grade 2 rash, ezabenlimab (BI 754091) and BI 1387446may be continued, in case of no improvement upon weekly monitoring, consider interruption of ezabenlimab (BI 754091) and BI 1387446 therapy. Treat topically, add systemic corticosteroid therapies as clinically appropriate.
- For Grade 3 rash, withhold ezabenlimab (BI 754091) and BI 1387446. 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 ezabenlimab (BI 754091) and BI 1387446 might be restarted, especially in case no alternative anti-neoplastic therapy is available.
- For Grade 4 rash, ezabenlimab (BI 754091) and BI 1387446 should be permanently discontinued.

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- Ezabenlimab (BI 754091) and BI 1387446 should also be discontinued for recurrent rash grade 3 or higher.

Bullous dermatosis
- For Grade 1 bullous dermatosis, use local wound care and observation. Ezabenlimab (BI 754091) and BI 1387446 can be continued.
- For Grade 2 bullous dermatosis, withhold ezabenlimab (BI 754091) and BI 1387446. Administer topical therapy, add systemic therapy as clinically adequate.
- For Grade 3 bullous dermatosis, withhold ezabenlimab (BI 754091) and BI 1387446, initiate topical and systemic therapy as per available guidelines. Upon recovery to grade 1 or less, and on corticosteroid ≤ 10 mg per day, restarting of ezabenlimab (BI 754091) and BI 1387446 may be considered after dermatology consultation.
- For Grade 4 bullous dermatosis, permanently discontinue ezabenlimab (BI 754091) and BI 1387446.

Severe cutaneous adverse reaction (SCAR), Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN)
- For Grade 2 events, withhold ezabenlimab (BI 754091) and BI 1387446, initiate treatment as per available guidelines. Closely monitor for improvement or worsening.
- For Grade 3 events, withhold ezabenlimab (BI 754091) and BI 1387446. 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 ezabenlimab (BI 754091) and BI 1387446, 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, ezabenlimab (BI 754091) and BI 1387446 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
- Ezabenlimab (BI 754091) and BI 1387446 should be permanently discontinued for any grade.

Myasthenia gravis
- For Grade 2 myasthenia gravis, withhold ezabenlimab (BI 754091) and BI 1387446,
- For Grade 3 or 4 myasthenia gravis, permanently discontinue ezabenlimab (BI 754091) and BI 1387446

Guillain Barré Syndrome (GBS)
- Discontinue ezabenlimab (BI 754091) and BI 1387446permanently for any grade GBS.

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Transverse Myelitis

- Discontinue ezabenlimab (BI 754091) and BI 1387446 permanently for any grade transverse myelitis.

Peripheral neuropathy, autonomic neuropathy

- For Grade 1 events, may continue ezabenlimab (BI 754091) and BI 1387446, but with low threshold to discontinue while monitoring closely for worsening.
- For Grade 2 events, withhold ezabenlimab (BI 754091) and BI 1387446 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 ezabenlimab (BI 754091) and BI 1387446.

Inflammatory Arthritis

- For Grade 1 arthritis, ezabenlimab (BI 754091) and BI 1387446 can be continued. Administer analgetic treatment (acetaminophen, NSAID).
- For Grade 2-4 arthritis, withhold ezabenlimab (BI 754091) and BI 1387446. Initiate treatment as per available guidelines, cave regarding reactivation of tuberculosis/opportunistic infections in case of prolonged immunosuppressive/disease modifying anti-rheumatic drugs (DMARD) therapy.

Ezabenlimab (BI 754091) and BI 1387446 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, ezabenlimab (BI 754091) and BI 1387446 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 ezabenlimab (BI 754091) and BI 1387446, discontinue permanently in patients with objective findings (elevated enzymes, abnormal EMG, abnormal muscle MRI or biopsy). Initiate therapy as per available guidelines. Resuming ezabenlimab (BI 754091) and BI 1387446 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 ezabenlimab (BI 754091) and BI 1387446.
- Ezabenlimab (BI 754091) and BI 1387446 should be permanently discontinued if there is any evidence of myocardial involvement.

Polymyalgia-like syndrome

- For Grade 1 event, ezabenlimab (BI 754091) and BI 1387446 can be continued.
- For Grade 2 event, withhold ezabenlimab (BI 754091) and BI 1387446 and promptly initiate adequate therapy. If no improvement, treat as grade 3.
- For Grade 3 or G4 event, withhold ezabenlimab (BI 754091) and BI 1387446, promptly initiate adequate therapy Rheumatology consultancy is highly recommended.

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Ezabenlimab (BI 754091) and BI 1387446 may be resumed after careful assessment of risks and benefits, rheumatology consultancy highly recommended prior to reinitiation. Ezabenlimab (BI 754091) and BI 1387446 may only be re-started upon recovery to grade 1 or less and on corticosteroid ≤ 10 mg per day.

Myocarditis

- Discontinue ezabenlimab (BI 754091) and BI 1387446 permanently for any grade of myocarditis.

Uveitis/Iritis, Episcleritis

- For Grade 1 events, treatment with ezabenlimab (BI 754091) and BI 1387446 can continue. Treat topically as needed.
- For Grade 2 events, withhold therapy with ezabenlimab (BI 754091) and BI 1387446, urgent ophthalmology referral is recommended. Initiate topical treatment, consider systemic therapy if needed. Restart of ezabenlimab (BI 754091) and BI 1387446 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 ezabenlimab (BI 754091) and BI 1387446 therapy.
- For Grade 3 or 4 events, permanently discontinue ezabenlimab (BI 754091) and BI 1387446 therapy. Seek emergent ophthalmology consultation. Initiate adequate local and systemic treatment.

Autoimmune-haemolytic anaemia (AIHA)

- For Grade 1 AIHA, continue treatment with ezabenlimab (BI 754091) and BI 1387446. Close follow-up of anaemia and other lab values.
- For Grade 2-4 AIHA, discontinue ezabenlimab (BI 754091) and BI 1387446 permanently. Initiate systemic therapy as per guideline. Consult Haematology.

Acquired thrombotic thrombocytopenic purpura (TTP), haemolytic uremic syndrome.

Timely recognition upon suggestive findings is essential, timely/immediate involvement of haematology consultancy may be beneficial.

- For any grade TTP, permanently discontinue ezabenlimab (BI 754091) and BI 1387446.
- For HUS (TTP excluded), withhold ezabenlimab (BI 754091) and BI 1387446 for grade 1 and grade 2, provide supportive care. Upon full recovery, ezabenlimab (BI 754091) and BI 1387446 may be restarted after carefully weighing of risks and benefits.
- For Grade 3 or Grade 4 HUS, discontinue ezabenlimab (BI 754091) and BI 1387446 permanently.

Immune thrombocytopenia (ITP)

- In case of Grade 1 ITP, ezabenlimab (BI 754091) and BI 1387446 can be continued.
- For Grade 2 or Grade 3 ITP, withhold ezabenlimab (BI 754091) and BI 1387446 and initiate systemic therapy. Ezabenlimab (BI 754091) and BI 1387446 may be restarted upon resolution to at least grade 1.
- For Grade 4 ITP, permanently discontinue ezabenlimab (BI 754091) and BI 1387446.

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Infusion related reactions (IRRs):
Signs and symptoms of IRRs usually develop during or shortly after ezabenlimab (BI 754091) infusion and generally resolve completely within 24 hours of completion of infusion. If symptoms develop during infusion, they may be managed with slowing or transient interruption of infusion (Section 4.1.4.3).

10.2 MANAGEMENT OF CRS

CRS grading should be performed according to ASBMT consensus grading [R19-0309].

Treatment of CRS should be based on published recommendations [R19-0310, R19-0311], the recommendations in Table 10.2: 1 should be considered by the Investigator as guidance.

Table 10.2: 1 CRS grading, treatment and management of trial drugs

Grade	Definition of grade	Recommendation for treatment of CRS	Management of trial drugs
Grade 1	Fever >38°C without hypotension or hypoxia	- symptomatic management of fever with acetaminophen or ibuprofen unless contraindicated - maintenance fluids for hydration - symptomatic management of constitutional symptoms or organ toxicities - for persistent and refractory fever (>3 days) in absence of infection consider corticosteroids	- stop administration of BI 1387446 and ezabenlimab (BI 754091) if not fully administered - continue treatment with the subsequent administration of BI 1387446 and ezabenlimab (BI 754091) provided that all symptoms have completely resolved for at least 48 hours - delay/skip the subsequent administration if needed to ensure that all symptoms have completely resolved for at least 48 hours

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Table 10.2: 1 CRS grading, treatment and management of trial drugs (cont.)

Grade	Definition of grade	Recommendation for treatment of CRS	Management of trial drugs
Grade 2	Fever >38°C with either hypotension not requiring vasopressors and/or hypoxia requiring low-flow nasal cannula or blow-by	- manage fever and constitutional symptoms as in grade 1 - supplemental oxygen as needed - IV fluid bolus of normal saline (500-1000 mL) - consider second IV fluid bolus if systolic blood pressure remains <90 mmHg - dexamethasone 10 mg IV every 6h - if hypotension persists after 2 fluid boluses and dexamethasone, start vasopressors and consider transfer to ICU - anti-IL6-therapy, e.g. tocilizumab or siltuximab, may be considered - symptomatic management of organ toxicities as per standard guidelines	- stop administration of BI 1387446 and ezabenlimab (BI 754091) if not fully administered - continue treatment with the subsequent administration of BI 1387446 and ezabenlimab (BI 754091) provided that all symptoms have completely resolved for at least 48 hours - delay/skip the subsequent administration if needed to ensure that all symptoms have completely resolved for at least 48 hours - at the subsequent administration of the respective drug, patients should be under close surveillance of appropriate duration
Grade 3	Fever >38°C with either hypotension requiring one vasopressor with or without vasopressin and/or hypoxia requiring high-flow nasal cannula, facemask, non-rebreather mask or Venturi mask	- IV fluid boluses and vasopressors as needed - transfer to ICU, initiate hemodynamic monitoring - dexamethasone 10 mg IV every 6h, if refractory increase to 20 mg IV every 6h - supplemental oxygen as needed - manage fever and constitutional symptoms as indicated for grade 1 - anti-IL6-therapy, e.g. tocilizumab or siltuximab, may be considered - symptomatic management of organ toxicities as per standard guidelines	- stop administration of BI 1387446 and ezabenlimab (BI 754091) if not fully administered - if CRS is considered unequivocally related to BI 1387446: do not re-expose the patient to BI 1387446, ezabenlimab (BI 754091) may be continued as per protocol once CRS has completely resolved for at least 7 days - if CRS is unequivocally related to ezabenlimab (BI 754091): permanently discontinue ezabenlimab (BI 754091) - If there is uncertainty about causality assessment: permanently discontinue BI 1387446 and ezabenlimab (BI 754091) -

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Table 10.2: 1 CRS grading, treatment and management of trial drugs (cont.)

Grade	Definition of grade	Recommendation for treatment of CRS	Management of trial drugs
Grade 4	Fever >38°C with either hypotension requiring multiple vasopressors (excl. vasopressin) and/or hypoxia requiring positive pressure, e.g. continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), intubation and mechanical ventilation	- ICU transfer, IV fluids, vasopressors and hemodynamic monitoring as indicated for grade 3 - manage fever and constitutional symptoms as indicated for grade 1 - methylprednisolone 1 g/day IV - respiratory support including mechanical ventilation - anti-IL6-therapy, e.g. tocilizumab or siltuximab, may be considered - symptomatic management of organ toxicities as per standard guidelines	- same as for grade 3

10.3 TUMOUR ASSESSMENTS

Tumour assessments will be performed according to Response criteria for intratumoural immunotherapy in solid tumours (itRECIST) (R20-2734).

At baseline, tumour lesions and lymph nodes will first be categorised as measurable or non-measurable. Measurable lesions are then classified as target (selected to be observed quantitatively) or non-target (selected to be observed qualitatively), and the decision about which lesion is to be injected is made. In this trial, a lesion selected for injection must be measurable (see Section 10.3.1 for details).

At baseline, one lesion projected for injection should be classified as target injected (T-I), only in exceptional cases, two lesions may be projected for injection and thus be classified as T-I (refer to Section 4.1.4.1). Up to 5 lesions can be classified as target non-injected (T-NI). All lesions not chosen as target are observed qualitatively as non-target. See Figure 10.3: 1 for details on the classifications of lesions at baseline. As in this trial, a lesion selected for injection must be measurable, lesions selected for injection at baseline can only be target (refer to Section 4.1.4.1).

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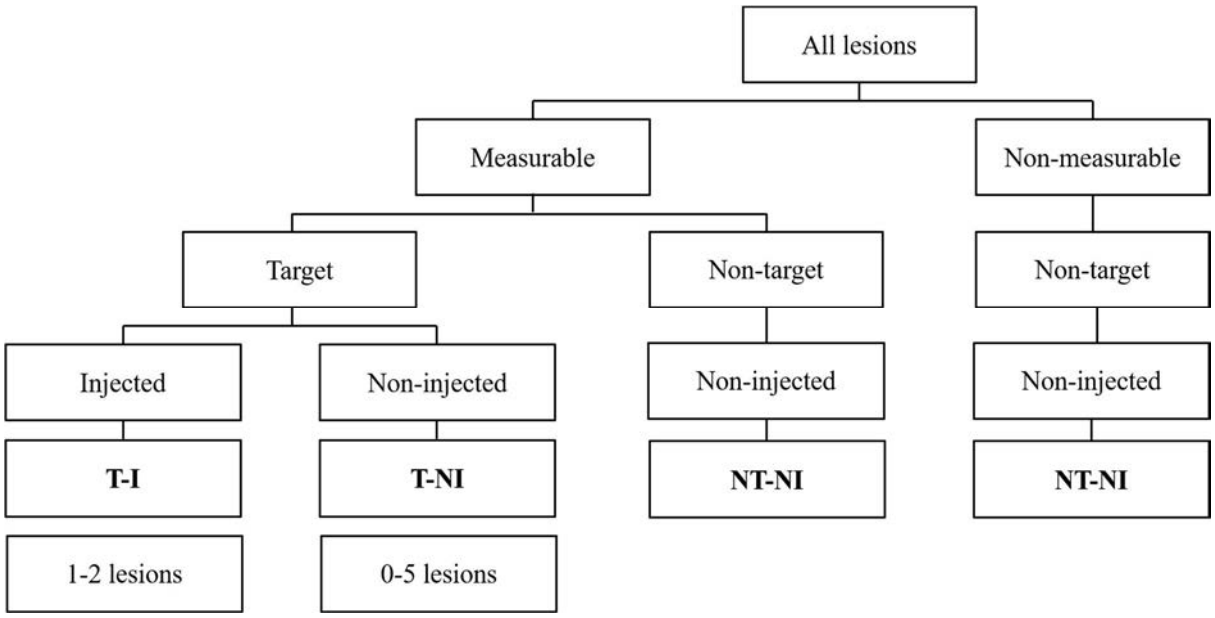

Figure 10.3: 1 Classification of lesions at baseline

Lesions designated as T-I will be used to evaluate the injected lesion response. Lesions designated as T-NI should remain non-injected for as long as possible to allow assessment of the maximal non-injected lesion response. However, in the case that there is no other lesion available for injection, or the T-NI lesions are enlarging, T-NI lesions may be injected and recategorized to T-I, if they meet the criteria for injection.

Similarly to T-NI lesions, also NT-NI lesions may be injected and recategorized to NT-I, if they meet the criteria for injection (in particular if they are measurable according to Section 10.3.1). However, even though measurable, these lesions will contribute to the overall response only with their qualitative assessment.

A sum of diameters (SOD; longest diameters for extranodal lesions and short axis for lymph nodes) will be calculated for all target lesions combined and separately for T-I and T-NI-lesions.

The overall response for each visit will be based on the changes in the SOD of all target lesions together (SOD of T-I and T-NI combined versus combined SOD at baseline and at nadir), the qualitative assessment of all non-target lesions, and the evaluation for possible new lesions. The same response categories and their logical combination as with RECIST 1.1 will be used. The following overall response categories may be assigned: Complete Response (itCR), Partial Response (itPR), Stable Disease (itSD), Unconfirmed Progressive Disease (itUPD), and Confirmed Progressive Disease (itCPD). See Figure 10.3: 2 for details.

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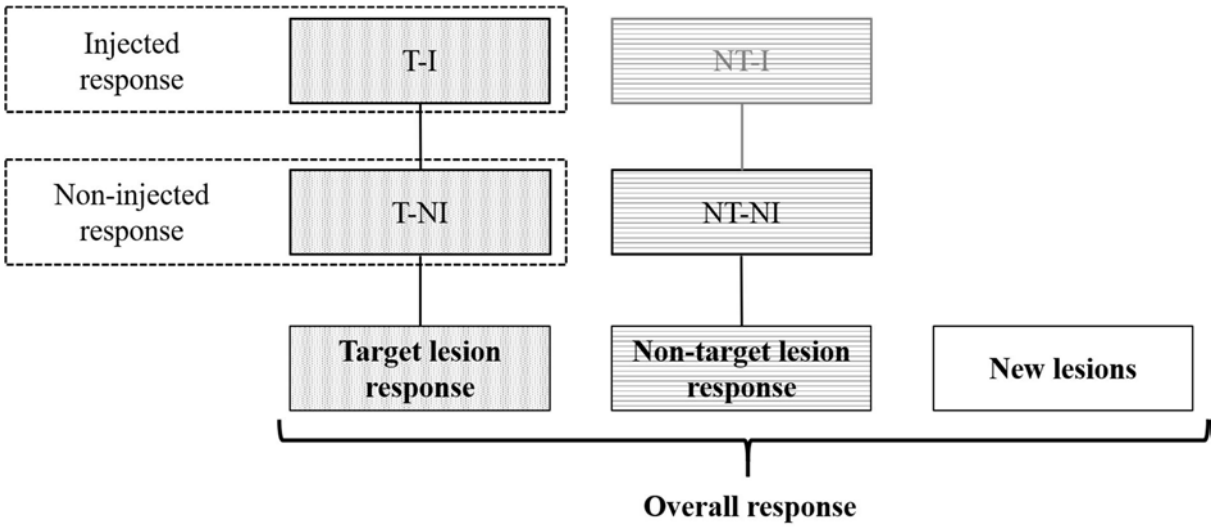

Figure 10.3: 2 Overall response by itRECIST

For the purpose of this trial, assessment of individual lesions, injected and non-injected, as well as the overall response assessment for each visit will be reported in the eCRF, but the injected and non-injected response (including the quantitative best percentage change from baseline in size of injected and non-injected lesions) will only be derived retrospectively for the final analysis. Both, the non-injected lesion response and the injected lesion response, will be based on the respective target lesions' SODs (See Section 7 for details).

10.3.1 Injected lesions

At screening the Investigator will select a tumour lesion which is projected to be injected. All injected tumour lesions need to be measurable as per RECIST 1.1, i.e. the longest diameter must have a minimum size of

- 10 mm if measured by CT scan or MRI (lymph nodes have to be at least 15mm in short axis)
- 20 mm by chest X-ray.

The following modifications to RECIST 1.1 apply according to itRECIST:

- Ultrasound is acceptable to guide injection into any lesion location for which ultrasound guidance is indicated. For tumour assessments ultrasound may be used for measurement of lesions classified as superficial, e.g. soft tissue lesions, which cannot be effectively imaged by CT scan. However, ultrasound is not acceptable for tumour assessments of deep/visceral lesions which can be measured on CT or MRI scans. The longest diameter of a non-visible lesion measured by ultrasound must have a minimum size of 10 mm.
- All visible tumour lesions potentially suitable for injection need to be assessed at baseline by digital photography with the use of a caliper/digital scale. The longest diameter of a visible lesion has to be at least 1 cm to qualify for injection. The injected lesion has to be measured and documented by digital photography with caliper/digital scale at each tumour assessment timepoint. If more than one visible

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lesion is present, non-injected visible lesions may be selected as target lesions if the longest diameter meets the minimum criteria as required per RECIST 1.1 (see Section 10.3.2.1).

One measurable lesion will be selected for injection at baseline and classified as target injected (T-I) according to itRECIST. Only in exceptional cases, two lesions may be selected for injection and classified as T-I. Each lesion selected for injection will be unequivocally identified in the eCRF. Radiologic images as well as photographic images of visible lesions will be collected for central review. If available, additional information, e.g. screenshots or marks on imaging studies submitted for central review may be considered in addition. Visible tumour lesions, e.g. skin lesions, have to be documented by digital photography with the use of a caliper/digital scale.

Measurable lesions not pre-selected for injection at baseline can be re-categorized as injected lesions during the course of the trial if the decision is made to inject them after baseline assessment. In case different lesions are injected during the course of the trial, all injected lesions need to be identified at baseline or in retrospect on the imaging study or photodocumentation at baseline and captured in the eCRF.

Location of lesions will be classified as skin, other connective tissue, lymph node, liver, other organ.

10.3.2 Non-injected lesions

Photodocumentation for visible lesions as outlined in Section 10.3.1 and ultrasound for superficial lesions not measurable on CT may be used for the assessment of non-injected lesions too.

Optimal anatomic coverage of imaging studies should encompass all areas of known predilection for metastases in the disease under evaluation, and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

10.3.2.1 Target non-injected (T-NI) lesions

Measurable non-injected tumour lesions must be accurately measured in at least one dimension, the longest diameter in the plane of measurement is to be recorded with a minimum size of

- 10 mm by CT scan,
- 10 mm by caliper measurement by clinical exam or ultrasound, or
- 20 mm by chest X-ray.

Malignant lymph nodes must be ≥15 mm in short axis.

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When more than one measurable non-injected lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at all tumour assessment timepoints indicated in the Flow Chart.

Preferably, a non-injected lesion which is selected for biopsy should not be classified as target non-injected lesion.

10.3.2.2 Non-target non-injected (NT-NI) lesions

Non-measurable non-injected lesions, e.g. malignant effusions, lymphangitic involvement of skin or lung, leptomeningeal disease, or measurable lesions not selected as target lesions will be captured as non-target lesions and qualitatively assessed at the tumour assessment timepoints indicated in the Flow Chart.

10.3.2.3 Confirmation of response

According to RECIST1.1, a CR or PR should be confirmed if possible at the subsequent planned scanning timepoint at least 4 weeks later.

10.4 PHARMACOKINETIC METHODS AND ANALYSES

Pharmacokinetic analysis

The exploratory parameters (refer to Section 5.3.1) will be calculated according to internal SOPs. All evaluable patients who received at least one dose of BI 1387446 or ezabenlimab (BI 754091) and provide at least one plasma concentration value will be included in the PK analysis. Patients who are considered as not evaluable will be listed with their individual plasma concentrations and individual PK parameters, and will be not included in descriptive statistics for plasma concentrations, PK parameters or other statistical assessment.

The following descriptive statistics will be calculated for all analyte concentrations as well as for all PK parameters: N, arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations.

Handling of missing data

Drug concentration - time profiles
Concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analysed), and BLQ (below the limit of quantification) will be ignored and not replaced by zero at any time point (applies also to the lag phase including the pre-dose value(s)).
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

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defined as the period between time 0 and the first time point with a concentration above the quantification limit. All other BLQ and NOP values of the profile will be ignored. Pharmacokinetic parameters which cannot be determined will be identified by "not calculated" (NC).

Every effort will be made to include all concentration data in an analysis. If not possible, a case to 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 CTR associated with an appropriate flag.

If the actual sampling time will not be recorded or will be 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).

10.5 STATISTICAL APPENDIX

A joint BLRM with overdose control will be used to guide dose escalation in Arms A and B of the trial. The model is introduced in Section 7, which also specifies the priors for the model. After patients in each cohort have completed at least one cycle of treatment, the prior distribution will be updated through No-U-Turn sampling procedures (Hamiltonian Monte Carlo, [R21-3791]) with the accumulated DLT data from the MTD evaluation period. Posterior probabilities for the rate of DLTs will be summarised from the joint BLRM for Arms A and B. Selection of the next dose in each arm 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. For simplicity reasons, a cohort size of 3 patients who are all evaluable starting at 50 µg (Arms A and B) is assumed for calculation of the operating characteristics.

In addition, recommendations of the next dose level in each arm by the joint BLRM with overdose control principle are also provided under various hypothetical outcome scenarios to show how it facilitates on-trial dose-escalation decisions (see Table 10.5: 1).

Hypothetical data scenarios

Hypothetical data scenarios are shown in Table 10.5: 1 for Arms A and B. These scenarios reflect potential on-trial data constellations and related escalation as allowed by the model and the 100% escalation limit. For each scenario and each arm, 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.

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For example, Scenario 1 represents the case where 2 patients have been treated at the starting dose of [redacted] Arm A and did not experience a DLT. In Arm B no patients have been treated yet in this scenario. Then, the BLRM would allow for an escalation up to [redacted] as the next dose in Arm A. Since escalation is only allowed up to [redacted] per protocol, the next dose to be tested in Arm A of the trial would be [redacted]

Similarly, Scenarios 4 and 7 represent cases where no patient in either arm has a DLT. In these cases, the model recommends escalating to higher doses. In some cases the recommended doses exceed the protocol specified margin given by the 100% escalation rule. The next tested dose in these scenarios will always be the dose given by the 100% rule.

Scenario 2 shows that if one of 2 patients treated with the starting dose level in Arm A has a DLT, the EWOC criterion does not allow any of the pre-specified dose levels. Doses lower than [redacted] could be chosen in practice if agreed between sponsor and SMC. In particular, starting Arm B at the intended dose level of [redacted] would not be allowed based on the overdose control of the BLRM.

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

Scenario 02 represents the case where one patient has been treated at the starting dose of [redacted] in Arm A and has experienced a DLT. Based on the BLRM the probability for overdosing at the current dose is 0.656 and the model does not allow treating further patients on 50 µg in Arm A.

In scenario 03, three patients were treated at [redacted] in Arm A of which only the first one experienced a DLT, i.e. no DLTs were observed in the additional two patients. In this scenario the model again does not allow any of the pre-specified dose levels, indicating that any DLT in the first cohort leads to recommended doses [redacted]

Only if none of the patients in the first cohort [redacted] experience DLT (Scenarios 04 and 4), the model allows escalation [redacted] While doses up [redacted] Arm A and [redacted] in Arm B would be allowed by the EWOC principle in Scenario 4, the recommended next dose in Arm A would be [redacted] (due to the maximum increment of 100%) and the starting dose in Arm B would be [redacted]

Scenario 05 follows scenario 04 and represents the case in which three patients were treated at the second dose level [redacted] in Arm A. One patient experienced a DLT. In this scenario, no escalation [redacted] is allowed, but further patients can be treated [redacted]

In scenario 06 the dose escalation has proceeded with another cohort of 3 patients [redacted] following the data observed in scenario 05. No DLTs have been observed with the additional 3 patients at the dose level [redacted] in Arm A. In this case, the model allows escalation to 200 µg in Arm A and also allows starting Arm B at the intended dose level [redacted]

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Scenarios 6 and 10 explicitly show the characteristics of the joint model. If DLTs are only observed in one of the three arms, escalation is also influenced in the other arms. For example in Scenario 10, although no DLTs are observed in Arm B, no escalation [redacted] is allowed by the overdose control implemented in the model since 3 of 6 patients in Arm A experienced DLTs [redacted] In Scenario 6, the DLTs that are observed in Arm B [redacted] result in de-escalation of the dose in Arm A [redacted] although in Arm A no DLTs have been observed.

Finally, Scenarios 13 and 14 illustrate cases where escalation has proceeded up to the highest dose [redacted] in Arm A and [redacted] in Arm B. In both Arms, this dose (combination) could be declared as MTD as it satisfies the conditions for MTD declaration specified in Section 7.

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Table 10.5: 1 Hypothetical data scenarios for Arms A and B

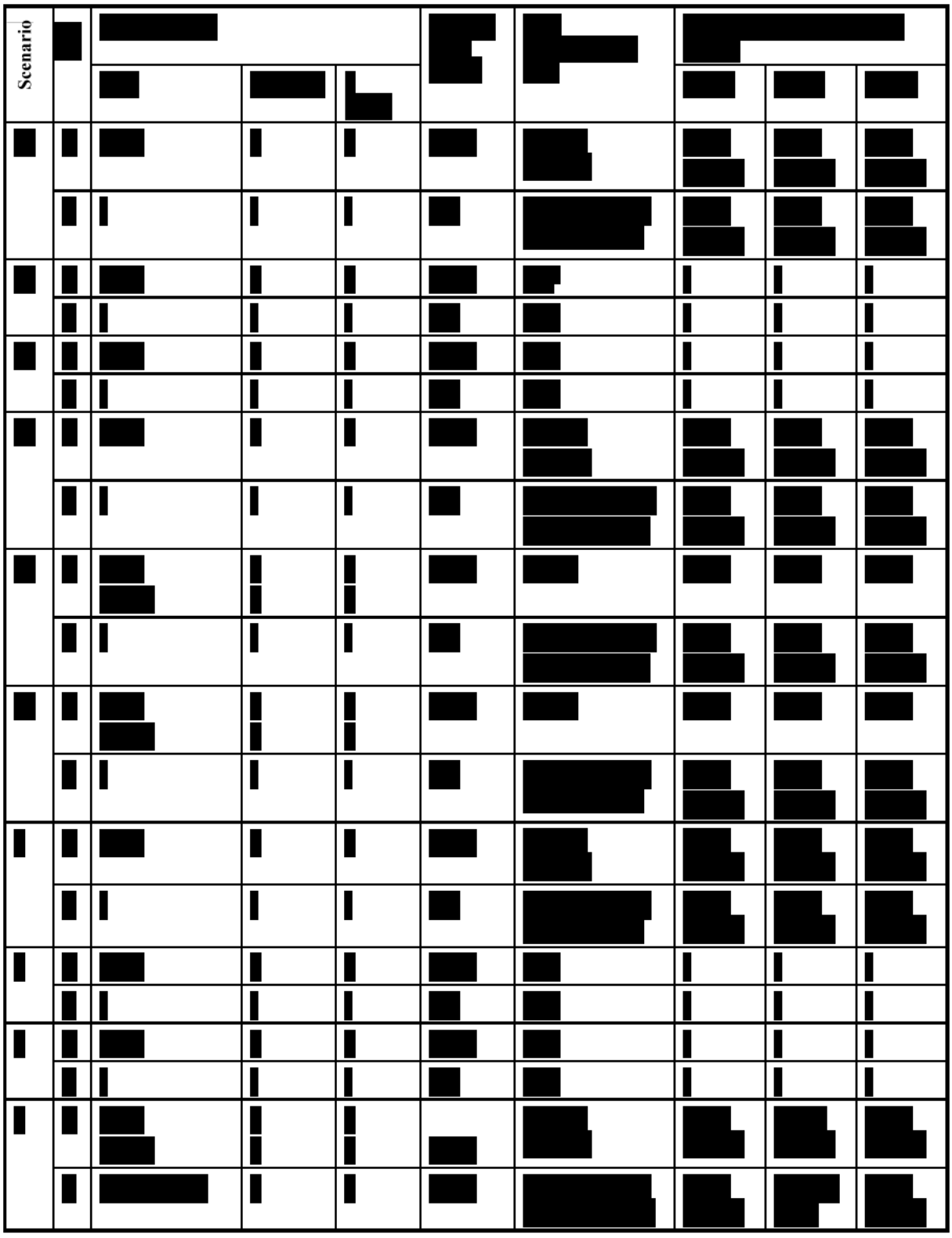

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Table 10.5: 1 Hypothetical data scenarios for Arms A and B (cont.)

Scenario	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]		
		[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Table 10.5: 1 Hypothetical data scenarios for Arms A and B (cont.)

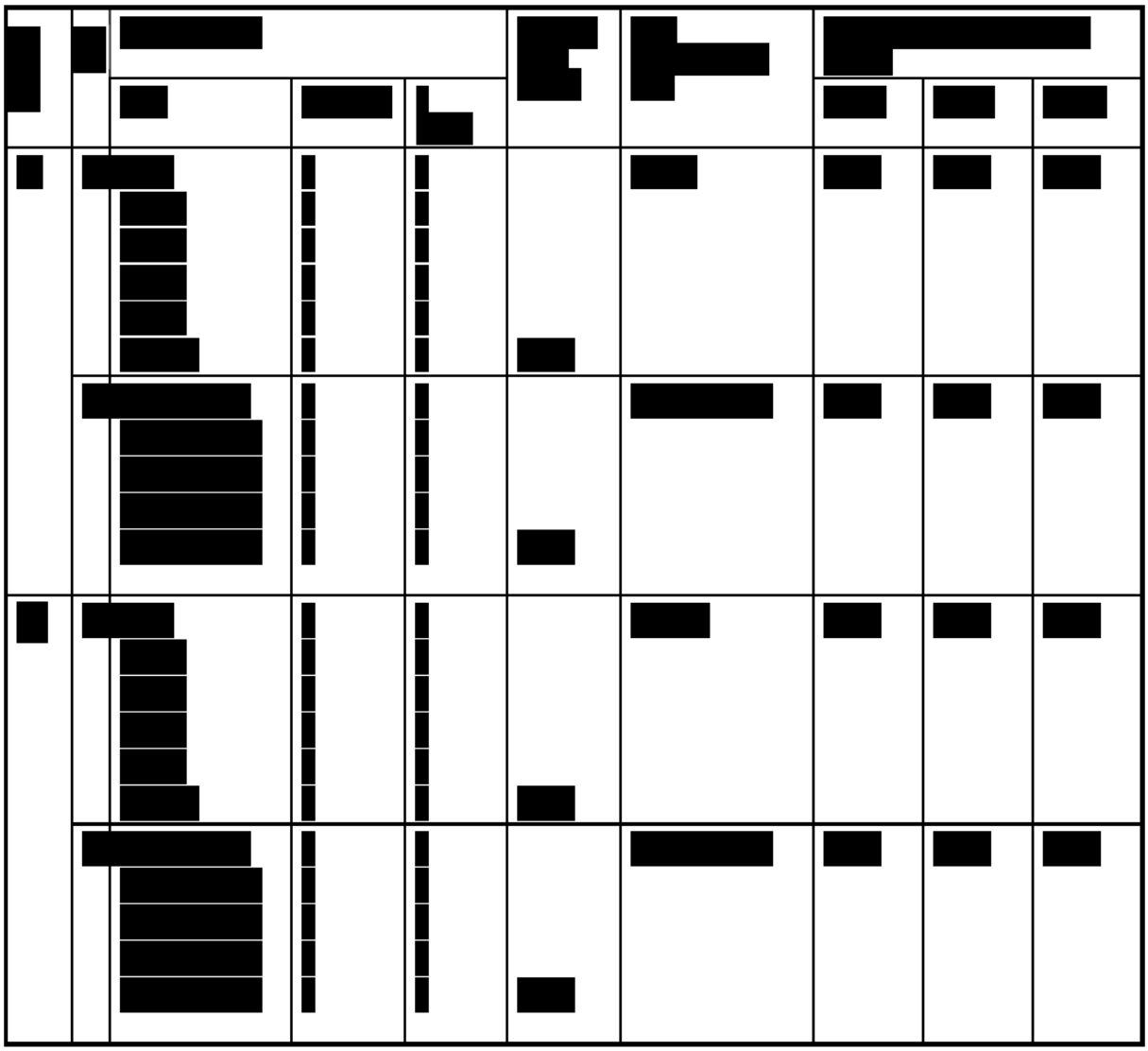

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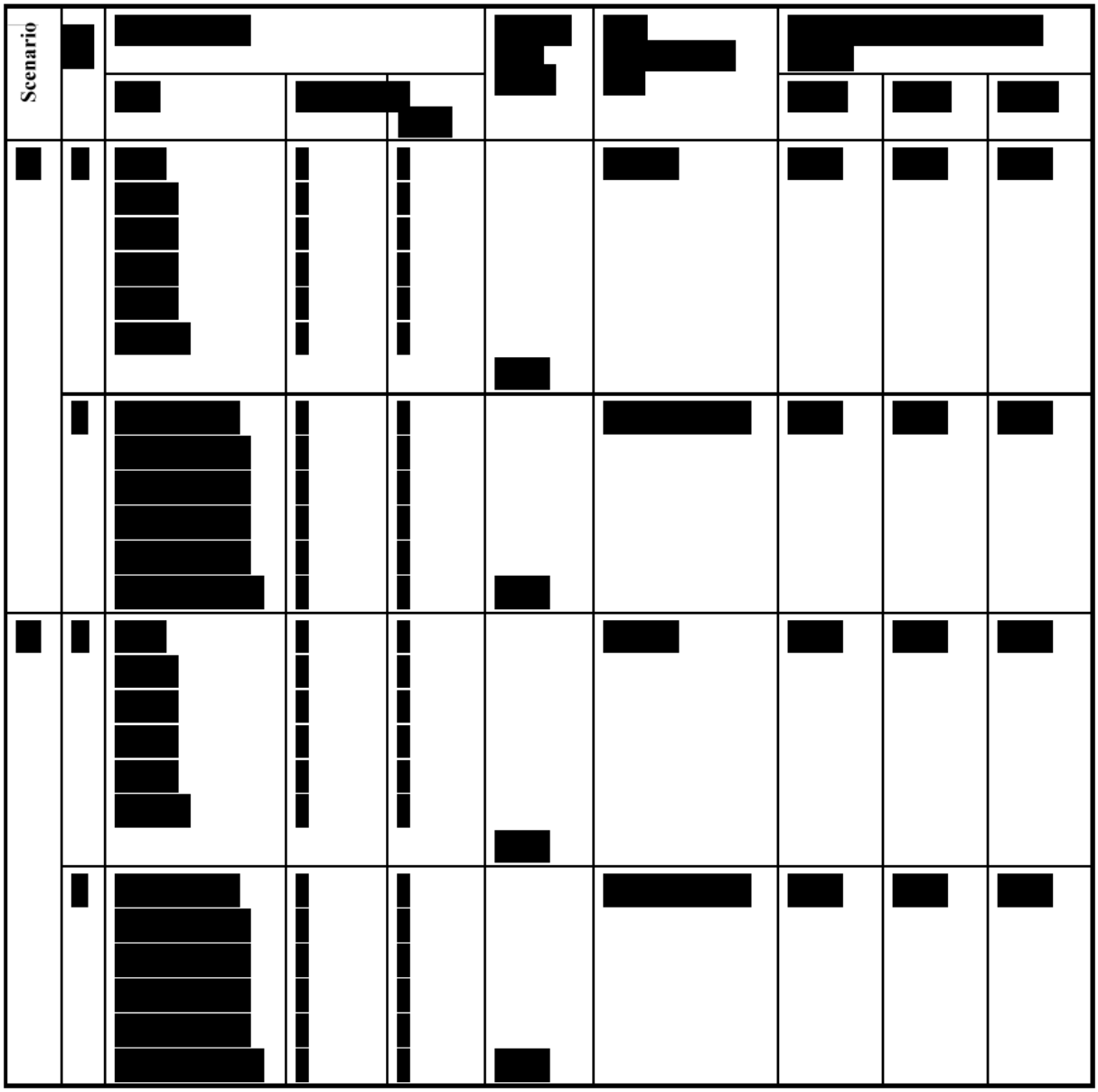
Table 10.5: 1 Hypothetical data scenarios for Arms A and B (cont.)



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

$ None of the pre-specified doses in the CTP would be allowed based on EWOC, lower doses than the pre-specified ones could be chosen in practice if agreed between sponsor and SMC.

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 7 assumed true dose-toxicity scenarios for Arms A and B which were used to assess the operating

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characteristics of the joint model for these arms. The toxicity scenarios reflect a wide range of possible cases as follows:

- Scenario 1: moderate-toxicity scenario
- Scenario 2: high-toxicity scenario
- Scenario 3: low-toxicity scenario
- Scenario 4: non-logistic dose-toxicity scenario
- Scenario 5: all planned doses in overdose range

For Arms A and B, two additional scenarios were used to assess the operating characteristics, especially to assess the effect of the interaction between BI 1387446 and ezabenlimab (BI 754091).

- Scenario 6: data for ezabenlimab (BI 754091) largely deviates from data for BI 1387446, represented by a very flat dose-toxicity curve (as indicated by currently available data on ezabenlimab (BI 754091)) that lies in the overdose range (indicating a quite toxic behaviour of BI 1387446, contrarily to the ezabenlimab (BI 754091) data, which indicate a very low toxicity overall)
- Scenario 7: Large interaction effect between BI 1387446 and ezabenlimab (BI 754091)

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Table 10.5: 2 Assumed true dose-toxicity scenarios for Arms A and B

Scenario	Arm		Dose					
			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1: Moderate	A	P(DLT)	0.075	0.099	0.136	**0.203**	0.350	0.524
	B		0.157	**0.176**	**0.210**	**0.276**	0.424	0.566
2: High Tox	A		0.134	**0.179**	**0.287**	**0.326**	0.478	0.579
	B		0.157	**0.206**	**0.291**	0.383	0.490	0.592
3: Low Tox	A		0.014	0.076	0.112	**0.185**	**0.201**	**0.249**
	B		0.081	0.104	**0.162**	**0.198**	**0.235**	**0.287**
4: Non-Logistic	A		0.014	0.076	0.112	**0.326**	0.478	0.579
	B		0.081	0.104	**0.162**	0.383	0.490	0.592
5: All too toxic	A		0.341	0.378	0.403	0.457	0.526	0.599
	B		0.367	0.400	0.489	0.534	0.596	0.626
6: Large deviation	A		0.075	0.099	0.136	**0.203**	0.350	0.524
	B		0.351	0.356	0.359	0.361	0.368	0.370
7: High interaction	A		0.075	0.099	0.136	**0.203**	0.350	0.524
	B		**0.172**	**0.211**	**0.292**	0.472	0.780	0.927

Numbers in bold represent assumed toxicity probabilities lying in the target toxicity interval

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 dose level with the highest posterior probability that the true DLT rate lies in the target interval which is still ≤100% increase from the current dose.

The MTD was considered reached (per arm) if at least 12 patients have been evaluated in the specific trial arm, a dose level is the model's recommendation for the next dose cohort two times in a row, and if for this dose the posterior probability of targeted toxicity was at least 50% or at least 6 patients have been treated at this dose in the respective arm of the trial. In this case, the dose satisfying these conditions is declared MTD of the trial arm, in accordance with the rules stated in Section 7. 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 simulated trial and the average number of DLTs per simulated trial are reported. Results are shown in Table 10.5: 3.

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Table 10.5: 3 Simulated operating characteristics for Arms A and B

[redacted]	[redacted]	[redacted]				[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In Scenario 1 which reflects the case of a moderate true dose-toxicity, around 29% of trials in Arm A have found an MTD with true DLT rate in the target interval. In addition to that, 288 trials [redacted] as MTD, which has an assumed true toxicity probability of 0.136 which is very close to the lower boundary of the target interval. In Arm B, around 82% of the simulated trials have declared a dose as MTD that has an assumed true DLT rate in the target range.

In Scenario 2 (high-toxicity scenario), around 41% of trials in Arm A and around 27% of trials in Arm B have been stopped prematurely due to too toxic doses. This is an expected situation for a high-toxicity scenario. Nevertheless, around 55% of trials in Arm A and around 61% of trials in Arm B declared a dose as MTD that has an assumed true DLT rate in the target interval.

Scenario 3 (low-toxicity scenario) shows that in Arm A around 63% of trials declared MTDs with true DLT rate in the target interval. The majority of the rest of the trials (256 trials) [redacted] as the MTD, which has a true DLT rate in the underdose interval. In Arm B around 90% of trials declared a dose as MTD that has an assumed true toxicity rate in the target interval.

Scenario 4 represents a case where the assumed true dose-toxicity curve does not follow a logistic shape. In this scenario, 40.3% of trials in Arm A determined a dose as MTD which

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has a true DLT rate in the target interval. Additionally, 475 trials in Arm A declared [redacted] as the MTD, which has an assumed true toxicity probability of 0.112. In Arm B, 67.9% of trials declared a dose as MTD which has a true DLT rate in the target interval. In addition to that, 207 trials declared the combination of [redacted] 240 mg as MTD which has an assumed true toxicity probability of 0.383, which is close to the upper boundary of the target interval.

In scenario 5, all specified dose levels have an assumed toxicity rate in the overdose interval. In this case most of the simulated trials stop prematurely because all specified dose levels are too toxic. In all 3 arms several simulated trials (Arm A: 13.8%, Arm B: 12.4%) declare doses as MTD with true DLT rate in the overdose interval. Most of these trials choose [redacted] or [redacted] as MTD. These doses have assumed true toxicity rates not too far away from the target rate therefore this is still acceptable for such overly toxic scenarios.

In scenario 6, the data for ezabenlimab (BI 754091) largely deviates from the data for BI 1387446. While a flat dose-toxicity curve that lies in the overdose range is assumed for BI 1387446, very low toxicity is assumed for ezabenlimab (BI 754091). This results in high-toxicity for the combination arm B: Many of the simulated trials in Arm B stop prematurely because all specified dose levels are too toxic. Additionally, around 56% of trials in Arm B declare doses as MTD with true DLT rate in the overdose interval. Most of these trials choose [redacted] or [redacted] as MTD. These combinations have assumed true toxicity rates not too far away from the target rate. In Arm A, 51.6% of the simulated trials declare a dose as MTD which has an assumed true DLT rate in the underdose interval. In almost all of these cases [redacted] were chosen as MTD and these dose levels have an assumed true toxicity probability of 0.099 [redacted] and 0.136 [redacted]

In scenario 7 (high interaction between BI 1387446 and ezabenlimab (BI 754091)), 44.9% of the trials in Arm A declared a dose as MTD which has a true DLT rate in the underdose interval. 314 of these trials declared [redacted] as the MTD which has a true toxicity probability of 0.136 which is close to the lower boundary of the target interval. In Arm B around 74% of trials determined an MTD that has an assumed true toxicity rate in the target interval.

The mean patient numbers in Arm A range from approximately 5.6 patients (Scenario 5) to 17.3 patients (Scenario 3) and the maximum number of patients was 36 (Scenario 3). Similarly, for Arm B, the mean patient numbers range from 5.0 (Scenario 5) to 15.6 (Scenario 3), with a maximum number of 45 patients in a simulated trial under Scenario 3. 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 joint model is not sensitive to different scenarios of truth. Even under misspecification results are satisfactory. In general, these models are 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.

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On-trial recommendations based on the joint model for Arms A and B 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 4.0.5 and the rstan package version 2.21.2 were used for data scenarios and simulations.

Table 10.5: 4 provides a comparison between trials 1426-0001 and 1381-0001 regarding study population, DLT definition and treatment schedule.

Table 10.5: 4 Comparison of trials 1426-0001 and 1381-0001

Trial 1426-0001	**Trial 1381-0001**
Study population	
Inclusion criteria	**Inclusion criteria**
Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.	Provision of signed and dated, written ICF prior to any trial-specific procedures, sampling, or analyses.
Patients ≥18 years	Patients ≥18 years
Women of childbearing potential eligible if on highly effective methods of birth control	Women of childbearing potential eligible if on highly effective methods of birth control
Male patients must be willing to use barrier contraception methods	Male patients must be willing to use barrier contraception methods
ECOG 0 or 1	ECOG 0 or 1
Life expectancy at least 12 weeks	Life expectancy of at least 12 weeks

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Table 10.5: 4 Comparison of trials 1426-0001 and 1381-0001 (cont.)

Trial 1426-0001	**Trial 1381-0001**
Study population	
Inclusion criteria	**Inclusion criteria**
Histologically or cytologically confirmed diagnosis of an advanced, unresectable and/or metastatic malignant solid tumour and indication for treatment.	Patients with a histologically confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumours (any type). Patients with a histologically confirmed diagnosis of select advanced, unresectable, and/or metastatic solid tumours with specific histology/tumour types and/or specific genetic profiles
Patient must have exhausted established treatment options known to prolong survival for the malignant disease, or is not eligible for established treatment options	Patients who have received all therapy known to confer clinical benefit (including anti-PD-1 or anti-PD-L1 therapies, if relevant), or for whom no therapy of proven efficacy exists, or who are not amenable to standard therapies.
Adequate organ function or bone marrow reserve as demonstrated at screening by the following laboratory values: absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (≥ 1.5 x 10^3/µL, ≥ 1,500/mm^3) platelet count ≥ 100 x 10^9/L (≥ 100 x 10^3/µL, ≥ 100 x 10^3/mm^3) hemoglobin ≥ 90 g/L (≥9.0 g/dL, ≥ 5.6 mmol/L) total bilirubin ≤ 1.5 times the upper limit of normal (ULN), except for patients with Gilbert's syndrome: total bilirubin ≤ 3 x ULN or direct bilirubin ≤ 1.5 x ULN. alanine aminotransferase (ALT)/Aspartate aminotransferase (AST): patients without liver metastases: ALT/AST ≤2.5 x ULN patients with liver metastases with planned injection into liver lesion: ALT/AST ≤2.5 x ULN patients with liver metastases without planned injection into liver lesions:	Inadequate organ function or bone marrow reserve as demonstrated by the following laboratory values: Absolute neutrophil count <1.5 x 10^9/L (<1500/mm^3) Platelet count <100 x 10^9/L Haemoglobin <90 g/L (<9 g/dL) 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 Alanine aminotransferase (ALT) >2.5 times the upper limit of normal (ULN) if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases Aspartate aminotransferase (AST) >2.5 times ULN if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases

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Table 10.5: 4 Comparison of trials 1426-0001 and 1381-0001 (cont.)

Trial 1426-0001	**Trial 1381-0001**
Study population	
Inclusion criteria	**Inclusion criteria**
ALT/AST ≤ 5 x ULN Creatinine ≤ 1.5 x ULN. If creatinine is > 1.5 x ULN, patient is eligible if concurrent creatinine clearance ≥ 45 ml/min (measured or calculated by CKD-EPI formula). prothrombin time (PT) ≤ 1.5 x ULN activated partial thromboplastin time (aPTT) ≤1.5 x ULN	Creatinine >1.5 times ULN or creatinine clearance <50 mL/min (measured or calculated by Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation); confirmation of creatinine clearance is only required when creatinine is >1.5 times ULN

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Table 10.5: 4 Comparison of trials 1426-0001 and 1381-0001 (cont.)

Trial 1426-0001	**Trial 1381-0001**
Study population	
Inclusion criteria	**Inclusion criteria**
Lab criteria (IC)	**Lab criteria (EC)**
Exclusion criteria	**Exclusion criteria**
Any investigational or antitumour treatment (including antibodies targeting PD1- or PD-L1) within 4 weeks or 5 half-life periods (whichever is shorter) prior to the initial administration of BI 1387446	Any investigational or antitumour treatment within 4 weeks or 5 half-life period (whichever is shorter) prior to the initial administration of BI 754091.
Persistent toxicity from previous treatments (including irAEs) that has not resolved to ≤ Grade 1, except for alopecia, xerostomia, and immunotherapy related endocrinopathies which may be included if clinically stable on hormone supplements or antidiabetic drugs as per investigator judgement	
History or evidence of active, non-treatment related autoimmune disease, except for endocrinopathies which may be included if clinically stable on hormone supplements or antidiabetic drugs.	Active autoimmune disease or a documented history of autoimmune disease, except vitiligo or resolved childhood asthma/atopy
History of pneumonitis related to prior immunotherapy	History of pneumonitis within the last 5 years
Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 2 weeks prior to the first dose of BI 1387446 or ezabenlimab (BI 754091)	Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of BI 754091
The tumour at the projected injection site has a high risk for local complications, e.g. bleeding related to encasement/infiltration of major blood vessels or contact with liver capsule, compression of vital structures in case of swelling of injected lesion, in the opinion of the investigator (see Section 4.1.4.2).	

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Table 10.5: 4 Comparison of trials 1426-0001 and 1381-0001 (cont.)

Trial 1426-0001	**Trial 1381-0001**
Study population	
Inclusion criteria	**Inclusion criteria**
Lab criteria (IC)	**Lab criteria (EC)**
Exclusion criteria	**Exclusion criteria**
Presence or history of uncontrolled or symptomatic brain or subdural metastases, unless local therapy was completed and metastases considered stable by the investigator	Untreated brain metastasis(es) that may be considered active. Patients with previously treated brain metastases may participate provided they are stable (i.e., without evidence of PD by imaging for at least 4 weeks prior to the first dose of trial treatment, and any neurologic symptoms have returned to baseline), and there is no evidence of new or enlarging brain metastases
Presence of other active invasive cancers other than the one treated in this trial within 5 years prior to screening, with the exception of appropriately treated basal-cell carcinoma of the skin, in situ carcinoma of the uterine cervix, or other local tumours considered cured by local treatment	Presence of other active invasive cancers other than the one treated in this trial within 5 years prior to screening, with the exception of appropriately treated basal-cell carcinoma of the skin, *in situ* carcinoma of the uterine cervix, or other local tumours considered cured by local treatment.
Known history of human immunodeficiency virus (HIV) infection Active infection requiring systemic therapy at the start of treatment in the trial, including active viral hepatitis infection or active tuberculosis infection	Known history of human immunodeficiency virus infection or an active hepatitis B or C virus infection. (exceptions for some specific expansion cohorts defined)
Has received a live vaccine within 30 days prior to first dose of BI 1387446	Patients who must or wish to continue the intake of restricted medications (see Section 4.2.2.2) or any drug considered likely to interfere with the safe conduct of the trial Section 4.2.2.2: Live attenuated vaccines during the trial through 30 days after the last dose of investigational product are prohibited)

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Table 10.5: 4 Comparison of trials 1426-0001 and 1381-0001 (cont.)

Trial 1426-0001	**Trial 1381-0001**
Study population	
Inclusion criteria	**Inclusion criteria**
Lab criteria (IC)	**Lab criteria (EC)**
Exclusion criteria	**Exclusion criteria**
- Significant resting ECG abnormalities defined as ventricular tachyarrhythmias, presence of unstable atrial fibrillation (defined as ventricular response >100 bpm), significant bradycardia (defined as a heart rate of <50 bpm), complete left bundle branch block, right bundle branch block and left anterior hemiblock, third degree AV block, or a mean resting corrected QT interval (QTc) >470 msec	Any of the following cardiac criteria: - Mean resting corrected QT interval (QTc) >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 including congenital long QT syndrome, family history of sudden unexpected death from cardiac related causes, myocardial infarction or major cardiac surgery within 3 months prior to enrollment, history or presence of uncontrolled hypertension (>150 mmHg systolic or >100 mmHg diastolic bp)	- 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 known to prolong the QT interval
- Left ventricular ejection fraction < 50% measured by echocardiography or MUGA scan - Cardiac insufficiency NYHA III or IV	- 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.

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Table 10.5: 4 Comparison of trials 1426-0001 and 1381-0001 (cont.)

Trial 1426-0001	**Trial 1381-0001**
Study population	
Inclusion criteria	**Inclusion criteria**
Lab criteria (IC)	**Lab criteria (EC)**
Exclusion criteria	**Exclusion criteria**
History of severe hypersensitivity reactions to mAbs	History of severe hypersensitivity reactions to other mAbs
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 in the opinion of the investigators	Patients who must or wish to continue the intake of restricted medications (see Section 4.2.2.2) or any drug considered likely to interfere with the safe conduct of the trial
Chronic alcohol or drug abuse	Chronic alcohol or drug abuse or any condition that, in the Investigator's opinion, makes him/her an unreliable trial subject, unlikely to complete the trial, or unable to comply with the protocol procedures
Major surgery (major according to the investigator's assessment) performed within 4 weeks prior to first trial treatment	Major surgery (major according to the Investigator's assessment) performed within 12 weeks prior to first trial treatment or planned within 12 months after screening, e.g., hip replacement
Any pre-existing or concurrent disease or condition that, in the investigator's opinion, would compromise patient safety, poses an undue risk to the patient, makes him/her an unreliable trial subject, unlikely to complete the trial, or unable to comply with the protocol procedures	Chronic alcohol or drug abuse or any condition that, in the Investigator's opinion, makes him/her an unreliable trial subject, unlikely to complete the trial, or unable to comply with the protocol procedures
Women who are pregnant, nursing, or who plan to become pregnant or nurse during the trial or within 6 months after the last dose of study treatment	Inclusion criterion 7 on females of child bearing potential
Presence of any absolute contraindications to cataract surgery	

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Table 10.5: 4 Comparison of trials 1426-0001 and 1381-0001 (cont.)

Trial 1426-0001	**Trial 1381-0001**
Study population	
Inclusion criteria	**Inclusion criteria**
Lab criteria (IC)	**Lab criteria (EC)**
Exclusion criteria	**Exclusion criteria**
n.a. (cross over and re-screening permitted)	Previous enrolment in this trial
	Interstitial lung disease
DLT definition	
Haematological Toxicity	**Haematological Toxicity**
Any grade 5 toxicity	
Neutropenia grade 4 lasting for >5 days	Neutropenia ≥ Grade 4 present for >7 days
Neutropenia grade ≥3 with documented infection	Neutropenia Grade 3 with documented infection
Febrile neutropenia	Febrile neutropenia
Thrombocytopenia grade 4	≥ Grade 4 thrombocytopenia (platelets <25,000/μL)
Thrombocytopenia grade 3 with concomitant bleeding grade ≥2 (i.e. bleeding requiring intervention) (grade 2)	Any Grade 3 thrombocytopenia with bleeding or a requirement for platelet transfusions
Grade 4 anaemia	
Non-Hematological toxicity	**Non-Hematological toxicity**
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)	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)
AST or ALT elevation grade ≥ 4	≥Grade 4 AST or ALT of any duration
CRS grade ≥3	

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Table 10.5: 4 Comparison of trials 1426-0001 and 1381-0001 (cont.)

Trial 1426-0001	**Trial 1381-0001**
Study population	
Inclusion criteria	**Inclusion criteria**
Lab criteria (IC)	**Lab criteria (EC)**
Exclusion criteria	**Exclusion criteria**
Any other ≥Grade 3 non-haematologic toxicity with the following exceptions: o Grade 3 irAE that resolves to ≤ Grade 1 or to baseline with immunosuppressive therapy within 2 weeks o Grade 3 fatigue that persists <7 days o Grade 3 rash that resolves to ≤ Grade 1 within 2 weeks o Grade 3 or 4 elevation in serum amylase and/or lipase that is not associated with clinical or radiographic evidence of pancreatitis o Grade 3 electrolyte abnormality that lasts <72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical intervention o Grade 3 nausea or vomiting that lasts <48 hours, and resolves to ≤ Grade 1 either spontaneously or with conventional medical intervention o Alopecia o 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 o Grade 3 tumour flare syndrome	Any ≥Grade 3 non-haematologic toxicity with the following exceptions: o Grade 3 irAE that resolves to ≤ Grade 1 or to baseline with immunosuppressive therapy within 2 weeks o Grade 3 fatigue that persists <7 days o Grade 3 rash that resolves to ≤ Grade 1 within 2 weeks o Grade 3 or 4 elevation in serum amylase and/or lipase that is not associated with clinical or radiographic evidence of pancreatitis o Grade 3 electrolyte abnormality that lasts <72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical intervention o Grade 3 nausea or vomiting that lasts <48 hours, and resolves to ≤ Grade 1 either spontaneously or with conventional medical intervention o Alopecia o 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. o Grade 3 tumour flare
	Any Grade 4 or 5 AE
Pneumonitis Grade 2	

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Table 10.5: 4 Comparison of trials 1426-0001 and 1381-0001 (cont.)

Trial 1426-0001	**Trial 1381-0001**
Study population	
Inclusion criteria	**Inclusion criteria**
Lab criteria (IC)	**Lab criteria (EC)**
Exclusion criteria	**Exclusion criteria**
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 Grade 2 drug-related uveitis or 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 Grade ≥2 toxicity that persists and results in a delay of >14 days of Cycle 2 Day 1	Any treatment-related ≥ Grade 2 toxicity that persists and results in an inability to administer BI 754091 on Cycle 2 Day 1
Administration of treatment	
Ezabenlimab (BI 754091): intravenous infusion (i.v.) of 240 mg every 3 weeks BI 1387446: intratumoural injection (i.tu.)	BI 754091: intravenous infusion (i.v.) every 3 weeks

11 DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		25 Nov 2019
EudraCT number **EU number**		2019-001082-32
BI Trial number		1426-0001
BI Investigational Medicinal Product(s)		BI 1387446 BI 754091
Title of protocol		Phase I, first in human trial evaluating BI 1387446 alone and in combination with BI 754091 in solid tumours
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		Synopsis

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Description of change		Revised description of established treatment options known to prolong survival to remove the word meaningfully.
Rationale for change		Revision in response to FDA review comment to remove the word “meaningfully” from this requirement as it is not clear/specific.
Section to be changed		Synopsis
Description of change		Revised description of Main Exclusion criteria
Rationale for change		Revision to align with Exclusion criteria #1 in Section 3.3.3
Section to be changed		Flowchart
Description of change		, at the 30-day safety follow-up, and at any time during the treatment period, if clinically indicated.
Rationale for change		Based on non-clinical data and the pharmacological activity of BI 1387446, it is considered that a potential risk of eye lens toxicity cannot be completely ruled out and therefore mitigation procedures must be in place in this FIH study.
Section to be changed		Flowchart
Description of change		Revised requirement for pregnancy test to be performed in serum in flowchart and footnote #5.
Rationale for change		Revision in response to MHRA review comment that pregnancy tests must be in serum.
Section to be changed		Flowchart
Description of change		Revised Footnote #10
Rationale for change		Revision added to clarify that a single ECG will be obtained as clinically indicated prior to drug administration, at least every two to three cycles.
Section to be changed		Flowchart
Description of change		Revised Footnote #13 to clarify that injection of BI 1387446 should be preferably performed immediately after completion of BI 754091 infusion.
Rationale for change		Revision added to align with Blood sampling flowcharts for Arms B and C.
Section to be changed		Flowchart
Description of change		Revision to footnote #27 to clarify safety parameters

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Rationale for change		Revision added to clarify that prior to biopsy of deep visceral lesions appropriate safety lab parameters taken within 24h must be available.
Section to be changed		Flowchart
Description of change		Addition of Footnote #36 for lens opacity assessment.
Rationale for change		Based on non-clinical data and the pharmacological activity of BI 1387446, it is considered that a potential risk of eye lens toxicity cannot be completely ruled out and therefore mitigation procedures must be in place in this FIH study.
Section to be changed		
Description of change		Footnote #37 created and added to echocardiography
Rationale for change		Addition of footnote #37 to clarify that although echocardiography is the preferred method, MUGA scans are permitted to quantify LVEF. The same method should be used in a single patient throughout the trial.
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		Flowchart
Description of change		Revised Footnote #23
Rationale for change		Revision added to clarify imaging should be performed via CT/MRI. PET-CT may be performed if clinically indicated based on tumour type, however, in this case a diagnostic-quality CT scan needs to be acquired as part of the PET-CT for RECIST measurements. The CT portion of a PET-CT can be used as the basis for RECIST measurements if the site has documented that a CT with appropriate radiation dose for diagnostic quality and IV/oral contrast was used (if not medically contraindicated).
Section to be changed		Blood Sample Flowchart: Arm A
Description of change		Description regarding triplicate ECGs at C1V1, moved from ECG to Event column. Description

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		regarding triplicate ECGs at C2V1, and C5V1 updated and move from ECG to Event column.
Rationale for change		Revised column placement for clarity. For C2V1 and C5V1, revised to clarify that only 1 set of triplicate ECGs is required prior to sampling.
Section to be changed		Blood Sample Flowchart: Arm A, Blood Sample Flowchart: Arm B
Description of change		Revised to add footnote 6.
Rationale for change		Revision added to clarify that when triplicate ECGs are scheduled prior to blood sampling, the 3 single ECG recordings should be performed within a maximum period of 5 minutes prior to blood sampling.
Section to be changed		Blood Sample Flowchart: Arm B, Blood Sample Flowchart: Arm C
Description of change		Revised timing for BI 754091 administration
Rationale for change		Revision to clarify timing between BI 754091 and BI 1387446 administration on visits when both drugs are scheduled to be administered.
Section to be changed		Abbreviations
Description of change		Revised to align with check of abbreviations throughout document
Rationale for change		Revision to align with content updates for lens opacity assessment.
Section to be changed		Section 1.4.2
Description of change		Revised to add description of potential risk of eye lens toxicity. Clarification on classification of risks and terminology.
Rationale for change		Based on non-clinical data and the pharmacological activity of BI 1387446, it is considered that a potential risk of eye lens toxicity cannot be completely ruled out and therefore mitigation procedures must be in place in this FIH study.
Section to be changed		Section 3.1
Description of change		Revised to extend the DLT monitoring period to include echocardiographic/MUGA scan measurements acquired on Day 1 of Cycle 2 and related findings for MTD evaluability.
Rationale for change		Revision in response to FDA review comment.

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Section to be changed		Section 3.1
Description of change		Revised to add statement that during dose escalation the BLRM will be evaluated after the occurence of each DLT before enrolling any further patients at the respective dose level.
Rationale for change		Revision in response to MHRA review comment.
Section to be changed		Section 3.1
Description of change		Revised to remove statement "Further patients may be included to confirm this MTD estimate, i.e. to confirm that the EWOC criterion is still fulfilled."
Rationale for change		
Section to be changed		Section 3.1.2
Description of change		Revised to clarify that following the occurrence of a drug related Grade 2 or greater AE, excluding asymptomatic Grade 2 laboratory abnormalities that resolve without medical intervention within 48 hours and transient Grade 2 local injection site reactions that resolve within 48 hours (whereby supportive treatment is allowed), a minimum of 3 patients will be required per dose cohort.
Rationale for change		Revised in response to FDA review comment.
Section to be changed		Section 3.1.3
Description of change		Revised description of locations where administration of BI 1387446 is not permitted.
Rationale for change		Revision in response to FDA review comment that injection into lesions which would be most often require the use of techniques other than percutaneous intratumoural injection, such endoscopic injection, is not permitted
Rationale for change		Section 3.3
Section to be changed		Revision to update wording regarding patient(s) determined eligible in error.
Description of change		Revision added to clarify that patients who may not meet eligibility are to be reported to the sponsor immediately. Patients are considered enrolled once informed consent has been signed and would be proceed to be assessed for eligibility.
Section to be changed		Section 3.3.2

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Description of change		Revised Inclusion criteria #7 to remove word meaningfully.
Rationale for change		Revision in response to FDA review comment to remove the word "meaningfully" from this requirement as it is not clear/specific.
Section to be changed		Section 3.3.2
Description of change		Revised Inclusion criteria #11 to adjust concurrent creatinine clearance from ≥ 50 ml/min to ≥ 45 ml/min.
Rationale for change		Revision in response to FDA review comment.
Section to be changed		Section 3.3.3
Description of change		Revised Exclusion criteria #14 to exclude patients with any clinically important resting ECG abnormalities and factors that may increase the risk of QTc prolongation or risk of arrhythmic events.
Rationale for change		Revision in response to MHRA review comment. This change to exclusion criteria will ensure patient safety while allowing to enroll a population that more closely represents the intended future population.
Section to be changed		Section 3.3.3
Description of change		Added Exclusion criteria #22 for presence of any absolute contraindication to cataract surgery.
Rationale for change		Revision in response to MHRA review comment. Based on non-clinical data and the pharmacological activity of BI 1387446, it is considered that a potential risk of eye lens toxicity cannot be completely ruled out and therefore mitigation procedures must be in place in this FIH study.
Section to be changed		Section 3.3.3
Description of change		Added Exclusion criteria #23 for any factors that increase the risk of QTc prolongation or risk of arrhythmic events.
Rationale for change		Revision in response to MHRA review comment. This change to exclusion criteria will ensure patient safety while allowing to enroll a population that more closely represents the intended future population.
Section to be changed		Section 3.3.4.4

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Description of change		Revised to clarify that patients withdrawn for a reason other than having a DLT, or who miss any dose of study medication during Cycle 1, are not evaluable for the MTD determination.
Rationale for change		Revision in response to MHRA review comment. Patients who miss more than one treatment visit during Cycle 1 are not evaluable for the MTD determination. Furthermore, none of the provisional dose levels for dose escalation (see CTP Table 4.1.2.1.1: 1) can be skipped during the dose escalation as the maximum allowable dose increment for the subsequent cohort will always be no more than 100% (see CTP Section 7).
Section to be changed		Section 4.1.2.1.2
Description of change		Revised to clarify the concentration of the ready to use solution will be [redacted]
Rationale for change		Revision due to typographical error.
Section to be changed		Section 4.1.2.2
Description of change		Revised to remove statements "No dose escalation or de-escalation is foreseen. In case the recommended Phase II dose or schedule would be modified based on evidence from ongoing trials, the SMC may recommend to amend the dose of BI 754091 used in this study."
Rationale for change		Revision in response to FDA review comment.
Section to be changed		Section 4.1.4
Description of change		Revised to remove statements "BI 754091 is currently being used in several clinical trials. In case the recommended Phase II dose or schedule would be modified based on evidence from ongoing trials, the SMC may recommend to amend the dose of BI 754091 used in this study."
Rationale for change		Revision in response to FDA review comment.
Section to be changed		Section 4.1.4.4
Description of change		Revised to extend the DLT monitoring period to include echocardiographic/MUGA scan measurements acquired on Day 1 of Cycle 2 and related findings for MTD evaluability.
Rationale for change		Revision in response to FDA review comment.
Section to be changed		Section 4.1.4.5

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Description of change		Revision to Table 4.1.4.5: 1 for clarification of collection of vital signs
Rationale for change		Revision to collection for superficial and non-visceral deep lesions.
Section to be changed		Section 4.1.4.6
Description of change		Revised to include minimum 8 hours of monitoring for CRS post-administration of Cycle 2 Day 1 dose of BI 1387446.
Rationale for change		Revision in response to FDA review comment.
Section to be changed		Section 4.2.2.1
Description of change		Revised to clarify that in Arms B and C, the use of live attenuated viruses has to be delayed until 70 days after the last dose of BI 754091 or 30 days after the last dose of BI 1387446, whatever comes later.
Rationale for change		Revision in response to MHRA review comment. The use of live vaccines should be prohibited until the end of the relevant systemic exposure (5 half-lives after the last dose) of the IMP with the longest half-life.
Section to be changed		Section 5.2.3
Description of change		Revised requirement in Table 5.2.3: 1 for pregnancy test to be performed in serum.
Rationale for change		Revision in response to MHRA review comment that pregnancy tests must be in serum.
Section to be changed		Section 5.2.3
Description of change		Revised Footnote #2 in Table 5.2.3: 1 to clarify if Nt proBNP not available, it may be replaced with a decline in preference by mid-regional pro-ANP, total BNP or ANP.
Rationale for change		Revision due to typographical error.
Section to be changed		Section 5.2.3
Description of change		Revised entry for Coagulation in Table 5.2.3: 1 to add PT
Rationale for change		Revision included to align with Inclusion criteria #11 in Section 3.3.2
Section to be changed		Section 5.2.3
Description of change		Revised footnote #4
Rationale for change		Revision included to clarify reference to FACS and to align with Section 5.4.2 and Flowchart

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Section to be changed		Section 5.2.4
Description of change		Revised to clarify that in Arm C, single ECGs will be taken as clinically indicated, at least every two to three cycles. In case emerging data from the ECGs in Arm A and/or B suggest any potential signal, additional ECG measurements will be introduced in Arm C.
Rationale for change		Revision in response to FDA review comment.
Section to be changed		Section 5.2.4
Description of change		Revision to clarify that all ECGs will be transmitted to the central vendor for analysis.
Rationale for change		Revision included to clarify that central reading of all ECGs needed in support assessment of ECGs in relation to PK.
Section to be changed		Section 5.2.4
Description of change		Revised to add clarification that when triplicate ECGs are scheduled prior to blood sampling, the 3 single ECG recordings should be performed within a maximum period of 5 minutes prior to sampling.
Rationale for change		Revision added to align with Blood Sample Flowchart: Arm A and Blood Sample Flowchart: Arm B
Section to be changed		Section 5.2.6
Description of change		, at the 30-day safety follow-up, and at any time during the treatment period, if clinically indicated.
Rationale for change		Based on non-clinical data and the pharmacological activity of BI 1387446, it is considered that a potential risk of eye lens toxicity cannot be completely ruled out and therefore mitigation procedures must be in place in this FIH study.
Section to be changed		Section 5.2.7.2.2
Description of change		Revised to clarify that SAEs may be submitted to BI by means other than Fax.
Rationale for change		Revision to add administrative update.
Section to be changed		Section 6.2.1

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Description of change		Revised to clarify the patient's reason(s) for not being eligible for established treatment options will be documented in the patient record and in the eCRF.
Rationale for change		
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		Section 7.5
Description of change		Revised to remove statement "Fewer or more patients might be needed based on the recommendation of the SMC."
Rationale for change		Revision in response to FDA review comment.
Section to be changed		Section 8.6
Description of change		Revised to clarify the definition of the LPLVPE as the date on which the last patient finalised the first cycle and underwent echocardiogram/MUGA scan on Day 1 of Cycle 2.
Rationale for change		Revision in response to FDA review comment.
Section to be changed		Section 9.1
Description of change		Update of references
Rationale for change		Revised to align with check of references throughout document
Section to be changed		Section 10.1.2
Description of change		Revised management for immune-related AEs
Rationale for change		Revision to align with current instructions for the management of irAEs under treatment with PD1-inhibitor.
Section to be changed		Section 10.2

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Description of change		Revised text for management of trial drugs for treatment of CRS.
Rationale for change		Revision to align with Section 4.1.4.3.
Section to be changed		Section 10.5
Description of change		Revised to add description of scenarios 02-06 and to updated Table 10.5: 1 to add scenarios 01-06.
Rationale for change		Revision in response to FDA review comment to address the possibility of enrolling cohorts of 1 at doses [redacted] in particular investigating scenarios in which the first dose level enrols one patient who experiences a DLT.
Section to be changed		Section 10.5
Description of change		Revised Table 10.5: 4 to reflect the Inclusion and Exclusion criteria changes described for Sections 3.3.2 and 3.3.3.
Rationale for change		Revision to align with updates to other sections.
Section to be changed		Miscellaneous
Description of change		Revisions to formatting, punctuation, and/or spelling. Revision to update description of dose tier(s) to dose level(s).
Rationale for change		Clarifications added as applicable to address minor formatting updates and/or alignment of terms throughout document that do not affect protocol content and will not be listed as separate changes.

11.2 GLOBAL AMENDMENT 2

Date of amendment		26 May 2021
EudraCT number **EU number**		2019-001082-32
BI Trial number		1426-0001
BI Investigational Medicinal Product(s)		BI 1387446 Ezabenlimab (BI 754091)
Title of protocol		Phase I, first in human trial evaluating BI 1387446 alone and in combination with ezabenlimab (BI 754091) in solid tumours
Global Amendment due to urgent safety reasons		
Global Amendment		x

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Section to be changed		Miscellaneous
Description of change		Revisions to denote that the start of Arm C will be postponed.
Rationale for change		The start of Arm C will be postponed until further evidence supporting a development in deep visceral tumours becomes available from Arms A and B.
Section to be changed		Miscellaneous
Description of change		Change BI 754091 to ezabenlimab (BI 754091)
Rationale for change		Compound name has been assigned. Updates have been added throughout the protocol in relevant sections.
Section to be changed		Synopsis, Section 2.1.3
Description of change		Revision to secondary endpoints
Rationale for change		Objective response will be based on Response Criteria for Intratumoural Immunotherapy in Solid Tumours (itRECIST). The best percentage change from baseline will be analysed in size of injected target lesions and in size of non-injected target lesions.
Section to be changed		Blood Sample Flowchart: Arm A
Description of change		Removal of blank timepoint at C5V1 12:00.
Rationale for change		Typographical error.
Section to be changed		Blood Sample Flowchart: Arm B
Description of change		Addition of triplicate ECGs at C1V1 at -1:15 and -1:35 and at C2V1 -1:05.
Rationale for change		Typographical error.
Section to be changed		Flowchart
Description of change		Addition of new footnote #4
Rationale for change		Clarification added that at Cycle 2 Day 1, an overnight stay is recommended if logistically possible due to sampling planned at the visit. Footnotes renumbered from this point forward.
Section to be changed		Flowchart
Description of change		Revision to footnote #34
Rationale for change		Clarification of the collection of echocardiography at Cycle 4 (within -7 days) and at Cycle 2 Day 1 (within 72 hours). Footnote is renumbered as #35 due to addition of footnote #4 described above.
Section to be changed		Section 1.4.2
Description of change		Revision to general safety measures for the trial.
Rationale for change		Addition of description of sequential start of backfill enrolment.
Section to be changed		Section 1.4.2

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Description of change		Addition of language regarding potential identification of a confirmed SARS-CoV-2 infection.
Rationale for change		Adjustment added based upon an assessment of the COVID-19 related risks to trial participants.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		Section 3.1
Description of change		Clarification added regarding the start of the study arms and backfill enrollment.
Rationale for change		Arm A and B will start in a staggered manner (refer to Section 3.1.1). The start of Arm C will be postponed until further evidence supporting a development in deep visceral tumours becomes available from Arms A and B. To acquire additional data to more fully inform dose selection, additional patients may be enrolled to backfill cohorts at dose levels that have been previously cleared (refer to Section 3.1.1).
Section to be changed		Section 3.1.1, Figure 3.1.1:1
Description of change		Revisions to describe postponement of Arm C and clarification of handling of cross-over patients for MTD analysis.
Rationale for change		Figure 3.1.1: 1 revised to reflect postponement to start of Arm C. For the main analysis of the MTD, cross-over patients will only be included while being treated with BI 1387446 monotherapy in Arm A. However, cross-over patients will be included in the sensitivity analyses of the MTD and thus be considered in addition.
Section to be changed		Section 3.1.2
Description of change		Clarification added regarding the starting dose in Arm C and handling of DLTs in backfill patients.
Rationale for change		The starting dose in Arm C will depend on the highest dose determined to be safe for patients in Arm B. The starting dose may be delayed to a higher dose level to avoid putting patients at procedural risks for doses with lack of activity.

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		However, the starting dose in Arm C will fulfill the EWOC criterion and will be lower than the MTD and recommended dose, respectively, established for the combination of BI 1387446 and ezabenlimab (BI 754091) in superficial tumours. Furthermore, dose escalation in Arm C will start at least one dose level lower than the recommended starting dose based on the joint BLRM. Backfill patients who have either experienced a DLT or have been observed for at least the MTD evaluation period without experiencing a DLT will be included into the main BLRM at the next subsequent SMC meeting. Particularly, in case DLTs are observed in 'backfill' patients, this information may affect the magnitude of dose escalation or even result in dose de-escalation. In case of the occurrence of DLTs, the SMC may decide about intervals between enrollment of patients, if applicable.
Section to be changed		Section 3.2
Description of change		Addition of language for the postponement to start of Arm C.
Rationale for change		The start of Arm C will be postponed.
Section to be changed		Section 3.3.2, Section 4.1.4.5, Section 10.5.4
Description of change		Addition of commonly used SI units.
Rationale for change		To provide clarification for laboratory parameters which are used for eligibility assessment and management of AEs.
Section to be changed		Section 3.3.4.1
Description of change		Revision to the criteria for discontinuation of trial treatment to address if a patient experiences an infection with SARS-CoV-2.
Rationale for change		Adjustment added based upon an assessment of the potential COVID-19 impact to trial participants.
Section to be changed		Section 3.3.4.4
Description of change		Clarification regarding replacement of patients
Rationale for change		A patient who misses the echocardiography/MUGA scan measurements acquired on Day 1 of Cycle 2 may be replaced.
Section to be changed		Section 4.1.2.3
Description of change		Clarification of treatment beyond progression
Rationale for change		PD assessment will be based on itRECIST and refers to the overall response assessment

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		including all injected and non-injected lesions. Overall PD assessment after initial progression is comparable to iUPD with iRECIST (the possibility of iTPD will not be considered in this study).
Section to be changed		Section 4.1.3
Description of change		Clarification regarding the method of assigning patients to treatment groups.
Rationale for change		The start of Arm C will be postponed. The start of Arm A and Arm B will be started sequentially.
Section to be changed		Section 4.1.4
Description of change		Revision to clarify that injection of BI 1387446 should be performed as soon as possible but not to exceed 4 hours after completion of ezabenlimab (BI 754091) infusion.
Rationale for change		Revision to align with description in other sections of the protocol.
Section to be changed		Section 4.1.4
Description of change		Clarification of visit handling due to potential disrupting circumstances.
Rationale for change		Adjustment added based upon an assessment of the potential COVID-19 impact to trial participants.
Section to be changed		Section 4.1.4.5
Description of change		Clarification of BI 1387446 administration and the decline in haemoglobin that must result in a prolongation of surveillance.
Rationale for change		BI 1387446 may only be administered by a physician who is experienced in diagnostic biopsy or intratumoural injection of immunotherapy drugs (physician, radiologist/interventional radiologist, or surgeon). A decline in Hgb by ≥2.0 g/dL (≥ 20 g/L, ≥ 1.24 mmol/L) must result in a prolongation of surveillance.
Section to be changed		Section 4.1.4.6
Description of change		Revisions to surveillance for CRS
Rationale for change		Revisions added that in patients with clinically manifested CRS, it is recommended to measure cytokines in the local laboratory at onset of symptoms, approximately 24 hours, and 48 hours thereafter or upon discharge from hospitalization (whichever occurs earlier).
Section to be changed		Section 4.1.8
Description of change		Clarification of investigational drug handling

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Rationale for change		Unused and partially used trial drug will be destroyed on site according to local site procedure after relevant reconciliations have been completed.
Section to be changed		Section 4.2.2.1
Description of change		Revision to include information regarding COVID-19 vaccination
Rationale for change		Adjustment added based upon an assessment of the potential COVID-19 impact.
Section to be changed		Section 5.1, Section 5.7, Section 10.3
Description of change		Clarification of tumour assessment
Rationale for change		Response assessment will be performed according to response criteria for intratumoural immunotherapy in solid tumours (itRECIST) (R20-2734).
Section to be changed		Section 5.2.7.1.4
Description of change		Revision to the definition of hepatic injury
Rationale for change		Revisions added for the alterations of hepatic laboratory parameters that define a hepatic injury in patients with abnormal liver parameters at baseline.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		Section 6.1
Description of change		Clarification of handling of COVID-19 related deviations from the original schedule of visits and procedures.
Rationale for change		Adjustment added based upon an assessment of the potential COVID-19 impact to trial participants.
Section to be changed		Section 6.2.1
Description of change		Addition of collection of molecular characteristics of the tumour
Rationale for change		Microsatellite status, Tumour mutational burden (TMB), Expression levels of PD-L1, ER, PR, HER2, HPV status and any available information on tumour mutations will be recorded in the eCRF.
Section to be changed		Section 7
Description of change		Revisions to Statistical Methods

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Rationale for change		Changes included minor formatting updates and additional details on when the MTD may be considered reached.
Section to be changed		Section 7.2.3
Description of change		Revision to the secondary endpoint
Rationale for change		Removal of OR based on RECIST 1.1, addition of OR based on itRECIST.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		Section 8.3.2
Description of change		Clarification regarding direct access to data.
Rationale for change		Adjustment added based upon an assessment of the potential COVID-19 impact.
Section to be changed		Section 9.1
Description of change		Update of references
Rationale for change		Revised to align with check of references throughout document
Section to be changed		Miscellaneous
Description of change		Clarification of laboratory units throughout
Rationale for change		Laboratory values used for determination of patient eligibility or other medical decisions are presented in SI and conventional units.
Section to be changed		Miscellaneous
Description of change		Revisions to formatting, punctuation, and/or spelling.
Rationale for change		Clarifications added as applicable to address minor formatting updates and/or alignment of terms throughout document that do not affect protocol content will not be listed as separate changes.

11.3 GLOBAL AMENDMENT 3

Date of amendment		10-Feb-2022
EudraCT number **EU number**		2019-001082-32
BI Trial number		1426-0001

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BI Investigational Medicinal Product(s)		BI 1387446 Ezabenlimab (BI 754091)
Title of protocol		Phase I, first in human trial evaluating BI 1387446 alone and in combination with ezabenlimab (BI 754091) in solid tumours
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		Clinical Trial Protocol Synopsis-Trial Rationale, Trial Objective, Trial Endpoints
Description of change		Added trial rationale, trial objective, trial endpoints for new arm, Arm C (radiotherapy)
Rationale for change		Describe Arm C (radiotherapy), a new trial arm
Section to be changed		Clinical Trial Protocol Synopsis-Total Number of Patients Entered, Total Number of Patients on Treatment; Section 3.3
Description of change		Updated the total number of patients to 120 and the number of patients in Arm C to 42
Rationale for change		42 patients are needed to enrolled in Arm C to evaluate the study objectives and endpoints
Section to be changed		Clinical Trial Protocol Synopsis-Main in- and exclusion criteria
Description of change		Added inclusion and exclusion criteria specific for Arm C
Rationale for change		Arm C has some inclusion and exclusion criteria different from Arms A and B due to the radiotherapy component
Section to be changed		Clinical Trial Protocol Synopsis-dose and mode of administration
Description of change		Added dose and mode of administration for radiotherapy
Rationale for change		Defined the dose of radiotherapy and mode of radiotherapy administration that will be used in Arm C
Section to be changed		Clinical Trial Protocol Synopsis-Statistical Methods

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Description of change		Defined Arm C statistical methods
Rationale for change		Clarify that a separate BLRM with overdose control will guide dose escalation in Arm C
Section to be changed		Flow Chart
Description of change		Separated Arm A/Arm B and Arm C into 2 separate Flow Charts
Rationale for change		Highlight the different assessments and assessment schedule between Arms A and B compared to Arm C
Section to be changed		Flow Chart Arm A and B, Flow Chart Arm C, Section 6.2.3.1, Section 7.2.5
Description of change		Added safety follow-up visit at 90 days after EoT visit
Rationale for change		To continue to monitor safety, namely AEs/SAEs/AESIs and concomitant treatments, 90 days after EoT
Section to be changed		Blood Sample Flow Chart-Arm C
Description of change		Updated assessments for Arm C
Rationale for change		Blood Sample Flow Chart updated to match new Flow Chart Arm C, accounting for radiotherapy
Section to be changed		Section 1.2.3
Description of change		Added statement regarding the combination of radiotherapy, BI 1387446, and Ezabenlimab
Rationale for change		Explain the potential response the triple combination of radiotherapy, BI 1387446, and ezabenlimab vs the double combination of BI 1387446 and ezabenlimab
Section to be changed		Section 1.3
Description of change		Added the triple combination of radiotherapy, BI 1387446, and ezabenlimab to study rationale
Rationale for change		Explain the objective of the triple combination
Section to be changed		Section 1.4.1
Description of change		Added radiotherapy to the benefits section
Rationale for change		Explained why radiotherapy may be beneficial in this trial

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Section to be changed		Section 1.4.2
Description of change		Added potential risks of radiotherapy in combination with BI 1387446 and ezabenlimab
Rationale for change		Explained potential risks of local radiation therapy combined with BI 1387446 and ezabenlimab
Section to be changed		Section 2.1.1
Description of change		Update Main Objective
Rationale for change		Main Objective updated to include triple combination of BI 1387446 and ezabenlimab following local radiotherapy
Section to be changed		Section 2.1.2, Section 8.6
Description of change		Update MTD for Arm C
Rationale for change		With the introduction of radiotherapy to Arm C and the shift of the start of ezabenlimab treatment to C2D1 , the MTD was increased from 3 weeks to 6 weeks
Section to be changed		Section 3.1, Section 3.2
Description of change		Removed references to injection into deep visceral lesions in Arm C and summarized the revised Arm C radiotherapy cohort
Rationale for change		Describe the new study design, priority of cohorts, and dose escalation plan in the revised Arm C radiotherapy cohort
Section to be changed		Section 3.3.2
Description of change		Updated inclusion criteria #9 to include radiotherapy requirement for Arm C
Rationale for change		A patient must have a lesion suitable for injection and local radiation therapy to be included in Arm C
Section to be changed		Section 3.3.3
Description of change		Added requirement for Arm C that patient should not have had radiation therapy of the lesion proposed for injection within 6 months of initial administration of BI 1387446. Removed requirement for Arm C that patients cannot be on therapeutic doses of anticoagulants.

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Rationale for change		Changes in exclusion criteria due to change in Arm C design and the addition of radiotherapy.
Section to be changed		Section 3.3.4.4
Description of change		Updated requirements for patient replacement in Arm C, Parts 1 and 2.
Rationale for change		Addition of radiotherapy required updating patient replacement requirements in Arm C.
Section to be changed		Section 4.1.2.1, Section 4.1.2.1.1
Description of change		Updated the starting dose of Arm C to [redacted] and the overall total dose of BI 1387446 to [redacted]
Rationale for change		Dose escalations in Arms A and B to date led to revising Arm C parameters and overall total dose of BI 1387446
Section to be changed		Table 4.1.2.1.1:1, Table 4.1.2.1.1:2
Description of change		Separated the provisional levels for dose escalation for the cohorts into separate tables (Arms A and B; Arm C)
Rationale for change		Distinguish between the provisional levels for dose escalation for Arms A and B compared to Arm C
Section to be changed		Section 4.1.2.3
Description of change		Added new section on the dose of radiation to be used in Arm C
Rationale for change		Define the dose of radiation to be used in Arm C
Section to be changed		Table 4.1.2.4:3
Description of change		Added radiotherapy to the treatment schedule
Rationale for change		Define the treatment days/cycles for radiotherapy, BI 1387446, and Ezabenlimab in Arm C.
Section to be changed		Section 4.1.3
Description of change		Remove statement indicating Arm C will be postponed
Rationale for change		The newly defined Arm C with radiotherapy will not be postponed
Section to be changed		Section 4.1.4.1
Description of change		Removed statement about patients allocated to arm C only receiving injections into deep/visceral

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		lesions; added statement that a suitable lesion for injection within the area of radiation should be prioritized if feasible for Arm C.
Rationale for change		Arm C no longer requires deep/visceral lesions for injection and also includes radiation
Section to be changed		Section 4.1.4.2
Description of change		Removed liver lesion injection requirements
Rationale for change		Since deep/visceral lesions will no longer be injected in Arm C, this section is not applicable
Section to be changed		Section 4.1.4.4
Description of change		Defined late DLT for Arm C
Rationale for change		Since the MTD evaluation period for Arm C is different from Arms A and B, late DLT will also be defined differently in Arm C
Section to be changed		Table 4.1.4.3:1
Description of change		Removed deep visceral lesions from table
Rationale for change		Deep visceral lesions are no longer injected in Arm C
Section to be changed		Section 4.2.2.1
Description of change		Removed restrictions on anti-coagulant usage in Arm C
Rationale for change		Since Arm C no longer involves injections into deep/visceral lesions, anti-coagulant usage is no longer restricted
Section to be changed		Section 5.1
Description of change		Revised/clarified when tumour assessments would be performed in each arm
Rationale for change		Tumour assessments in Arm C are now performed at the same visits as in Arms A and B
Section to be changed		Section 5.2.7.1.1
Description of change		Removed progressive disease as an AE that needs to be reported
Rationale for change		Align with oncology standards and not consider progressive disease as a reportable AE
Section to be changed		Section 5.1.7.2.3

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Description of change		Remove requirement for cancers of new histology and exacerbations of existing cancer to be classified and reported as serious events
Rationale for change		Align with oncology standards and not consider cancers of new histology and exacerbations of existing cancer to be reportable serious adverse events
Section to be changed		Section 5.2.7.2.4
Description of change		Added new section, Exemptions to AE/SAE reporting
Rationale for change		Provide rules to be followed for reporting disease progression and associated signs and symptoms for the safety analysis
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		Section 7
Description of change		Defined the two separate BLRM modelling approaches for 1.)Arms A and B and 2.) Arm C and recalculated doses used to determine the MTD
Rationale for change		With the introduction of radiotherapy in Arm C, the BLRM modelling was updated as well as the MTD
Section to be changed		Section 7.2.2, Section 10.5
Description of change		Described the separate methods that will be used for the main analyses of MTD in 1.)Arms A and B and 2.) Arm C
Rationale for change		The additional of radiotherapy in Arm C required an update to the BLRM method used to determine MTD
Section to be changed		[redacted]
Description of change		

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Rationale for change		[redacted]
Section to be changed		Section 7.2.6
Description of change		Revised sample size calculations based on new Arm C (radiotherapy)
Rationale for change		New triple treatment combination in Arm C required a sample size different from the previously defined Arm C
Section to be changed		Section 10.5
Description of change		Updated the performance metrics used to estimate the MTD; updated the joint BLRM hypothetical outcome scenarios to make recommendations of the next dose in each arm
Rationale for change		Due to the addition of Arm C and the doses already tested in Arms A and B of the study, this appendix, specifically the performance metrics used to estimate the MTD as well as the joint BLRM hypothetical outcome scenarios needed to be revised.
Section to be changed		Miscellaneous
Description of change		Revisions to formatting, punctuation, and/or spelling.
Rationale for change		Clarifications added as applicable to address minor formatting updates and/or alignment of terms throughout document that do not affect protocol content will not be listed as separate changes.

11.4 GLOBAL AMENDMENT 4

Date of amendment		05 Oct 2022
EudraCT number **EU number**		2019-001082-32
BI Trial number		1426-0001
BI Investigational Medicinal Product(s)		BI 1387446 Ezabenlimab (BI 754091)

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Title of protocol		Phase I, first in human trial evaluating BI 1387446 alone and in combination with ezabenlimab (BI 754091) in solid tumours
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		Clinical Trial Protocol Synopsis-Trial Rationale, Trial Objective, Trial Endpoints
Description of change		Removed trial rationale, trial objective, trial endpoints for Arm C (radiotherapy)
Rationale for change		Eliminating Arm C
Section to be changed		Clinical Trial Protocol Synopsis-Total Number of Patients Entered, Total Number of Patients on Treatment; Section 3.3
Description of change		Updated the total number of patients planned to 78 and removed mention of Arm C
Rationale for change		Eliminate Arm C and the patient count associated with it
Section to be changed		Clinical Trial Protocol Synopsis-Main in- and exclusion criteria
Description of change		Removed inclusion and exclusion criteria specific for Arm C
Rationale for change		Eliminate Arm C and the patient inclusion and exclusion criteria associated with it
Section to be changed		Clinical Trial Protocol Synopsis-dose and mode of administration
Description of change		Removed dose and mode of administration for radiotherapy
Rationale for change		Eliminating Arm C and thus the mention of the dose of radiotherapy and mode of radiotherapy administration that was to have been used in Arm C
Section to be changed		Clinical Trial Protocol Synopsis-Statistical Methods
Description of change		Removed Arm C statistical methods
Rationale for change		Eliminating arm C and thus the methods section

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Section to be changed		Flow Chart: Overview Arm C
Description of change		Removed Arm C Flow Chart
Rationale for change		Eliminating Arm C
Section to be changed		Blood Sample Flow Chart: Arm C
Description of change		Removed Blood Sample Flow Chart Arm C
Rationale for change		Arm C eliminated so Blood Sample Flow Chart not needed
Section to be changed		Section 1.2.3
Description of change		Removed statement regarding the combination of radiotherapy, BI 1387446, and ezabenlimab
Rationale for change		Arm C combination with radiotherapy eliminated so no need to explain the potential response of the triple combination of radiotherapy, BI 1387446, and ezabenlimab vs the double combination of BI 1387446 and ezabenlimab
Section to be changed		Section 1.3
Description of change		Removed the triple combination of radiotherapy, BI 1387446, and ezabenlimab from study rationale
Rationale for change		Arm C being eliminated so no need for an objective of the triple combination
Section to be changed		Section 1.4.1
Description of change		Removed radiotherapy from the benefits section
Rationale for change		Arm C being eliminated so no need to explain why radiotherapy may be beneficial in this trial
Section to be changed		Section 1.4.2 and Section 1.4.3
Description of change		Removed potential risks of radiotherapy in combination with BI 1387446 and ezabenlimab and associated discussion
Rationale for change		Arm C being eliminated so no need to explain the potential risks of local radiation therapy combined with BI 1387446 and ezabenlimab
Section to be changed		Section 2.1.1
Description of change		Main Objective updated to remove the triple combination of BI 1387446 and ezabenlimab following local radiotherapy

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Rationale for change		Eliminated Arm C
Section to be changed		Section 2.1.2, Section 8.6
Description of change		Remove mention of MTD for Arm C
Rationale for change		No longer need mention since Arm C eliminated
Section to be changed		Section 3.1, Section 3.2, and Figure 3.1.1: 1
Description of change		Removed mention of Arm C in the outline and figure of the trial design and its discussion
Rationale for change		Arm C eliminated
Section to be changed		Section 3.3
Description of change		Changed approximate number of patients planned for the trial from 120 to 78
Rationale for change		Decrease in patient number due to elimination of Arm C
Section to be changed		Section 3.3.2
Description of change		Updated inclusion criteria #9 to remove mention of radiotherapy requirement for Arm C
Rationale for change		Elimination of Arm C
Section to be changed		Section 3.3.3
Description of change		Removed requirement for Arm C patients and prior radiation therapy
Rationale for change		Change in exclusion criteria due to elimination of Arm C design
Section to be changed		Section 3.3.4.5
Description of change		Eliminated requirements for patient replacement in Arm C, Parts 1 and 2.
Rationale for change		Elimination of Arm C
Section to be changed		Section 3.3.5
Description of change		Added text stating sponsor may stop enrolment for the trial if development of compound is terminated
Rationale for change		BI 1387446 development discontinued
Section to be changed		Section 4.1.2.1.1
Description of change		Removed references to Arm C dosing
Rationale for change		Elimination of Arm C

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Section to be changed		Table 4.1.2.1.1: 2
Description of change		Removed table referencing Arm C dosing
Rationale for change		Elimination of Arm C
Section to be changed		Section 4.1.2.3
Description of change		Removed section on the dose of radiation to be used in Arm C
Rationale for change		Elimination of Arm C
Section to be changed		Section 4.1.2.4, Table 4.1.2.4: 3
Description of change		Removed text and table describing treatment schedule for Arm C
Rationale for change		Elimination of Arm C
Section to be changed		Section 4.1.3
Description of change		Remove mention of Arm C for patient allocation
Rationale for change		Elimination of Arm C
Section to be changed		Section 4.1.4.1
Description of change		Removed statement that a suitable lesion for injection within the area of radiation should be prioritized if feasible for Arm C.
Rationale for change		Elimination of Arm C
Section to be changed		Section 4.1.4.3
Description of change		Removed reference to with or without local radiation
Rationale for change		Elimination of Arm C
Section to be changed		Section 4.1.4.4
Description of change		Removed definition of late DLT for Arm C
Rationale for change		Elimination of Arm C
Section to be changed		Section 4.1.4.6
Description of change		Removed details of length of surveillance for CRS for patients in Arm C
Rationale for change		Elimination of Arm C
Section to be changed		Section 4.2.2.1
Description of change		Removed reference to Arm C in the vaccine section

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Rationale for change		Elimination of Arm C
Section to be changed		Section 5.1
Description of change		Removed reference to when tumour assessments would be performed for patients on Arm C
Rationale for change		Elimination of Arm C
Section to be changed		Section 5.2.4
Description of change		Removed reference to Arm C ECGs
Rationale for change		Arm C eliminated
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		Section 6.2.3.1
Description of change		Removed reference to Arm C Flow Chart
Rationale for change		Eliminated Arm C
Section to be changed		Section 7, Figure 7.1 and 7.2, Table 7.2 and 7.5
Description of change		Eliminated mention of BLRM modelling approach for Arm C and associated revisions to Figure 7.1 and elimination of Figure 7: 2, Table 7: 2, and Table 7: 5
Rationale for change		With the elimination of Arm C, aspects of BLRM modelling and discussion are not needed
Section to be changed		Section 7.2.2, Section 10.5
Description of change		Remove mention of analytical methods for Arm C
Rationale for change		Elimination of Arm C
Section to be changed		Section 7.5
Description of change		Removed sample size calculations based on Arm C
Rationale for change		Elimination of Arm C
Section to be changed		Section 10.3.2.3
Description of change		Removed sentences describing methodology for confirming tumour response for Arm C
Rationale for change		Elimiation of Arm C

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Section to be changed		Section 10.5
Description of change		Updated the performance metrics used to estimate the MTD; updated the joint BLRM hypothetical outcome scenarios to make recommendations of the next dose in each arm
Rationale for change		Due to the removal of Arm C and the doses already tested in Arms A and B of the study, this appendix, specifically the performance metrics used to estimate the MTD as well as the joint BLRM hypothetical outcome scenarios needed to be revised.
Section to be changed		Miscellaneous
Description of change		Revisions to formatting, punctuation, and/or spelling.
Rationale for change		Clarifications added as applicable to address minor formatting updates and/or alignment of terms throughout document that do not affect protocol content will not be listed as separate changes.

11.5 GLOBAL AMENDMENT 5

Date of amendment		18 Oct 2023
EudraCT number **EU number**		2019-001082-32
BI Trial number		1426-0001
BI Investigational Medicinal Product(s)		BI 1387446 Ezabenlimab (BI 754091)
Title of protocol		Phase I, first in human trial evaluating BI 1387446 alone and in combination with ezabenlimab (BI 754091) in solid tumours
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		Table 4.1.1:3

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Description of change		New table added with additional ezabenlimab drug substance description
Rationale for change		Required due to change in CMC (chemistry, manufacturing, and controls) for ezabenlimab

APPROVAL / SIGNATURE PAGE

Document Number: c26016868 **Technical Version Number:6.0**

Document Name: clinical-trial-protocol-version-06

Title: Phase I, first in human trial evaluating BI 1387446 alone and in combination with ezabenlimab (BI 754091) in solid tumours

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Trial Leader	[redacted]	19 Oct 2023 17:14 CEST
Author-Trial Statistician		19 Oct 2023 18:18 CEST
Approval-Clinical Program Leaders		19 Oct 2023 22:27 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed